frontiers | Research Topics

Advances in drug-induced diseases, volume II

Edited by
Yao Liu, Patricia Moriel, Linan Zeng, Jia-bo Wang, Miao Yan and Maxine Deborah Gossell-Williams

Published in
Frontiers in Pharmacology
Frontiers in Oncology

ISSN 1664-8714
ISBN 978-2-8325-6755-5
DOI 10.3389/978-2-8325-6755-5

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Advances in drug-induced diseases, volume II

Topic editors

Yao Liu — Daping Hospital, China
Patricia Moriel — State University of Campinas, Brazil
Linan Zeng — McMaster University, Canada
Jia-bo Wang — Capital Medical University, China
Miao Yan — Central South University, China
Maxine Deborah Gossell-Williams — University of the West Indies, Jamaica

Citation

Liu, Y., Moriel, P., Zeng, L., Wang, J.-b., Yan, M., Gossell-Williams, M. D., eds. (2025). *Advances in drug-induced diseases, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6755-5

Table of contents

frontiers | Frontiers in Pharmacology

TYPE Brief Research Report
PUBLISHED 19 May 2023
DOI 10.3389/fphar.2023.1191608

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Dong Ji,
Peking University, China
Zhiyan Liu,
Peking University, China

*CORRESPONDENCE
Zihui Wang,
wangzihui@bjcyh.com
Pengfei Li,
lee-pf@163.com

†These authors have contributed equally to this work

RECEIVED 22 March 2023
ACCEPTED 02 May 2023
PUBLISHED 19 May 2023

CITATION
Zhang X, Jiao F, Li G, Yu X, Pei Y, Zhang Y, Wang Z and Li P (2023), Elevated INR in a COVID-19 patient after concomitant administration of azvudine and anticoagulants.
Front. Pharmacol. 14:1191608.
doi: 10.3389/fphar.2023.1191608

Elevated INR in a COVID-19 patient after concomitant administration of azvudine and anticoagulants

Xi Zhang[1†], Fengwei Jiao[2†], Guangrun Li[1], Xiaojia Yu[1], Yuqing Pei[1], Ying Zhang[1], Zihui Wang[1,3*] and Pengfei Li[4*]

[1]Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [2]Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [3]Department of Chinese Communist Youth League Committee, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [4]Research Ward/Phase I Clinical Trial Unit, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

Background: Azvudine (FNC) is a promising treatment candidate for managing coronavirus disease 2019 (COVID-19). However, drug interactions with azvudine have been poorly studied, especially with no reported cases of azvudine with anticoagulants such as warfarin and rivaroxaban.

Case summary: The patient was diagnosed with lower limb venous thrombosis and took warfarin regularly. The international normalized ratio (INR) was stable (2.0–3.0). However, the INR increased to 7.52 after administering azvudine. The patient had no other factors justifying this change. This increase in INR occurred again with the administration of azvudine in combination with rivaroxaban, and the INR increased to 18.91. After azvudine administration was stopped, the INR did not increase when rivaroxaban was used alone.

Conclusion: Azvudine, warfarin, and rivaroxaban might have previously unidentified drug interactions that increased the INR. Therefore, the INR must be closely monitored when they are concomitantly administered in COVID-19 patients.

KEYWORDS

azvudine, warfarin, rivaroxaban, DDI, international normalized ratio (INR)

1 Introduction

Azvudine (FNC) is the first double-target nucleoside drug, which has demonstrated significant and broad-spectrum *in vitro* antiviral effects against targets such as HIV (Peng et al., 2014), HBV (Peng et al., 2014), HCV (Smith et al., 2009), and EV71 (Xu et al., 2020). It is also a promising treatment candidate for managing coronavirus disease 2019 (COVID-19) (Ren et al., 2020). FNC is completely absorbed by passive diffusion and active transport mechanisms. P-gp, MRP2, and BCRP could influence the absorption of FNC in the small intestine (Liu et al., 2017). FNC is not metabolized by cytochrome P-450 (CYP); therefore, drug–drug interactions (DDIs) are less likely.

Warfarin is a direct oral anticoagulant and also a narrow therapeutic index drug that requires frequent dose adjustments to minimize both thrombosis and bleeding-related adverse events (Gallagher et al., 2011). Drug interaction is one of the multiple factors that

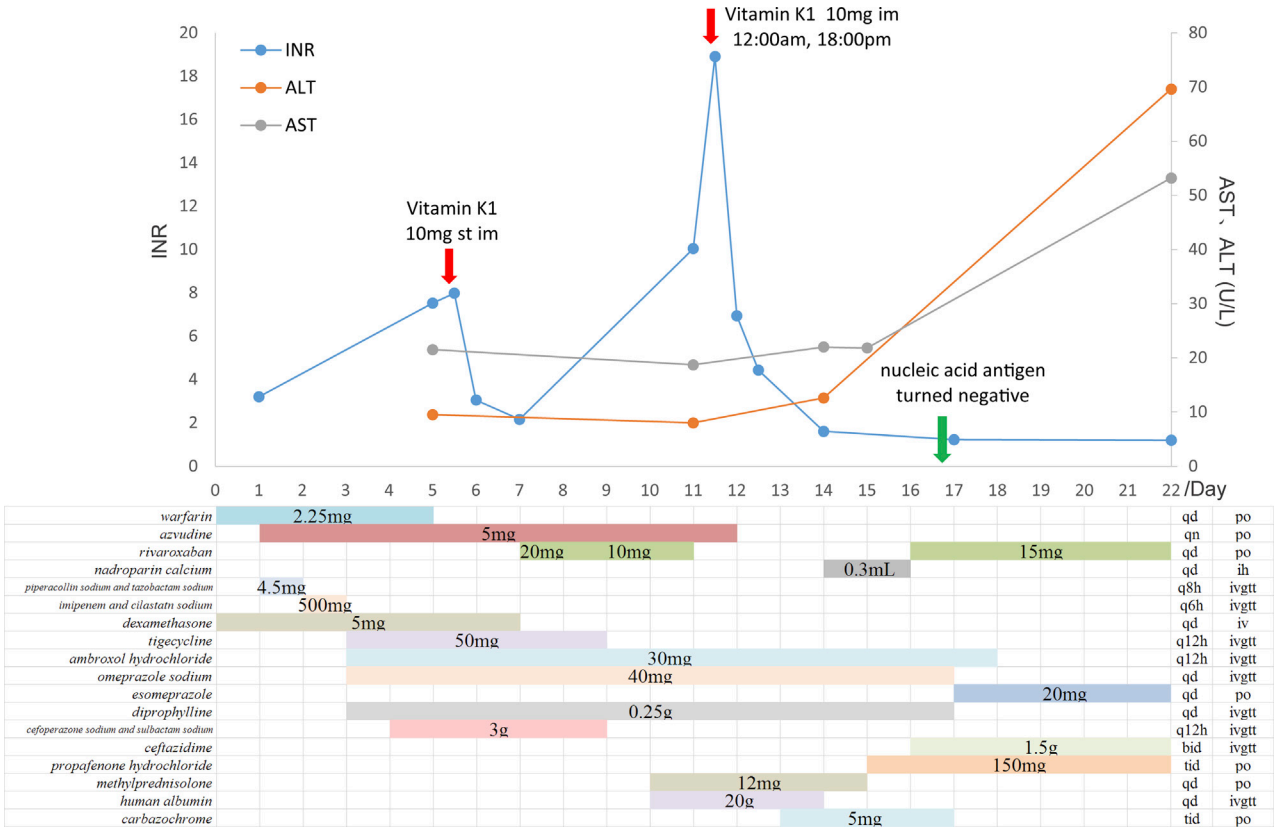


FIGURE 1
Time course of administration of azvudine and anticoagulants and changes in the INR and AST/ALT.

alter individual drug responses and thus contribute to international normalized ratio (INR) instability (Witt et al., 2016).

Rivaroxaban is an oral direct factor Xa inhibitor and has been developed as a favored alternative to coumarin derivatives (Kvasnicka et al., 2017). Approximately 2/3 of rivaroxaban is metabolized by hepatic cytochrome P450 (CYP) enzymes 3A4/5, 2J2, and CYP-independent enzymes, while the remaining 1/3 is eliminated unchanged via the kidney, involving transporters in active renal secretion such as P-glycoprotein (P-pg) and breast cancer resistance protein (BCRP) (Mueck et al., 2014). Many drugs, including aspirin (Perzborn et al., 2015), fluconazole (Mueck et al., 2013), and amiodarone (Cheong et al., 2017), had been reported to interact with rivaroxaban, increasing the risk of bleeding.

However, no reports are found indicating that azvudine interacts with warfarin and rivaroxaban. Here, we report a case of elevated INR in a COVID-19 patient, when azvudine and these two anticoagulants were concomitantly administered.

2 Case summary

A 70-year-old man, diagnosed with fever, cough, and wheezing on December 23rd, was hospitalized in Fangshan Hospital of Traditional Chinese Medicine on December 26th (day 1). Laboratory results showed elevated C-reactive protein of 72.25 mg/L and WBC of 1.96 × 10^9/L, and the chest CT image showed pneumonia and emphysema in both lungs. The patient was diagnosed with COVID-19 infection complicated with respiratory failure; he received azvudine (day 2) and dexamethasone; nasal catheter oxygen therapy (the oxygen flow rate was 3-4 L/min); and broad-spectrum antibiotics considering the accompanying bacterial infection (Figure 1). Given a past medical history of lower limb venous thrombosis, the patient took 2.25 mg of warfarin once a day, with the INR being monitored regularly (between 2.0 and 3.0). On day 4, the patient's oxygenation index was as low as 78 mmHg, and he was transferred to Beijing Chaoyang Hospital for treatment. The baseline characteristics (day 4) are shown in Table 1. Relevant imaging materials are shown in Figure 2. The INR was 3.2, and the blood test showed that his liver function was normal on day 4. Due to deterioration in the condition, warfarin, azvudine, and dexamethasone were administered continuously, and broad-spectrum antibiotics were still used but adjusted to tigecycline, ambroxol hydrochloride, omeprazole, and diprophylline, which were added on day 4; in addition, high-flow nasal cannula oxygen therapy (FiO_2 needed up to 90%) and intermittent prone positioning were applied. The detailed drug dosages and duration are shown in Figure 1. At 9 a.m. on day 5, the critical value showed that the INR was 7.52, and no hemorrhage was observed. The change in the INR is shown in Figure 1. Then, warfarin was discontinued, and vitamin K1 was given on day 5. The CRP was 21.6 mg/L and WBC was 4.4 × 10^9/L on day 5; it was suggested that the infection

TABLE 1 Baseline patient characteristics.

Subject		Normal range
Gender	Male	—
Age (years)	70	—
Body weight (kg)	65	—
Body temperature (°C)	36.0	—
Pulse (times per minute)	90	—
Respiratory frequency (times per minute)	25	—
Blood pressure(mmHg)	127/87	—
APACHE score	10	—
Serum creatinine (umol/L)	81.3	(53.0–115.0)
Serum albumin (g/L)	28.6	(35.0–53.0)
WBC ($\times 10^9$/L)	4.7	(4.0–10.0)
CRP (mg/L)	21.6	(0.0–10.0)
Platelet (*10^9/L)	173.0	(100.0–300.0)
Total bilirubin (umol/L)	6.5	(3.4–20.5)
AST (U/L)	21.5	(4.0–40.0)
ALT (U/L)	9.5	(4.0–40.0)
LDH (U/L)	310.6	(80.0–250.0)
INR	3.2	(2.0–3.0)
APTT (seconds)	44.7	(28.0–42.0)
D-dimer (mg/L)	0.39	(0.00–0.30)

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C- reactive protein; LDH, lactic dehydrogenase; WBC, white blood cell.

was serious, and cefoperazone sodium and sulbactam sodium were added for anti-infection treatment later. However, the INR decreased to 2.16 on day 7. Then, rivaroxaban was added on day 8. On day 10, the WBC was 3.8×10^9/L, and the oxygenation index of the patient increased to 156 mmHg, so antibiotics were stopped and the FiO_2 was adjusted to 60%. At 4 a.m. on day 11, the critical value showed that the INR increased again to 10.04, rivaroxaban was discontinued, and VK1 was given immediately. However, the INR continued to increase, and by 9 p.m. on day 11, the INR returned to 18.91, and vitamin K1 was given again. Azvudine was discontinued the next day. At 6 a.m. on day 12, the INR decreased to 6.94 and continued to decrease until it reached 1.61 on day 14. The patient was given nadroparin calcium and rivaroxaban successively. Since then, the patient was managed with nadroparin calcium and rivaroxaban successively for anticoagulation therapy, and the INR did not increase again and remained at about 1.2. On day 16, laboratory tests showed that CRP was 0.9 mg/L, and WBC was 4.9×10^9/L; the oxygenation index of the patient increased to 252 mmHg, the patient's condition improved, the FiO_2 was adjusted to 37%, and ceftazidime antiinfective therapy was administered. On day 17, the patient's nucleic acid antigen turned negative. The patient's condition improved significantly, and he was discharged on day 24.

3 Discussion

3.1 Evaluation of the DDI between azvudine and warfarin

Factors that affect the INR include medication adherence, diet, disease (such as liver dysfunction), and concomitant use of drugs (Reddy et al., 2015). In this case, the patient was taking warfarin properly for 2 years, and his INR was stable at 2.0–3.0, demonstrating that his medication adherence was good. The increased INR was not due to the improving adherence to hospitalization. The patient did not change his diet and adhered to a warfarin-only diet while taking warfarin and azvudine. His liver function was also normal before and during admission. A retrospective study (Zou et al., 2020) evaluated the correlation between coagulation function and COVID-19 and reported that coagulation dysfunction is common in patients with COVID-19, especially fibrinogen and D-dimer elevation, and the degree of elevation is related to the severity of the disease. As the disease recovers, fibrinogen and activated partial thromboplastin time also returned to normal. However, the impact of COVID-19 on the INR has been very mild; as COVID-19 became more severe, the INR only increased from 1.01 in mild cases to 1.04 in severe cases. The initial INR of this patient was 3.2, which is due to the novel coronavirus

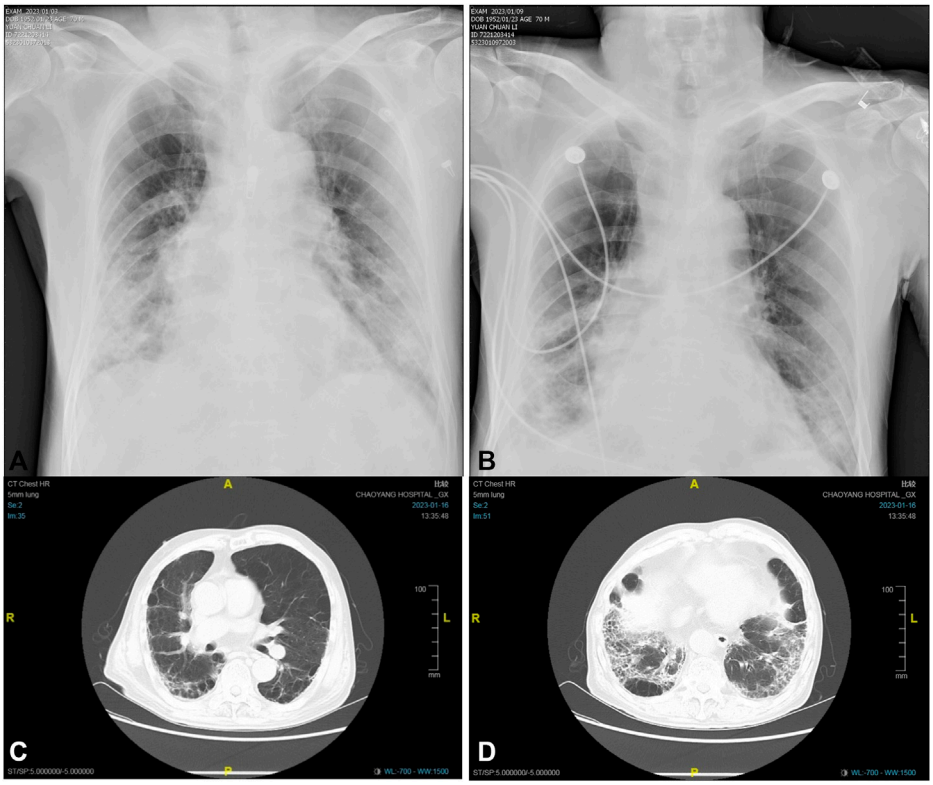


FIGURE 2
Dynamic chest X-ray and CT images of the patient:**(A)** the X-ray image on day 9, **(B)** the X-ray image on day 15, **(C)** the CT image on day 22, and **(D)** the CT image on day 22.

disease possibly. Therefore, the INR increased to 7.98, and the correlation between increased INR and COVID-19 progression was not considered. The patient was treated with multiple drugs, including azvudine, piperacillin sodium and tazobactam sodium, imipenem and cilastatin sodium, dexamethasone, tigecycline, omeprazole sodium, and diprophylline. Although warfarin was associated with piperacillin sodium and tazobactam sodium, imipenem and cilastatin sodium, the INR continued to increase 1 or 2 days after discontinuation of the two drugs, so the interaction between warfarin and the two drugs was not considered. INR increase has been reported when high-dose dexamethasone (>40 mg/day) and warfarin are concomitantly administered (Sellam et al., 2007), which may be due to the action of high-dose synthetic glucocorticoids on Niemann–Pick C1-like 1 protein (Ito et al., 2019). However, the dose of dexamethasone in this patient was 5.0 mg once a day, which was too low to cause any DDIs. Although tigecycline could reduce warfarin clearance, it did not significantly change the effect of warfarin on the INR. Omeprazole is a moderate inhibitor of CYP2C19, which reduces warfarin metabolism when combined with warfarin. On the other hand, omeprazole is a CYP1A2 gateway agent, and when combined with warfarin, it reduces warfarin exposure and INR; research studies reported that the coagulation time was not significantly changed (Unge et al., 1992). There was no report about the interaction between diprophylline and warfarin. At 9 a.m. on day 5, the critical value showed that the INR was 7.52, but cefoperazone sodium and sulbactam sodium were added at 1 p.m. on day 5, so there was no temporal–causal relationship between the drug and the increase in INR. The effect of these drugs on INR was excluded. The INR increased to 7.52 after 3 days of administering azvudine. There was a reasonable time relationship between drug combination and INR elevation. Then, warfarin was discontinued and vitamin K1 was given. As needed to treat COVID-19, the patient continued to take azvudine. On day 7, the INR decreased again to 2.16. There was a temporal–causal relationship between the improvement time of adverse events and the discontinuation time of the combination of the two drugs. To avoid the risk of bleeding, warfarin was not subsequently resumed, so it was unclear whether the INR increase will occur again after warfarin and azvudine were taken orally simultaneously.

The metabolism of warfarin primarily involves CYP2C9, CYP3A4, CYP1A2, and CYP2C8 (Sekimoto et al., 2022). However, azvudine is not metabolized by the P450 enzyme and is not an inhibitor or inducer of the P450 enzyme. The interaction between the two drugs is unlikely to be due to drug metabolism. In terms of pharmacodynamics, warfarin can inhibit the biosynthesis of functional vitamin K-dependent (VKD) coagulation factors (Chen et al., 2020). Although no azvudine-induced bleeding or related adverse events has been reported to date. We suspect that maybe azvudine could affect the biosynthesis of active VKD coagulation factors with possible synergy with warfarin. However, there is no evidence, and further verification studies are needed at a later stage.

The Drug Interaction Probability Scale (DIPS) has been widely used as a criterion for determining adverse events caused by DDIs (Horn et al., 2007). By using the DIPS evaluation of the interaction between azvudine and warfarin, the result was "probable," which supported an interaction possibility.

3.2 Evaluation of the DDI between azvudine and rivaroxaban

The patient started oral rivaroxaban on day 8. At 4:00 a.m. on day 11, the INR was 10.04, which increased again. Moore et al. (2015) reported that the INR is abnormally elevated several hours after an oral administration of rivaroxaban and decreased significantly after a few hours because of the drug properties of rivaroxaban. This situation is completely different from the principle of abnormal increase in the INR caused by an oral overdose of warfarin. At 9:00 p.m. on day 11 (17 h later), the INR did not decrease but continued to increase to 18.91. Therefore, it was excluded that the increase in INR was caused by rivaroxaban alone. The patient had good medication compliance during hospitalization and normal liver function. While taking rivaroxaban, the patient also took tigecycline, ambroxol hydrochloride, omeprazole, diprophylline, cefoperazone sodium and sulbactam sodium, and azvudine. Tigecycline is a *P-gp* substrate, and rivaroxaban increases the activity of *P-gp* (Liu et al., 2017); the combination did not lead to increased exposure to rivaroxaban. Ambroxol hydrochloride, omeprazole, and diprophylline were again combined with rivaroxaban on day 17, and no increase in the INR was observed. The INR increased 2 days after cefoperazone sodium and sulbactam sodium were discontinued. Concomitantly, azvudine had been taken in combination with rivaroxaban, and the INR increased; there was a temporal–causal relationship between the increase in the INR and the combination of the two medicines. The INR did not increase again on day 17 when rivaroxaban was taken alone. Rivaroxaban and azvudine were not used in combination again, so it was unclear whether the INR increase will occur again after rivaroxaban and azvudine were taken orally simultaneously.

As reported by previous articles about rivaroxaban (Fernandez et al., 2021), the types of interactions assessed were PK interactions mediated by CYP3A, *P-gp* modulators, and/or gastric pH modifiers, and PD interactions mediated by other antithrombotic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) for interaction studies. Azvudine is not metabolized by the P450 enzyme and is a mild P-gp inducer (Liu et al., 2017), and when combined with rivaroxaban, there was no increase in rivaroxaban exposure, which further increased PT or INR. Azvudine is not a gastric pH modifier. Vitamin K does not affect the anticoagulant activity of rivaroxaban, so if the anticoagulant effect is reversed by rivaroxaban, procoagulant reversal agents such as prothrombin complex thickener, activated prothrombin complex thickener. or recombinant factor Vlla should be used. Vitamin K could not reverse clotting abnormalities caused by rivaroxaban overdose. In this case, rivaroxaban was discontinued and vitamin K1 was given, then INR decreased to 1.61 on day 14. We suspected that the interaction between azvudine and rivaroxaban affects the biosynthesis of active VKD coagulation factors, and this phenomenon is consistent with our speculation about the interaction mechanism between azvudine and warfarin. Chen et al. (2020) reported three ways to inhibit VKD carboxylation: inhibit vitamin K epoxide reductase (VKOR) (such as warfarin), inhibit vitamin K reductase (VKR) in vitamin K redox cycling (such as clofazimine), and inhibit vitamin K availability within the cells. Coagulopathy from drugs that inhibit the VKOR, but not vitamin K, can be rescued by administering vitamin K. So, it may be that azvudine inhibited VKOR and played a synergistic anticoagulant effect with rivaroxaban, but this evidence needs to be confirmed in further studies.

Finally, as described previously, using DIPS results, the interaction between azvudine and rivaroxaban was rated as "probable."

4 Conclusion

Azvudine, warfarin, and rivaroxaban might have previously unidentified drug interactions that increased the INR. Therefore, the INR must be closely monitored when they are concomitantly administered in COVID-19 patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XZ contributed to case data collation, case analysis, and relevance assessment; FJ contributed to case data collation and case analysis; GL, XY, YP, and YZ contributed to literature research; ZW contributed to case analysis; PL contributed to case analysis and relevance assessment; XZ drafted the manuscript; ZW and PL contributed to the conception of the work and critically revised the final version to be published. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Chen, X., Li, C., Jin, D.Y., Ingram, B., Hao, Z., Bai, X., et al. (2020). A cell-based high-throughput screen identifies drugs that cause bleeding disorders by off-targeting the vitamin K cycle. *Blood* 136, 898–908. doi:10.1182/blood.2019004234

Cheong, E. .J., Goh, J.J., Hong, Y., Venkatesan, G., Liu, Y., Chiu, G.N., et al. (2017). Application of static modeling --in the prediction of *in vivo* drug-drug interactions between rivaroxaban and antiarrhythmic agents based on *in vitro* inhibition studies. *Drug Metab. Dispos.* 45, 260–268. doi:10.1124/dmd.116.073890

Fernandez, S., Lenoir, C., Samer, C.F., and Rollason, V. (2021). Drug-drug interactions leading to adverse drug reactions with rivaroxaban: A systematic review of the literature and analysis of VigiBase. *J. Pers. Med.* 11, 250. doi:10.3390/jpm11040250

Gallagher, A.M., Setakis, E., Plumb, J.M., Clemens, A., and van Staa, T.P. (2011). Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb. Haemost.* 106, 968–977. doi:10.1160/TH11-05-0353

Horn, J.R., Hansten, P.D., and Chan, L.N. (2007). Proposal for a new tool to evaluate drug interaction cases. *Ann. Pharmacother.* 41, 674–680. doi:10.1345/aph.1H423

Ito, S.M., Yamanashi, Y., Takada, T., and Suzuki, H. (2019). Clinical importance of drug-drug interaction between warfarin and prednisolone and its potential mechanism in relation to the niemann-pick C1-like 1-mediated pathway. *Circ. J.* 83, 471–480. doi:10.1253/circj.CJ-18-0807

Kvasnicka, T., Malikova, I., Zenahlikova, Z., Kettnerova, K., Brzezkova, R., Zima, T., et al. (2017). Rivaroxaban - metabolism, pharmacologic properties and drug interactions. *Curr. Drug Metab.* 18, 636–642. doi:10.2174/1389200218666170518165443

Liu, Y., Liu, B., Zhang, Y., Peng, Y., Huang, C., Wang, N., et al. (2017). Intestinal absorption mechanisms of 2'-deoxy-2'-beta-fluoro-4'-azidocytidine, a cytidine analog for AIDS treatment, and its interaction with P-glycoprotein, multidrug resistance-associated protein 2 and breast cancer resistance protein. *Eur. J. Pharm. Sci.* 105, 150–158. doi:10.1016/j.ejps.2017.05.009

Moore, K.T., Byra, W., Vaidyanathan, S., Natarajan, J., Ariyawansa, J., Salih, H., et al. (2015). Switching from rivaroxaban to warfarin: An open label pharmacodynamic study in healthy subjects. *Br. J. Clin. Pharmacol.* 79, 907–917. doi:10.1111/bcp.12559

Mueck, W., Kubitza, D., and Becka, M. (2013). Co-Administration of rivaroxaban with drugs that share its elimination pathways: Pharmacokinetic effects in healthy subjects. *Br. J. Clin. Pharmacol.* 76, 455–466. doi:10.1111/bcp.12075

Mueck, W., Stampfuss, J., Kubitza, D., and Becka, M. (2014). Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin. Pharmacokinet.* 53, 1–16. doi:10.1007/s40262-013-0100-7

Peng, Y., Cheng, T., Dong, L., Zhang, Y., Chen, X., Jiang, J., et al. (2014). Quantification of 2'-deoxy-2'-beta-fluoro-4'-azidocytidine in rat and dog plasma using liquid chromatography-quadrupole time-of-flight and liquid chromatography-triple quadrupole mass spectrometry: Application to bioavailability and pharmacokinetic studies. *J. Pharm. Biomed. Anal.* 98, 379–386. doi:10.1016/j.jpba.2014.06.019

Perzborn, E., Heitmeier, S., and Laux, V. (2015). Effects of rivaroxaban on platelet activation and platelet-coagulation pathway interaction: *In vitro* and *in vivo* studies. *J. Cardiovasc Pharmacol. Ther.* 20, 554–562. doi:10.1177/1074248415578172

Reddy, U., Mallepaddi, N.R., and Chevassut, T. J. (2015). High INR on warfarin. *BMJ* 350, h1282. doi:10.1136/bmj.h1282

Ren, Z., Luo, H., Yu, Z., Song, J., Liang, L., Wang, L., et al. (2020). A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study. *Adv. Sci. (Weinh)* 7, e2001435. doi:10.1002/advs.202001435

Sekimoto, M., Imai, T., Hidaka, S., Chiba, N., Sakurai, A., Hata, M., et al. (2022). Elevated INR in a COVID-19 patient after concomitant administration of favipiravir and warfarin: A case report. *J. Clin. Pharm. Ther.* 47, 407–410. doi:10.1111/jcpt.13499

Sellam, J., Costedoat-Chalumeau, N., Amoura, Z., Aymard, G., Choquet, S., Trad, S., et al. (2007). Potentiation of fluindione or warfarin by dexamethasone in multiple myeloma and AL amyloidosis. *Jt. Bone Spine* 74, 446–452. doi:10.1016/j.jbspin.2006.12.006

Smith, D.B., Kalayanov, G., Sund, C., Winqvist, A., Maltseva, T., Leveque, V.J., et al. (2009). The design, synthesis, and antiviral activity of monofluoro and difluoro analogues of 4'-azidocytidine against hepatitis C virus replication: The discovery of 4'-azido-2'-deoxy-2'-fluorocytidine and 4'-azido-2'-dideoxy-2',2'-difluorocytidine. *J. Med. Chem.* 52, 2971–2978. doi:10.1021/jm801595c

Unge, P., Svedberg, L.E., Nordgren, A., Blom, H., Andersson, T., Lagerstrom, P.O., et al. (1992). A study of the interaction of omeprazole and warfarin in anticoagulated patients. *Br. J. Clin. Pharmacol.* 34, 509–512. doi:10.1111/j.1365-2125.1992.tb05656.x

Witt, D.M., Clark, N.P., Kaatz, S., Schnurr, T., and Ansell, J.E. (2016). Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J. Thromb. Thrombolysis* 41, 187–205. doi:10.1007/s11239-015-1319-y

Xu, N., Yang, J., Zheng, B., Zhang, Y., Cao, Y., Huan, C., et al. (2020). The pyrimidine analog FNC potently inhibits the replication of multiple enteroviruses. *J. Virol.* 94, e00204–e00220. doi:10.1128/JVI.00204-20

Zou, Y., Guo, H., Zhang, Y., Zhang, Z., Liu, Y., Wang, J., et al. (2020). Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. *Biosci. Trends* 14, 285–289. doi:10.5582/bst.2020.03086

frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 25 May 2023
DOI 10.3389/fmed.2023.1167759

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Reinhold Munker,
University of Kentucky, United States
Douglas James Grider,
Virginia Tech Carilion, United States

*CORRESPONDENCE
Shuye Wang
✉ wsywangshuye@126.com

RECEIVED 09 March 2023
ACCEPTED 09 May 2023
PUBLISHED 25 May 2023

CITATION
Zhao D, Song Q, Wu C and Wang S (2023) Case report: A rare case of acute hemolysis in advanced rectal cancer after XELOX and nivolumab treatment: analysis of drug-dependent antibodies.
Front. Med. 10:1167759.
doi: 10.3389/fmed.2023.1167759

Case report: A rare case of acute hemolysis in advanced rectal cancer after XELOX and nivolumab treatment: analysis of drug-dependent antibodies

Dengke Zhao[1], Qiao Song[2,3], Chunyan Wu[2,3] and Shuye Wang[1,4]*

[1]Harbin Medical University, Harbin, China, [2]Department of Medicine, Qingdao University, Qingdao, China, [3]Department of Hematology, Affiliated Hospital, Qingdao University, Qingdao, China, [4]Department of Hematology, The First Affiliated Hospital, Harbin Medical University, Harbin, China

Objective: To investigate the mechanism, *in vitro* differential test and clinical significance of hemolytic anemia after receiving oxaliplatin and nivolumab treatment.

Methods: We encountered a male patient with stage IV rectal cancer who experienced acute hemolysis during the ninth cycle of treatment with XELOX combined with nivolumab and cetuximab. The patient's blood samples were collected and tested for the presence of oxaliplatin or nivolumab antibodies on red blood cells.

Results: Direct antiglobulin testing of red blood cells incubated with oxaliplatin was strongly positive, whereas cells incubated with nivolumab were negative, which suggested that oxaliplatin was responsible for the hemolysis. After short-term highdose glucocorticoid treatment, human normal immunoglobulin infusion, and other symptomatic treatments, the patient's condition rapidly improved, and he continued to receive nivolumab treatment without further hemolysis.

Conclusion: Attention should be paid to the possibility of acute hemolysis when using oxaliplatin and nivolumab, and it is important to recognize and manage this adverse event early. We detected oxaliplatin-related antibodies on the surface of red blood cells *in vitro*, which provided evidence for the following treatments.

KEYWORDS

drug-related hemolytic anemia, colorectal cancer, oxaliplatin, nivolumab, treatment

Introduction

Oxaliplatin is a key component of chemotherapy used as a first-line treatment for advanced colorectal cancer with relatively few side effects (1). Oxaliplatin immune-induced syndrome (OIIS) includes severe acute hemolytic anemia and/or thrombocytopenia and symptoms such as fever, sudden back pain, and hematuria (2–4). Programmed death cell protein 1 (PD-1) inhibitors can block tumor immune tolerance, among them, nivolumab has been used to treat mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (5). Nivolumab can cause side effects such as hypothyroidism, diarrhea, decreased appetite, colitis, pneumonitis, hepatic function abnormal, sepsis, acute kidney injury, uveitis (6). Nivolumab also has several immune-related adverse reactions including rash, pruritus, and rarely, immune hemolytic anemia, which could be life-threatening (7–9). Drug-induced hemolytic anemia may be either

"warm" or "cold" depending on the temperature at which the autoantibodies become active. Warm autoimmue hemolytic anemia (AIHA) is caused mainly by warm-reactive IgG-mediated extravascular hemolysis, Cold AIHA results from IgM activation of classic complement pathway and the autoantibodies are active at temperatures 4°C (10). Some cases that both types of autoantibodies may exist simultaneously are labeled as "mixed" AIHA (10). Increasing reports of oxaliplatin-induced or nivolumab-induced hemolytic anemia have been published, however, cases of acute hemolysis after receiving oxaliplatin and nivolumab treatment were rarely reported. Only few of the published cases did drug-dependent red blood cell (RBC) antibodies tests *in vitro* which confirmed that hemolysis was directly related to the drug. We encountered a case of acute hemolysis in a patient with stage IV rectal cancer during treatment with XELOX combined with nivolumab and cetuximab. Oxaliplatin-related antibodies were detected on the surface of erythrocytes *in vitro*, which provided evidence for the following treatments.

Case report

A 47-year-old Chinese male patient initially presented with a malignant rectal tumor (pTxN2bM1b, stage IV B). PET-CT revealed liver and bone metastasis. From November 2020 to March 2021, he completed eight cycles of XELOX combined with nivolumab and cetuximab. The cumulative dose of oxaliplatin was 716 mg/m^2 (1,440 mg), and that of nivolumab was 955 mg/m^2 (1,920 mg). Two hours after the end of oxaliplatin administration during the ninth treatment cycle, the patient complained of sudden lower back pain and fatigue, and his urine was strongly brown. Laboratory analysis revealed hematuria (urine RBC count, 90.6/μL) and liver dysfunction (serum glutamic oxaloacetic transaminase, 142U/L; total bilirubin, 136.5 μmol/L). The direct antiglobulin test (DAT) was positive, and the indirect antiglobulin test (IAT) was negative. Considering drug-related hemolysis, follow-up chemotherapy drug was immediately stopped. He was managed with 1 mg/kg/day methylprednisolone from the first day after hemolysis was suspected (D1) at decreasing doses over 1 month, and human immunoglobulin (0.4 g/kg/day) was administered from D3 to D7. He received renal protective therapy (D3 to D21) because of the creatinine elevation. The symptoms of hemolysis resolved on D4. Laboratory examination showed decreased serum creatinine levels and increased hemoglobin levels. DAT was negative on D26. Oxaliplatin was discontinued, the patient resumed treatment with capecitabine, cetuximab, and nivolumab. There was no hemolysis syndrome, and the patient's hemoglobin and creatinine levels normalized (Figure 1).

We obtained peripheral blood samples from the patient to test for drug-related hemolysis. The concentration of oxaliplatin injection [Qilu Pharmaceutical (Hainan) Co., Ltd, Haikou, China] was 2 mg/mL, Nivolumab (Bristol Myers Squibb Holdings Pharma, Ltd, New York, United States) was prepared at a concentration of 5 mg/mL (11). Mixtures of patient sera and 5% oxaliplatin-treated RBC suspension were incubated at 37°C for 1 h, centrifuged, washed three times in 0.9% saline, assessed for hemolysis/agglutination via visual assessment, and Coombs test by microcolumn agglutination method. As a control, sera from healthy AB donor instead of patient sera, and type O RBC suspension instead of oxaliplatin-treated RBC suspension. The experiment was repeated for nivolumab in the same manner. Patient sera incubated with oxaliplatin-treated RBC suspension group was positive on DAT, and the other results were negative.

Discussion

Our patient was treated with oxaliplatin and nivolumab, both of which could cause hemolysis. To further clarify the drug causing hemolysis, we detected drug-dependent RBC antibodies *in vitro*. DAT using patient sera and oxaliplatin-treated red blood cells (RBCs) was positive, indicating that anti-IgG/C3 antibodies were present on the surface of RBCs. Meanwhile, IAT was negative, indicating that there were no anti-IgG/C3 antibodies in the patient's serum. DAT using RBCs incubated with nivolumab was negative, suggesting the absence of nivolumab-dependent antibodies on the RBC membrane. The patient continued to receive nivolumab after the resolution of hemolysis, and there was no further evidence of acute hemolysis, indicating that the hemolysis was caused by oxaliplatin.

Oxaliplatin is the third generation platinum antineoplastic drug, which inhibits the replication and transcription of DNA in tumor cells, thus inducing cell death. Combined with 5-fluorouracil derivatives and vascular endothelial growth factor in the treatment of advanced colorectal cancer, it can effectively improve patient survival and reduce disease recurrence (1, 12). Increasing reports of oxaliplatin-induced hemolytic anemia have been published, and some cases were accompanied by thrombocytopenia and neutropenia. It is characterized by fever, lower back pain, hematuria, abnormal liver function and renal function (2–4). Timely detection and treatment of these symptoms will help to prevent further deterioration of OIIS. The mechanism of oxaliplatin-induced hemocytopenia may include immune system activation (immune complex, non-immunologic drug adsorption, and true autoimmune), oxaliplatin pharmacokinetic, and genetic background predisposition, all of these may have played a role during the process (4, 11, 13–16). We consider that the antibody was already induced by previous oxaliplatin exposure. With repeated drug exposure, the immune response was enhanced until the antibody reached the threshold level, leading to hemolysis (17).

Several cases of acute renal injury after treatment with oxaliplatin have been reported, and these events were believed to be caused by the direct damage of renal tubules or the accumulation of hemolytic products in the renal tubules (18–20). In our case, the increased creatinine level appeared after hemolysis and improved rapidly after short-term high-dose glucocorticoid and immunoglobulin infusion. It is speculated that drug treatment can reduce the concentration of autoantibodies, resolve the cause of renal tubular necrosis, and gradually normalize renal function while hemolysis is alleviated. This clinical process supported the finding that renal insufficiency was caused by acute hemolysis.

Of the 61 patients reported, 27 (44.26%) received repeated oxaliplatin treatment. The median number of cycles before the occurrence of OIIS was four, which was significantly earlier than observed in patients who received other regimens (2). Vyskocil

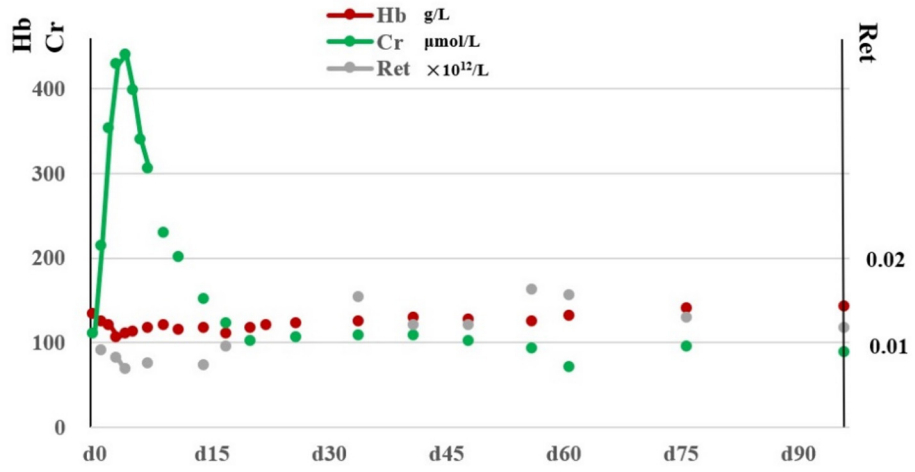


FIGURE 1
Changes of hemoglobin, creatinine and reticulocyte count after hemolysis. *Hb, hemoglobin; Cr, creatinine levels; Ret, reticulocyte.

et al. (20) reported that they did Coombs test using patient's sera 6 months/12 months after the hemolysis with oxaliplatin-treated RBCs, the results showed long-term antibodies on the surface of RBCs, and platinum drug cross-reaction. Therefore, oxaliplatin treatment is no longer recommended for patients with OIIS.

Nivolumab blocks the binding of PD-1 and programmed death-ligand 1 (PDL-1) to tumor cells and stimulates T cells to target tumor cells. This effect of relieving T cell inhibition may be uncontrolled, resulting in autoimmune adverse reactions, including rash, pruritus, hemolytic anemia (21), immune hemocytopenia (7, 8, 22, 23). The mechanism of nivolumab-induced hemocytopenia is not clear but is likely related to reaction of T cells and drug-induced autoantibodies (24). DAT using RBCs incubated with nivolumab was negative, suggesting the absence of nivolumab-dependent antibodies on the RBC membrane. Thus, the patient continued to receive nivolumab, and there was no further evidence of acute hemolysis. Anemia usually occurs in the early stage of treatment. In the course of subsequent treatment, although RBC antibodies may already exist, the patient can still tolerate nivolumab (7).

Conclusion

It is crucial to identify symptoms and signs of hemolysis and signs promptly as possible while receiving nivolumab and oxaliplatin anticancer treatment. The drug causing to hemolysis should be identified to provide evidence for follow-up drug selection.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DZ, QS, and CW were responsible for collecting data, sorting out data, and writing the article. SW was responsible for guiding the writing and participating in the revision of the article. All authors read and approved the final manuscript.

Funding

This work was supported by a grant from the Natural Science Foundation of Shandong Province (No. ZR2019MH096).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. *Eur J Cancer Oxf Engl.* (2019) 109:70–83. doi: 10.1016/j.ejca.2018.12.019

2. Bencardino K, Mauri G, Amatu A, Tosi F, Bonazzina E, Palmeri L, et al. Oxaliplatin immune-induced syndrome occurs with cumulative administration and rechallenge: single institution series and systematic review study. *Clin Colorectal Cancer.* (2016) 15:213–21. doi: 10.1016/j.clcc.2016.02.001

3. Forcello NP, Khubchandani S, Patel SJ, Brahaj D. Oxaliplatin-induced immune-mediated cytopenias: a case report and literature review. *J Oncol Pharm Pract.* (2015) 21:148–56. doi: 10.1177/1078155213520262

4. Nguyen TN, Maenulein E, Fihman V, Vinatier I, Moh Klaren J. Serologic characteristics of oxaliplatin antibodies in 15 patients with drug-induced immune hemolytic anemia. *Transfusion (Paris).* (2021) 61:1609–16. doi: 10.1111/trf.16360

5. Smith KM, Desai J. Nivolumab for the treatment of colorectal cancer. *Expert Rev Anticancer Ther.* (2018) 18:611–8. doi: 10.1080/14737140.2018.1480942

6. Soldatos TG, Dimitrakopoulou-Strauss A, Larribere L, Hassel JC, Sachpekidis C. Retrospective side effect profiling of the metastatic melanoma combination therapy ipilimumab-nivolumab using adverse event data. *Diagn Basel Switz.* (2018) 8:76. doi: 10.3390/diagnostics8040076

7. Tardy MP, Gastaud L, Boscagli A, Peyrade F, Gallamini A, Thyss A. Autoimmune hemolytic anemia after nivolumab treatment in Hodgkin lymphoma responsive to immunosuppressive treatment. *A case report Hematol Oncol.* (2017) 35:875–7. doi: 10.1002/hon.2338

8. Cooling LL, Sherbeck J, Mowers JC, Hugan SL. Development of red blood cell autoantibodies following treatment with checkpoint inhibitors: a new class of anti-neoplastic, immunotherapeutic agents associated with immune dysregulation. *Immunohematology.* (2017) 33:15–21. doi: 10.21307/immunohematology-2019-004

9. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol.* (2015) 33:2092–9. doi: 10.1200/JCO.2014.60.0379

10. Park SH. Diagnosis and treatment of autoimmune hemolytic anemia: classic approach and recent advances. *Blood Res.* (2016) 51:69–71. doi: 10.5045/br.2016.51.2.69

11. Leger RM, Arndt PA, Garratty G. How we investigate drug-induced immune hemolytic anemia. *Immunohematology.* (2014) 30:85–94. doi: 10.21307/immunohematology-2019-102

12. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* (2017) 18:1182–91. doi: 10.1016/S1470-2045(17)30422-9

13. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med.* (2007) 357:580–7. doi: 10.1056/NEJMra066469

14. James E, Podoltsev N, Salehi E, Curtis BR, Saif MW. Oxaliplatin-induced immune thrombocytopenia: another cumulative dose-dependent side effect? *Clin Colorectal Cancer.* (2009) 8:220–4. doi: 10.3816/CCC.2009.n.037

15. Sperati CJ, Moliterno AR. Thrombotic microangiopathy: focus on atypical hemolytic uremic syndrome. *Hematol Oncol Clin North Am.* (2015) 29:541–59. doi: 10.1016/j.hoc.2015.02.002

16. Taleghani BM, Meyer O, Fontana S, Ahrens N, Novak U, Borner MM, et al. Oxaliplatin-induced immune pancytopenia. *Transfusion (Paris).* (2005) 45:704–8. doi: 10.1111/j.1537-2995.2005.04373.x

17. Chen VMY, Thrift KM, Morel-Kopp M-C, Jackson D, Ward CM, Flower RL. An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion (Paris).* (2004) 44:838–43. doi: 10.1111/j.1537-2995.2004.03111.x

18. Ito I, Ito Y, Mizuno M, Suzuki Y, Yasuda K, Ozaki T, et al. A rare case of acute kidney injury associated with autoimmune hemolytic anemia and thrombocytopenia after long-term usage of oxaliplatin. *Clin Exp Nephrol.* (2012) 16:490–4. doi: 10.1007/s10157-012-0620-8

19. Ulusakarya A, Misra S, Haydar M, Habert H, Castagne V, Gumus Y, et al. Acute renal failure related to oxaliplatin-induced intravascular hemolysis. *Med Oncol Northwood Lond Engl.* (2010) 27:1425–6. doi: 10.1007/s12032-009-9263-3

20. Vyskocil J, Tucek S, Kiss I, Fedorova L, Nevrlka J, Zdrazilova-Dubska L. Type II hypersensitivity reactions after oxaliplatin rechallenge can be life threatening. *Int Immunopharmacol.* (2019) 74:105728. doi: 10.1016/j.intimp.2019.105728

21. Hwang SR, O'Dowd T, Markovic SN, Wolanskyj-Spinner AP. Recurrent checkpoint inhibitor-induced warm agglutinin autoimmune hemolytic anemia in a patient with metastatic melanoma. *Am J Hematol.* (2020) 95:E169–71. doi: 10.1002/ajh.25812

22. Palla AR, Kennedy D, Mosharraf H, Doll D. Autoimmune Hemolytic Anemia as a Complication of Nivolumab Therapy. *Case Rep Oncol.* (2016) 9:691–7. doi: 10.1159/000452296

23. Kentaro T, Takeshi M, Takahiko M, Shinichiro M, Kakuhiro Y, Shinjiro S, et al. Nivolumab-induced severe pancytopenia in a patient with lung adenocarcinoma. *Lung Cancer.* (2018) 119:21–24. doi: 10.1016/j.lungcan.2018.02.018

24. Mqadmi A, Zheng X, Yazdanbakhsh K. CD4+CD25+ regulatory T cells control induction of autoimmune hemolytic anemia. *Blood.* (2005) 105:3746–8. doi: 10.1182/blood-2004-12-4692

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 01 August 2023
DOI 10.3389/fphar.2023.1231401

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Gabriel Tao,
Merck Sharp & Dohme Corp,
United States
Meike Kaehler,
University Hospital Schleswig-Holstein,
Germany

*CORRESPONDENCE
Lin Song,
songlin@hospital.cqmu.edu.cn
Cheng Peng,
pengcheng@cdutcm.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 30 May 2023
ACCEPTED 18 July 2023
PUBLISHED 01 August 2023

CITATION
Cheng F, Zhang R, Sun C, Ran Q, Zhang C, Shen C, Yao Z, Wang M, Song L and Peng C (2023), Oxaliplatin-induced peripheral neurotoxicity in colorectal cancer patients: mechanisms, pharmacokinetics and strategies. *Front. Pharmacol.* 14:1231401. doi: 10.3389/fphar.2023.1231401

Oxaliplatin-induced peripheral neurotoxicity in colorectal cancer patients: mechanisms, pharmacokinetics and strategies

Fang Cheng[1†], Ruoqi Zhang[1†], Chen Sun[1], Qian Ran[1], Cuihan Zhang[1], Changhong Shen[1], Ziqing Yao[1], Miao Wang[1], Lin Song[2*] and Cheng Peng[1*]

[1]State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China, [2]Department of Pharmacy, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing, China

Oxaliplatin-based chemotherapy is a standard treatment approach for colorectal cancer (CRC). However, oxaliplatin-induced peripheral neurotoxicity (OIPN) is a severe dose-limiting clinical problem that might lead to treatment interruption. This neuropathy may be reversible after treatment discontinuation. Its complicated mechanisms are related to DNA damage, dysfunction of voltage-gated ion channels, neuroinflammation, transporters, oxidative stress, and mitochondrial dysfunction, *etc.* Several strategies have been proposed to diminish OIPN without compromising the efficacy of adjuvant therapy, namely, combination with chemoprotectants (such as glutathione, Ca/Mg, ibudilast, duloxetine, *etc.*), chronomodulated infusion, dose reduction, reintroduction of oxaliplatin and topical administration [hepatic arterial infusion chemotherapy (HAIC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), and hyperthermic intraperitoneal chemotherapy (HIPEC)]. This article provides recent updates related to the potential mechanisms, therapeutic strategies in treatment of OIPN, and pharmacokinetics of several methods of oxaliplatin administration in clinical trials.

KEYWORDS

oxaliplatin, peripheral neurotoxicity, colorectal cancer, adverse reaction, mechanism, pharmacokinetics, therapeutic strategies

1 Introduction

Over 1.88 million new cases and 915,880 deaths from colorectal cancer (CRC) were estimated in 2020, ranking it the world's third most commonly diagnosed cancer (after breast and lung cancers) but second in terms of mortality, with 10% incidence and 9.4% mortality, higher than in 2018, according to the GLOBOCAN 2020 estimates of cancer incidence and mortality (Sung et al., 2021; Erratum: Global cancer statistics, 2020; Bray et al., 2018). Developed countries showed the highest incidence of CRC, however recent data revealed a significant increase in CRC cases in heavily populated countries such as China, undergoing rapid economic development (Brody, 2015).

Oxaliplatin, a chemotherapeutic platinum-based agent for the treatment of metastatic CRC (mCRC), was approved by the US Food and Drug Administration in 2004 (De

Gramont et al., 2000; Rothenberg et al., 2003; Kuebler et al., 2007; André et al., 2009; Haller et al., 2011). However, oxaliplatin-induced peripheral neurotoxicity (OIPN) is a severe dose-limiting clinical problem that might lead to treatment interruption (Bécouarn et al., 1998; Díaz-Rubio et al., 1998; Lévi et al., 2000; Boku et al., 2007). OIPN was occurs in above 85% patients after treatment of oxaliplatin (Argyriou et al., 2013; Pachman et al., 2015). OIPN represents a clinical adverse reaction that might lead to dose reduction or treatment interruption. The prominent feature of OIPN is the presence of sensory peripheral neuropathy, including dysesthesias, numbness, and sensory loss in a distribution resembling a stocking-and-glove pattern, which is possibly concomitant with neuropathic pain and infrequent motor and/or autonomic damage (Argyriou et al., 2007; Argyriou, 2015; Avan et al., 2015; Staff et al., 2019). Additionally, OIPN has two distinct presentations: a distinctive acute peripheral sensory and motor toxicity which often occurs during or within a few hours after drug infusion. This type of sensory neuropathy is usually rapidly reversible. Alternatively, patients may present with peripheral sensory neuropathy as a result of cumulative dose. These patients further exhibit increases in incidence, intensity, and duration of sensory neuropathy with repeated treatments. This type of sensory neuropathy is moderate and slowly reversible, after treatment discontinuation (Lévi et al., 1992; Hartmann and Lipp, 2003). Oxaliplatin reversible neurotoxicity might result from virtually no accumulation in the plasma (Delord et al., 2003; Merkel et al., 2003), rather than in red blood cells (RBCs) (Gamelin et al., 1997).

Additionally, the oxaliplatin-induced physical damage in multiple ways to lead to functional impairment in neurons including DNA damage, dysfunction of voltage-gated ion channels, transporters, oxidative stress, and mitochondrial dysfunction, *etc.*

Therefore, various strategies are attempted to optimize chemotherapy regimens to prevent and treat OIPN by targeting molecular mechanisms and monitoring pharmacokinetics.

2 Oxaliplatin pharmacokinetics and OIPN

The NICE guideline [NG151] recommends that the standard practice for CRC management is appropriate surgery for eligible patients. Therapeutic regimens (FOLFOX and CAPOX) based on oxaliplatin are widely used as first-line treatment in CRC, and as an adjuvant systemic anti-cancer therapy (Table 1) (André et al., 1998; André et al., 1999; Maindrault-Goebel et al., 1999; Maindrault-Goebel et al., 2001; Cassidy et al., 2004; André et al., 2020; Conroy et al., 2021). Common chemotherapy regimens include FOLFOX4, FOLFOX6, mFOLFOX6, and CAPOX. Based on the above-mentioned guideline chemotherapy regimens, various strategies are attempted to optimize chemotherapy regimens to increase antitumor activity but reduce neurotoxicity, including adjustments in dose, duration of infusion, mode of administration, and combination drugs. Of these, the administration of oxaliplatin included intravenous infusion (IV), hepatic arterial infusion chemotherapy (HAIC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), and hyperthermic intraperitoneal chemotherapy (HIPEC). Both antitumor activity and OIPN are closely linked to dose per cycle, cumulative dose, treatment schedule, and duration of infusion. The antitumor

TABLE 1 Standard adjuvant chemotherapy regimens for CRC in guidelines.

Standard chemotherapy	Time	Oxaliplatin (mg/m^2)	Leucovorin (mg/m^2)	Fluorouracil (mg/m^2)	Others (mg/m^2)	Duration
FOLFOX 1	day1	infusion 130 2 h	infusion 500 2 h	infusion 1500-2000	-	q2w, 6 months
	day 2	-	infusion 500 2 h	infusion 1500-2000		
FOLFOX 2	day1	infusion 100 2 h	infusion 500 2 h	infusion 1500-2000		
	day 2	-	infusion 500 2 h	infusion 1500-2000		
FOLFOX 3	day1	infusion 85 2 h	infusion 500 2 h	infusion 1500-2000 22 h		
	day 2	-	infusion 500 2 h	infusion 1500-2000 22 h		
FOLFOX 4	day1	infusion 85 2 h	infusion 200 2 h	Bolus 400, infusion 600 22 h		
	day 2	-	infusion 200 2 h	Bolus 400, infusion 600 22 h		
FOLFOX 6	day1	infusion 100 2 h	infusion 400 2 h	Bolus 400 infusion 2400-3000 46 h		
FOLFOX 7	day 1	infusion 130 2 h	infusion 400 2 h	Bolus 400, infusion 2400 46 h		
mFOLFOX 6	day 1	infusion 85 2 h	infusion 400 2 h	Bolus 400, infusion 2400-3000 46 h		
CAPOX	day 1	infusion 130	-	-	capecitabine, 1000 orally twice daily	q3w, 3 months
Single-agent fluoropyrimidine	day 1–14	-	-	-	capecitabine, 1250 orally twice daily	q3w, 6 months
FOLFOXIRI		infusion 85 2 h	infusion 200 2 h	infusion 3200 48 h	Irinotecan, 165 1 h	

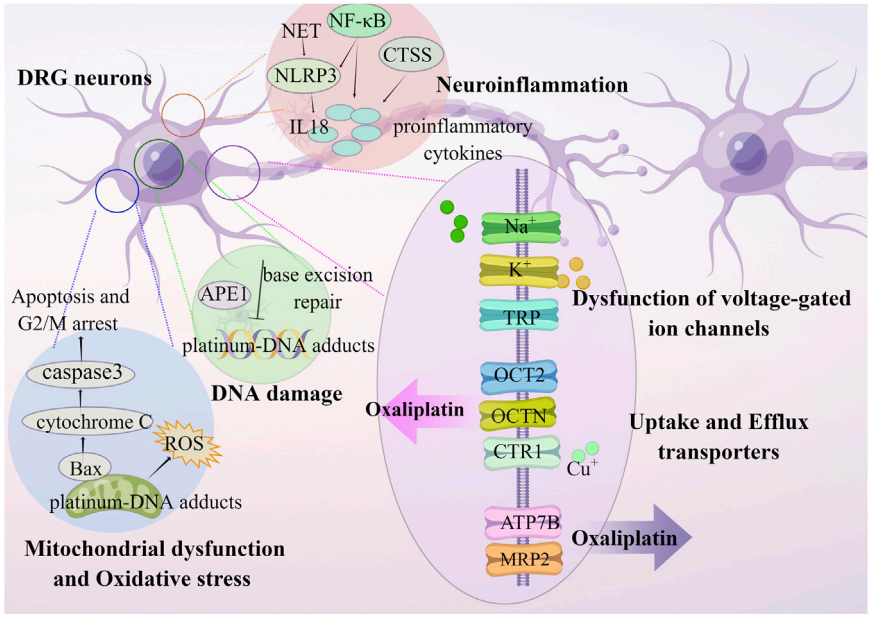


FIGURE 1
OIPN is related to mechanisms of DNA damage, dysfunction of voltage-gated ion channels, neuroinflammation, transporters, oxidative stress, and mitochondrial dysfunction.

activity and OIPN of oxaliplatin and its combined chemotherapy drugs (namely, erlotinib (Van Cutsem et al., 2008), CKD-732 (Shin et al., 2012), OSI-7904L (Clamp et al., 2008), sorafenib (Kupsch et al., 2005), nintedanib (Van Cutsem et al., 2015), bevacizumab (Loupakis et al., 2014), regorafenib (Schultheis et al., 2013), irinotecan (Wasserman et al., 1999; Falcone et al., 2002; Kemeny et al., 2002; Gil-Delgado et al., 2004; Fornaro et al., 2009), capecitabine (Pfeiffer et al., 2006), fluorouracil (5-FU) (Cattel et al., 2003), Ca/Mg (Han et al., 2013), ibudilast (Teng et al., 2020), glutathione (GSH) (Milla et al., 2009) are shown in Table 2. Dosing and pharmacokinetic parameters of total and ultrafiltrate platinum of oxaliplatin are shown in Supplementary Table S1, S2.

2.1 Reversibility of OIPN and pharmacokinetics

No accumulation of ultrafiltrate platinum in plasma may be an important explanation for OIPN reversibility. For the determination of plasma oxaliplatin concentrations, total platinum content is quantified for all platinum complexes, whereas ultrafiltrate platinum quantification considers only platinum complexes not bound to macromolecules. Ultrafiltrate platinum is considered to represent all the antitumor bioactive and toxicity. These are removed from the circulation via irreversible binding to plasma and/or blood components, tissue uptake, and urine elimination. Platinum that is irreversibly combined with plasma proteins or RBCs is believed to have no pharmacological activity (Culy et al., 2000; Graham et al., 2000). Therefore, monitoring platinum in the ultrafiltrate rather than in the plasma is an accepted strategy to control oxaliplatin metabolism. A cumulative pharmacokinetic pattern of oxaliplatin administration (130 mg/m^2) demonstrated that the platinum concentration showed a high peak 2 h after administration, followed by a rapid decrease (Gamelin et al., 1997). Subsequently, residual levels of total platinum on day 22 were quantified as 0.161 ± 0.045 ug/mL, with significant accumulation in RBCs, with $t_{1/2}$ equivalent to that of RBCs (Koury, 2014), rather than in plasma. The results showed a significant correlation between ultrafiltrate and total platinum concentration curves at all sampling times. In contrast, significant correlation was observed between RBC platinum levels and total platinum at late sampling times (day 8, 15, 22). Another study also reported that platinum accumulation was observed in RBCs except in total plasma or in ultrafiltrate plasma samples (Cho et al., 2006). Thus, OIPN may be reversible after treatment discontinuation.

2.2 Oxaliplatin IV and OIPN

IV was the most common mode of administration with high systemic exposure, suggesting a higher incidence of OIPN. The range of oxaliplatin dose administered as IV 2 h was 60–130 mg/m^2, with 85 and 130 mg/m^2 being the most frequent doses. Adversely, a single-dose study reported that grade 1 and 2 OIPN were observed in all patients at doses of 90 and 130 mg/m^2 (Shirao et al., 2006). Furthermore, pharmacokinetic study showed a dose-dependent increase in maximum concentration (C_{max}) and exposure/area under the curve (AUC) for ultrafiltrate and total platinum, with approximately 3%–4% of total platinum in ultrafiltrate, and that ultrafiltrate and total platinum were described by a tri-exponential and bi-exponential open model, respectively.

TABLE 2 Pharmacodynamics of oxaliplatin.

Study	Drug and dose (mg/m^2)	Population assessable n)	Antitumor activity n)					OIPN (%)	
			CR	PR	MR	SD	PD	All grades	Grade 3/4
IV									
Shirao et al. (2006)	Oxaliplatin 90/130	9	-	-	-	5	4	100	0
Van Cutsem et al. (2008)	Oxaliplatin 130+Erlotinib + capecitabine	18	1	4		11	2	61	9
Shin et al. (2012)	oxaliplatin 130+Capecitabine + CKD732	6	-	-	-	6	-	89	11.1
Clamp et al. (2008)	oxaliplatin 100 + OSI-7904L 6	3	-	-	-	11	1	100	0
	oxaliplatin 130+ OSI-7904L 6	3	-	-	-		1	100	0
	oxaliplatin 130+ OSI-7904L 9	8	-	-	-		-	100	13
Kupsch et al. (2005)	oxaliplatin 130+sorafenib	32		2		17		38	
Van Cutsem et al. (2015)	mFOLFOX6+ nintedanib	85	7	46	-	23	6	78	32
	mFOLFOX6+ bevacizumab	41	4	19	-	15	1	83	29
Loupakis et al. (2014)	FOLFOXIRI + bevacizumab	242	12	152	-	62	16	-	5.2
	FOLFIRI + bevacizumab	245	8	128		82	27	-	0
Schultheis et al. (2013)	FOLFOX + Regorafenib	38	-	4	-	14	-	44	4
	FOLFIRI + Regorafenib		-	3	-	12	-	20	0
Wasserman et al. (1999)	oxaliplatin 85+ irinotecan	24	-	7	-	9	-	-	32
	oxaliplatin 130+ irinotecan								20
Fornaro et al. (2009)	oxaliplatin 85+ irinotecan 165 + capecitabine	15	-	8	-	7	-	73	20
Kemeny et al. (2002)	Oxaliplatin30-50+ irinotecan 40	47	-	12	3	14	18	70	0
	Oxaliplatin 60+ irinotecan 40-75							79	8
Falcone et al. (2002)	Oxaliplatin 100+ irinotecan 175+ leucovorin 200 + 5-FU 3,800	42	5	25	3	8	1	66	5
Pfeiffer et al. (2006)	oxaliplatin 130+ capecitabine 1000	70	-	12	-	36	22	79	6
Cattel et al. (2003)	Oxaliplatin 25/30/35 +5-FU chronomodulated IV	13	-	7	-	4	2	-	15
Han et al. (2013)	oxaliplatin 130+Ca/Mg	19	-	-	-	-	-	84	0
	-Ca/Mg	19						84	0
Teng et al. (2020)	FOLFOX/CapeOx + ibudilast	14	-	-	-	-	-	86	0
	-ibudilast							86	0
Milla et al. (2009)	FOLFOX4 + GSH	14	-	-	-	-	-	100	0
	-GSH	13						69	31
HAI									
Kern et al. (2001)	Oxaliplatin 25–150+ leucovorin 200 and 5-FU 600	18	4	6	-	4	4	48	0
Boilève et al. (2020)	Oxaliplatin 100+ leucovorin 5-FU or FOLFIRI + cetuximab/panitumumab or bevacizumab	82	1	36	-	40	-	93	12
PIPAC									
Kim et al. (2021)	Oxaliplatin 45/60/90/120/150	16	-	-	-	10	6	-	-

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. IV, intravenous infusion; HAIC, hepatic arterial infusion chemotherapy; PIPAC, pressurized intraperitoneal aerosol chemotherapy.

In addition, oxaliplatin accumulation is also a significant contributor to OIPN. The incidence of grade 3 to 4 neurotoxicity increased with cumulative oxaliplatin dose when oxaliplatin (85–110 mg/m^2) was associated with irinotecan (150–250 mg/m^2), which was not observed at cumulative doses below 300 mg/m^2 but presented in 67% of patients receiving above 880 mg/m^2 oxaliplatin (Wasserman et al., 1999). Another study with patients receiving oxaliplatin (30–60 mg/m^2) plus irinotecan (40–85 mg/m^2) reported that 24 out of 49 patients received cumulative doses of oxaliplatin over 1000 mg/m^2 (Kemeny et al., 2002). In 12% of the subjects, grade 3 neurotoxicity was observed only for cumulative oxaliplatin doses equal or above 1110 mg/m^2. Grade 2 neurotoxicity was observed in 8 subjects: 6 subjects showed signs of neurotoxicity after receiving a cumulative dose of 960 mg/m^2 oxaliplatin, whereas 2 patients presented neurotoxicity for cumulative doses of 540 and 720 mg/m^2, respectively.

Chronotherapy refers to chemotherapy delivery according to 24-h biological rhythms, thus modulating cellular metabolism. Chronotherapy has been proven to be effective in improving drug efficacy and reducing toxicity (Smaaland et al., 1991). There is growing evidence that circadian pharmacokinetics can be transformed into chronotoxicity and chronoefficacy (Dong et al., 2020). Several studies further reported the effect of chronotherapy on oxaliplatin pharmacokinetics. The threshold oxaliplatin concentration (total plasma) at which OIPN was observed in patients submitted to chronomodulated oxaliplatin was 1.50 μg/mL. The correspondent threshold oxaliplatin concentration in ultrafiltrate plasma platinum concentrations was determined as 0.15 μg/mL (Cattel et al., 2003). Kern *et al.* observed that chronomodulated oxaliplatin administration at 20 mg/m^2 resulted in a higher maximum plasma level of ultrafiltrate platinum at 7 h compared to constant-rate infusion, with similar cumulative renal elimination of platinum in both simulations (Kern et al., 1999). Moreover, possible relationships between pharmacokinetics and patient specific parameters, such as renal function, were conducted by Cattel *et al* (Cattel et al., 2003). Mean total oxaliplatin C_{max} and AUC_{tot} were accumulated, accompanied by decrease of CL and apparent volume of distribution (Vd) from cycle 1 to cycle 6, with steady elimination constant (Ke). Reduction of median AUC_{tot}, CL and Vd in ultrafiltrate oxaliplatin over time, might result from changes in Ke or half-life ($t_{1/2}$).

2.3 Oxaliplatin HAIC and OIPN

HAIC, a locoregional treatment strategy for hepatic malignancies, consists in a pump or percutaneous port-catheter device surgically implanted into a branch of the hepatic artery. HAIC-based approaches have been used in the treatment of unresectable liver metastases from CRC for decades (Strnad et al., 2021). A retrospective study showed that OIPN was reported in 73.8% of 61 patients, including 9.8% with grade 3 to 4 neurotoxicity (Lim et al., 2017).

A recent study has shown that HAIC-oxaliplatin coupled with systemic chemotherapy and targeted therapy is feasible and safe for CRC patients with unresectable hepatic metastases, allowing resection/ablation in almost 27% of patients (Boilève et al., 2020). Additionally, grade 3/4 toxicities included 40% neutropenia, 43% HAI-related abdominal pain, and 12% neurotoxicity.

Moreover, Lévi *et al.* suggested that systemic drug exposure helped explain OIPN for HAIC oxaliplatin, possibly related to a slightly reduced systemic drug availability and higher availability at the liver organ during HAI as compared to IV (Lévi et al., 2017). Kern *et al.* reported ultrafiltrate platinum AUC increased linearly with increasing dose in oxaliplatin HAIC administration (Kern et al., 2001). A reduction of AUC and Vd was observed for oxaliplatin HAIC 135 mg/m^2 for 4 h compared to IV 130 mg/m^2 for 4 h (Kern et al., 1999).

2.4 Oxaliplatin PIPAC and OIPN

PIPAC, a novel laparoscopic intraperitoneal chemotherapy delivery technique, improves the distribution and tissue penetration of chemotherapeutic drugs used to treat peritoneal metastases. Repeated PIPAC with oxaliplatin appears to be a safe, feasible, and well-tolerated therapy with reduced toxicity, high intraperitoneal concentration, and low systemic concentration (Demtröder et al., 2016; Rovers et al., 2019). The pharmacokinetic study showed a linear response between dose, C_{max}, and AUC, indicating that systemic oxaliplatin exposure was enhanced with growing PIPAC dosing (Kim et al., 2021). The platinum level in the ultrafiltrate was calculated as 11% of that in total platinum at PIPAC oxaliplatin 120 mg/m^2. Systemic platinum exposure at 120 mg/m^2 was 3.8% of that reported for IV for 2 h of single-dose oxaliplatin at 130 mg/m^2 (Shirao et al., 2006). Additionally, OIPN was not observed in 16 patients. Another pharmacokinetic study reported that oxaliplatin concentrations were 3- to 4-times higher in tissue exposed to aerosol than in unexposed muscle at a dose of 90 mg/m^2 (Dumont et al., 2020). Overall safety showed Grade 1 to 2 neurotoxicity occurred in 4 out of 19 PIPAC sessions during PIPAC with oxaliplatin 90 mg/m^2; and grade 1 to 2 and grade 3 to 4 neurotoxicity occurred in 1 of 13 PIPAC sessions during PIPAC at a dose of 140 mg/m^2, respectively.

Electrostatic PIPAC (ePIPAC) had higher tissue penetration of the chemotherapeutic drugs compared to PIPAC due to addition of electrostatic precipitation into the aerosol (Kakchekeeva et al., 2016). Lurvink *et al.* described that ultrafiltrate platinum AUC after ePIPAC was similar to that of after IV oxaliplatin at 90 mg/m^2, and higher than that of PIPAC (Lurvink et al., 2021). Urine concentrations of oxaliplatin declined rapidly, and no oxaliplatin accumulation was detected between the various ePIPAC procedures. Unfortunately, the adverse effects are not described.

2.5 Oxaliplatin of HIPEC and OIPN

Peritoneal carcinomatosis (PC) is a general event in the natural history of CRC. A promising therapeutic option is cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC, also known as IPCH) for patients with isolated, resectable PC, capable of increasing median survival to approximately 63 months with a 5-year survival rate of 51% (Elias et al., 2009).

The pharmacokinetics of HIPEC with oxaliplatin after complete cytoreductive surgery indicated that peritoneal oxaliplatin concentration was 25-times higher than that in the plasma at 460 mg/m^2, whereas AUC was lower than that previously reported

for IV oxaliplatin (130 mg/m^2) (Elias et al., 2002). Oxaliplatin penetration was 17.8 times greater in the tumor than in non-bathed tissues. Moreover, the authors also failed to identify any serious hematological, renal, or neurological toxicities, except for 2 fistulas and 3 deep abscesses (Elias et al., 2002). Subsequently, the authors revealed that an additional combination of intraperitoneal irinotecan (400 mg/m^2) on the above regimen resulted in 2.5% hospital mortality, 25% non-hematological complication even 58% grade 3–4 hematological adverse effects (Elias et al., 2004). Similarly, Quenet *et al.* came to the same result: there was no advantage to intensifying HIPEC with the addition of irinotecan, as opposed to the results of intravenous combination therapy (Quenet et al., 2011). However, the most common grade 3–4 side effects with HIPEC were haemorrhage, digestive leakage, and haematological adverse events, and no neurotoxicity appeared to be observed (Goéré et al., 2020; Quénet et al., 2021). However, a retrospective study suggested that postoperative oxaliplatin-based HIPEC might contribute to improve ascites-free survival, but is accompanied by high neurotoxicity (Sun et al., 2021). Therefore, it requires further studies with large samples to observe the antitumor activity and OIPN of HIPEC oxaliplatin.

3 Molecular mechanisms

Oxaliplatin cause apoptosis of dorsal root ganglion (DRG) neurons, but has less neurotoxic to DRG neurons due to forming fewer platinum-DNA adducts compared to cisplatin (Ta et al., 2006). The oxaliplatin-induced physical damage leads to functional impairment in neurons through DNA damage, dysfunction of voltage-gated ion channels, neuroinflammation, transporters, oxidative stress, mitochondrial dysfunction, and apoptosis (Figure 1) (Sisignano et al., 2014; Cavaletti and Marmiroli, 2020; Sałat, 2020).

3.1 DNA damage in sensory neurons

OPIN was considered to be secondary to DNA damage of sensory neurons, and the base excision repair pathway was the main method for improving DNA damage (Hu et al., 2019). Kelley *et al.* reported that reduction of apyrimidinic endonuclease/redox factor-1 (APE1) in neuronal cultures increased OPIN (Kelley et al., 2014), and targeting of the APE1 small molecule APX3330 and APX2009 effectively protected against OIPN without affecting the anticancer activity (Kelley et al., 2014; Kelley et al., 2016). Moreover, both thymidylate synthase and the excision cross-complementing expression were predictive markers of OIPN sensitivity (Shirota et al., 2001; Arnould et al., 2003).

3.2 Dysfunction of voltage-gated ion channels

An ever-growing number of studies have shown that oxaliplatin increased cold sensation through regulating the transcription of different ionic conductances (Na^+ channels, K^+ channels) that together shape the response of sensory neurons to cold. Therefore, the prevention of OIPN should be based on ion channels' protection.

Acute OIPN is associated with regulation of axonal membrane Na^+ channels, and chronic dysfunction of sensory axonal excitability occurs with a growing accumulation of oxaliplatin. Oxaliplatin was enabled to alter the voltage-gated Na^+ channels via a pathway entailing Ca^{2+} which was possibly fixed by its metabolite oxalate (Grolleau et al., 2001). Imbalance of Na^+ voltage-operated channels caused transient axonal hyperexcitability, which contributed to sustained depolarization that motivated the reverse pattern of Na/Ca^{+++2+} exchanger 2, leading to toxic Ca^{2+} accumulation and axonal damage (Ballarini et al., 2022). Park *et al* assessed severity for OIPN by sensory axonal excitability techniques to identify pre-clinical nerve dysfunction (Park et al., 2009). In a recent study, the Na/H exchanger isoform-1 (NHE1) was also identified as an essential contributor to intracellular pH ($pH^{++}i$) homeostasis in nociceptors as a plasma membrane protein (Dionisi et al., 2023). They revealed that intracellular acidification induced by oxaliplatin in DRG neurons was primarily determined by Ca^{2+}/calmodulin-dependent phosphatase calcineurin-mediated NHE1 inhibition.

Oxaliplatin improved hyperexcitability by decreasing the expression of diverse K^+ channels (TREK1 and TRAAK) and improving the expression of pro-excitatory channels (hyperpolarization-activated channels) (Descoeur et al., 2011). Sittl *et al.* indicated that flupirtine, a clinically available analgesic activating slow axonal K^+ channels in the A-fibers of peripheral nerve, alleviated the acute OIPN by suppressing axonal hyperexcitability (Sittl et al., 2010). Thus, activation of slow K^+ channels potentially reduces OIPN in humans. Additionally, oxaliplatin antagonized voltage-operated K^+ channels on the peripheral myelinated nerve fibers with a similar pattern of action to that of 4-aminopyridine (a classical antagonist of voltage-operated K^+ channels) (Kagiava et al., 2008). Preclinical data showed that riluzole inhibited both sensory and motor dysfunctions through the TREK-1 potassium channel in a mouse model of chronic OIPN (Poupon et al., 2018). Argyriou *et al.* produced evidence that the repeat polymorphism of the voltage-gated K^+ channel KCNN3 had no effect on OIPN (Argyriou et al., 2019).

Transient receptor potential (TRP) channels are related to progression of oxaliplatin-induced neuropathic pain. Oxaliplatin-induced cold allodynia was partly involved with high expression of TRP melastatin 8 (TRPM8) in the primary afferents (Gauchan et al., 2009; Mizoguchi et al., 2016). Further animal experiments showed that oxaliplatin produced a distinct increase of TRPV1, TRPM8, and TRPA1 expression in the lumbar DRG (Chukyo et al., 2018; Miguel et al., 2022).

3.3 Neuroinflammation

OIPN is associated with increased pro-inflammatory responses in DRGs and peripheral nerves. As a result of neutrophil extracellular trap (NET), NLRP3 was activated, and IL18 was released, which contributed to the development of OIPN (Lin et al., 2022). Oxaliplatin-treated mice showed elevated levels of NF-κB p65 protein, pro-inflammatory cytokines, and immune cell infiltration, accompanied by loss of intraepidermal nerve fibers, mechanical hyperalgesia, and a decrease in sensory nerve amplitudes (Calls et al., 2022), all of which were effectively prevented by both minocycline and niclosamide treatment (Boyette-Davis and Dougherty, 2011; Cerles et al., 2017).

It is said that Cathepsin S (CTSS), a lysosomal cysteine protease located steadily in the cytoplasm of immune-relevant cells, facilitates the activation of microglial cells and then modulates the release of proinflammatory cytokines and chemokines. Chen *et al.* found that oxaliplatin increased CTSS expression though strengthening cytosol translocation of interferon response factor 1 (Chen et al., 2021). Thus, targeting the enzymatic activity of CTSS with pharmacological blocks and gene knockdown strategies could relieve OIPN by a mechanism related to inhibition of CTSS facilitating olfactory receptor transcription factor 1 release from P300/CBP binding and then driving IL-10 downstream signaling pathway.

3.4 Transporters

Transporters have been identified as crucial regulators of drug disposition, therapeutic efficacy, and adverse events, because they regulate the absorption, distribution, metabolism, and excretion of drugs (Sprowl et al., 2013a; Sprowl et al., 2016). OIPN is associated with uptake and efflux of oxaliplatin by the transporter expressed on DRG cells, such as organic cation transporter (OCT) 2, organic cation/carnitine transporters (OCTN), copper transporter 1 (CTR1), P-type ATPases, and multidrug resistance-associated protein 2 (MRP2).

Oxaliplatin was found to be a relatively good substrate for human OCT2 in the HEK293 cells transiently expressing OCTs (Yonezawa et al., 2006). The evidence was provided for the critical role of OCT2 in OIPN. Sprowl *et al.* found that cellular uptake of oxaliplatin was significantly increased in cells overexpressing mouse OCT2 or human OCT2 and was decreased by cimetidine (a known OCT2 competitive inhibitor) (Sprowl et al., 2013b). In addition, genetic and pharmacological knockouts of OCT2 prevented mice hypersensitivity to cold or mechanically-induced allodynia. Similarly, Huang *et al.* also demonstrated that targeting OCT2 with genetic and pharmacological means improved acute and chronic neurotoxicity in the satellite glial cells (Huang et al., 2020). Furthermore, Jong *et al.* reported that uptake and cytotoxicity of oxaliplatin increased in HEK293 cells overexpressing rat OCTN1, rat OCTN2, human OCTN1, and human OCTN2, and that OCTN1-mediated transport of oxaliplatin seemed to make a greater contribution to its neuronal accumulation and neurotoxicity compared to OCTN2 or OCTs (Jong et al., 2011).

Rat CTR1 (rCTR1) can transport copper and platinum drugs, and makes cells susceptible to their cytotoxicity (Liu et al., 2009; Liu et al., 2013). Interestingly, in cultured rat DRG and HEK/rCTR1 cells exposure to oxaliplatin, the accumulation of platinum was saturable and temperature-dependent, but was reduced by copper only in HEK/rCtr1 cells (Liu et al., 2013). Although CTR1 regulates cellular uptake of copper, its removal is mediated by two P-type ATPases, ATP7A and ATP7B, and ATP7B is closely related to resistance to platinum drugs through regulation of efflux (Martinez-Balibrea et al., 2009). A GEMCAD group study showed that the ATP-binding cassette subfamily G, member 2 (ABCG2) rs3114018 A/A genotypes were related to a higher risk of severe OIPN (Custodio et al., 2014). MRP2, encoded by the ABCC2 gene and highly expressed in the normal gastrointestinal system, functions as a poly-specific drug efflux pump to transport a number of substrates across cell membranes through benefiting from energy produced by ATP hydrolysis (Jemnitz et al., 2010). Overexpression of MRP2 inhibited oxaliplatin accumulation and cytotoxicity, which were reversed by suppression of MRP2 with myricetin or siRNA knockdown (Myint et al., 2019). A pharmacogenomic study reported that neurotoxicity above grade 2 was correlated with single-nucleotide polymorphisms in ABCC1 [rs2074087: odds ratio = 0.43 (0.22-0.86)], and ABCC2 [rs3740066: 2.99 (1.16-7.70); rs1885301: 3.06 (1.35-6.92); rs4148396: 4.69 (1.60-13.74); rs717620: 14.39 (1.63-127.02)] (Cecchin et al., 2013).

In conclusion, some data are available to support the function of the mentioned genetic variants of the transporter in the severity of OIPN, yet the results still need to be confirmed by appropriate comprehensive and prospective large-scale studies.

3.5 Oxidative stress

Oxidative stress, a core mediator of apoptosis, neuroinflammation, metabolic disorders, and bioenergetic depletion in neurons, is a vital pathogenic mechanism of OPIN (Areti et al., 2014). Oxaliplatin accumulation can lead to oxidative stress in the neurons directly by the formation of DNA adducts or indirectly by mitochondrial dysfunction of electron transport chain.

Mangafodipir, a magnetic resonance imaging contrast agent, possess SOD-, catalase-, and GSH reductase–like properties. A study was performed to suggest that mangafodipir prevented and/or alleviated OIPN in cancer patients by targeting multiple steps of the reactive oxygen species (ROS) cascade via detoxifying superoxide anions and hydrogen peroxide and via restoring GSH (Coriat et al., 2014). Calmangafodipir, originated from mangafodipir, simulates the mitochondrial enzyme manganese superoxide dismutase (MnSOD), thereby reducing ROS and protecting against OIPN without apparent influence on tumour outcomes (Karlsson et al., 2015; Glimelius et al., 2018; Canta et al., 2020).

Monosialotetrahexosylganglioside (GM1) is an effective drug for the treatment of diabetic peripheral neuropathy. GM1 decreased anti-oxidant stress by increasing superoxide dismutase and GSH levels to reduce the severity of chronic OIPN (Zhou et al., 2021). However, the phase III study of GM1 did not support the use of GM1 to prevent cumulative OIPN, although patients receiving GM1 were less disturbed by acute neuropathic symptoms (Wang et al., 2020). In addition, clinical data also suggest L-carnosine exhibited a neuroprotective activity against OIPN in CRC patients by targeting Nrf-2 and NF-κB pathways (Yehia et al., 2019).

3.6 Mitochondrial dysfunction

Mitochondrial dysfunction is a key factor of OIPN (Canta et al., 2015; Krukowski et al., 2015). Oxaliplatin exerted anticancer properties through crosslinks forming platinum-DNA adducts that led to inhibition of DNA synthesis, mitochondrial dysfunction and ROS production (McDonald and Windebank, 2002; Zheng et al., 2011). Xiao *et al.* indicated that additional mitochondrial dysfunction worsened the neuropathic pain (Xiao and Bennett, 2012). Oxaliplatin-induced apoptosis and G2/M arrest in colon cancer cells are mediated by the apoptotic cascade, with recruitment of Bax to mitochondria and release of cytochrome C into the cytosol, leading to activation of caspase3 (Arango et al., 2004). An animal experiment

showed that OIPN was concomitant with mitochondrial swelling and vacuolation of peripheral nerve axons, and that acetyl-L-carnitine protected mitochondrial function to inhibit the development of neuropathy (Zheng et al., 2011).

4 Neuroprotective strategies

Risk factors for OIPN consist of dose per cycle, cumulative dose, treatment regimen, duration of infusion, administration of chemotherapeutics, comorbidity and pre-existing peripheral neuropathy (Miltenburg and Boogerd, 2014). Several strategies have been proposed to reduce or prevent OIPN, including alternating chemotherapy protocols to decrease the cumulative dose of oxaliplatin and combining with chemoprotectants.

4.1 Dose and schedule modification

Considering reduction of treatment duration without loss of efficacy, cost of 3-month adjuvant CAPOX appears to be a promising option for high-risk stage II colon cancer (Iveson et al., 2021).

4.2 Reintroduction

Oxaliplatin reintroduction might be an operational choice in patients previously having moderate or severe OIPN. Intermittent oxaliplatin had a significant benefit on both time-to-treatment failure and time-to-tumor progression, and reduction of neurotoxicity compared with continuous oxaliplatin (Tournigand et al., 2006; Hochster et al., 2014). Compared with mFOLFOX6 and bevacizumab followed by FOLFIRI plus bevacizumab in patients with mCRC, Upfront FOLFOXIRI addition of bevacizumab and reintroduction after progression had a longer median progression-free survival (19.2 months *versus* 16.4 months, respectively), with no reduction of treatment efficacy and no increase in grade 3 or 4 side effects except for a predicted higher incidence of neurotoxicity (Kato et al., 2018; Cremolini et al., 2020). Oxaliplatin reintroduction in 25 mCRC patients after previously receiving FOLFOX or XELOX worsen the pre-existing OIPN, which significantly correlated with higher oxaliplatin cumulative dose. Argyriou *et al.* provided an explanation that the majority of reintroduced patients (having a clinically significant grade 1 or 2) progressed to a clinically significant (grade 2) OIPN instead of a treatment-emergent grade 3 (Argyriou et al., 2021). Surely, neurological and hypersensitivity reactions monitoring should be considered (Besora et al., 2018; Kim et al., 2018).

4.3 Chronomodulated oxaliplatin infusion

Circadian rhythms lead to predictable changes in the body's tolerance and responsiveness to drugs, including anticancer agents (Lévi, 2001). Chronotherapy, the chronomodulated infusion of oxaliplatin, 5-FU and leucovorin to treat mCRC patients, showed fewer side effects, including stomatitis and peripheral sensory neuropathy, and higher objective response, when compared to constant-rate oxaliplatin infusion (Ohdo, 2003). A study comparing the delivery of oxaliplatin by chronomodulation with constant-rate delivery was conducted by Lévi *et al.* The authors observed that chronomodulated oxaliplatin infusion was more effective and less toxic than oxaliplatin delivered at constant rate over time (Lévi et al., 1994). Severe stomatitis incidence (grade 3 and 4) was 5-fold higher in patients on constant-rate oxaliplatin, compared to those submitted to chronomodulated infusion. Peripheral sensitive neuropathy (grade 2) which was cumulative dose-limiting toxicity of chronomodulated oxaliplatin was reversible following oxaliplatin withdrawal.

4.4 Topical administration

CRC metastases are frequently found in the liver, lungs, and peritoneum. In this context, oxaliplatin pharmacokinetics of new drug delivery strategies (HAIC, PIPAC, and HIPEC) differed partly from these of IV. Ultrafiltrate platinum of HAIC for hepatic metastases CRC had lower Vd and comparable CL than that of intravenous infusion, possibly related to slightly reduction systemic availability and higher availability at the liver organ of the drug during HAIC than its IV. PIPAC and HIPEC are treatments for CRC patients with peritoneal metastases. Total and ultrafiltrate platinum from PIPAC at dose of 120 mg/m^2 were 3.8% and 10.2% respectively of that reported for 2-h IV of single-dose oxaliplatin at 130 mg/m^2, not likely to induce significant systemic adverse events. HIPEC resulted in high intratumoral oxaliplatin penetration and low concentration in plasma, thus improving local tissue concentrations and reducing systemic toxicity. HIPEC combined with cytoreductive surgery led to improve survival and lower peritoneal recurrence rates (Glehen et al., 2004). However, this review was limited by the inability to directly compare the pharmacokinetics, pharmacodynamics, and toxicity of oxaliplatin after IV administration with those after HIAC, PIPAC, and HIPEC.

4.5 Combination of oxaliplatin with chemoprotectants

There are no established agents recommended for the prevention of OIPN in CRC patients treated with neurotoxic agents, while duloxetine was recommended for patients with CRC experiencing OIPN (Albers et al., 2011; Hershman et al., 2014).

4.5.1 GSH

Cascinu *et al.* supported that GSH is a potential candidate in the prevention of OIPN, without reducing oxaliplatin activity. The authors found that neurophysiologic investigations (sural sensory nerve conduction) demonstrated a statistically significant decrease in the placebo arm than GSH-exposed group (Cascinu et al., 2002). Milla *et al.* later found that coadministration of GSH with FOLFOX4 is an effective strategy to reduce neurotoxicity without impairing the main pharmacokinetics of oxaliplatin, nor the platinum-DNA adduct formation (Milla et al., 2009). Twenty-seven CRC patients who underwent curative resection were treated with the FOLFOX regimen. Of those, 14 patients received

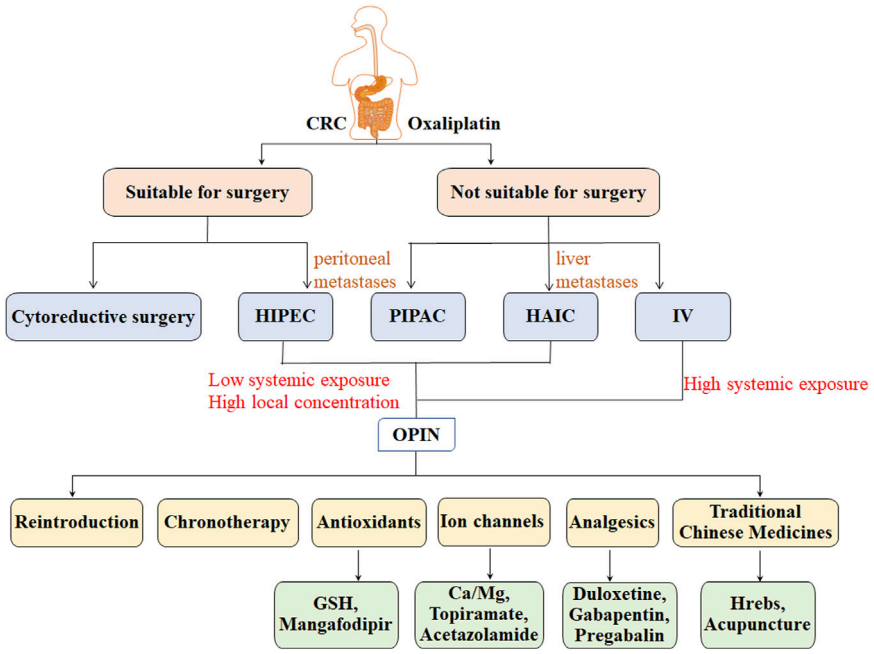


FIGURE 2
Administration routes of oxaliplatin and potential treatment options for OIPN in patients with CRC.

GSH before oxaliplatin, and 13 patients received physiological saline solution, for a maximum of 12 cycles. Upon completion of treatment, patients in the GSH arm revealed only moderate neurotoxicity with grade 1 (50%) and grade 2 (50%), whereas in the placebo arm the observed neurotoxicity was moderate to severe with grade 2 (69%) and grade 3 (31%). No grade 4 neurotoxicity was showed in any group. N-acetylcysteine, as an antioxidant thiol, enables whole blood concentration of GSH to increase, which may be protective against OIPN (Bondad et al., 2020). Overall, more studies are still needed to fully characterize the effects of GSH on OIPN in these environments.

4.5.2 Ibudilast

Moreover, ibudilast, a neuroimmune modulator that slowed the progression of neurological damage (Fox et al., 2018), might be a candidate for reducing OIPN. A 'before vs after' study showed that reduced grade 2 neurotoxicity in 2 out of 14 patients, whereas neurotoxicity had no worsening in 12 out of participants before and after ibudilast co-treatment (Teng et al., 2020). The feasibility of co-administration of ibudilast and oxaliplatin to reduce neurotoxicity urgently needs to be evaluated in large-scale studies.

4.5.3 Ca/Mg

Up to date, there is no consensus on the efficacy of Ca/Mg infusions to prevent induced neurotoxicity. Based on retrospective studies, Ca/Mg infusions inhibited the incidence and intensity of acute OIPN and might delay cumulative neuropathy (Gamelin et al., 2004; Grothey et al., 2011). Subsequently, numerous studies have questioned the benefits of Ca/Mg infusions in reducing acute OIPN (Gamelin et al., 2008; Wu et al., 2012; Han et al., 2013). Large-scale randomized, controlled clinical trials in CRC population are necessary to confirm these preliminary data.

4.5.4 Carbonic anhydrase inhibitor

FDA-approved drugs (namely, topiramate and acetazolamide) that inhibit carbonic anhydrase, an enzyme associated with haemoglobin in intracellular pH homeostasis, reverted oxaliplatin-induced modulation of TRPA1 and TRPV1 in cultured DRG neurons, as well as acute cold allodynia in mice without reducing oxaliplatin-induced cytotoxicity on cancer cells, and prevented oxaliplatin-related axonal hyperexcitability (Alberti et al., 2020; Potenzieri et al., 2020).

4.5.5 Serotonin–noradrenaline reuptake inhibitor

There is growing evidence that serotonin and norepinephrine reuptake inhibitors are an effective treatment for neuropathy-related pain (Saarto and Wiffen, 2007). The mechanism of duloxetine-induced analgesia is considered to be relevant to the blockade of serotonin and norepinephrine transporters. A clinical trial showed that 59% of duloxetine-treated patients reported a greater reduction in painful OIPN compared to 38% of placebo-treated patients for 5 weeks (Smith et al., 2013). Although duloxetine is the only drug recommended by the American Society of Clinical Oncology that can be used for the management of chemotherapy induced peripheral neuropathy (Loprinzi et al., 2020), this recommendation was not followed in clinical practice. An NIH Collaboratory study of claims data showed the following incidence of new analgesic prescriptions for neurotoxicity: 7.1% for gabapentin, 0.69% for

pregabalin, and 0.78% for duloxetine (Gewandter et al., 2020). Another cross-sectional study showed that the major analgesic drugs used by French oncologists were pregabalin (75.8%), amitriptyline (32.7%), gabapentin (25.5%), and duloxetine (11.8%) in the treatment of neurotoxicity (Selvy et al., 2021). A comparison of clinical trial studies indicated that a 60 mg dose of duloxetine was secondary to a 150 mg dose of pregabalin in relieving neuropathic pain (Salehifar et al., 2020).

Furthermore, venlafaxine has clinical activity against OIPN, with more frequent full relief (31.3% *versus* 5.3%) (Durand et al., 2012). A single-center retrospective case-control study reported the rates of obtaining over 75% symptomatic relief for OIPN under venlafaxine treatment were 53.5, 58.3, and 45.2% in the first, second, and third visits, respectively, compared to 0, 0, and 0% in the control group (Kus et al., 2016).

Additionally, animal experiments showed the potential of vortioxetine (Micov et al., 2020), milnacipran (Andoh et al., 2015), and fluoxetine (Baptista-de-Souza et al., 2014) against oxaliplatin-induced mechanical allodynia. Of these, the reduction of pain hypersensitivity by vortioxetine, a novel antidepressant, was comparable to that of duloxetine (1–15 mg/kg), which may be associated with increased levels of serotonin and norepinephrine in the brainstem of treated OIPN mice. Nonetheless, there is inadequate appropriate evidence to support the use of the above drugs for patients with established painful OIPN.

5 Conclusion

Ultrafiltrate platinum has an antitumor effect, at the cost of additional toxic properties. Peripheral neuropathy is recognized as a major long-term adverse effect of oxaliplatin chemotherapy, the risk of which increases due to oxaliplatin accumulation. Administration routes of oxaliplatin and potential treatment options for OIPN were shown in Figure 2.

Comparing the efficacy and OIPN of adjuvant therapy duration from 6 to 3 months in populations with different disease processes has been focused of recent studies, and patients with low-risk CRC may benefit from 3 months of CAPOX therapy (Yoshino et al., 2019; Petrelli et al., 2020; Yoshino et al., 2022). There is a positive trend towards a higher rate of organ preservation with total neoadjuvant therapy (chemoradiotherapy followed by consolidation chemotherapy, CRT-CNCT) and the watch-and-wait approach compared to induction chemotherapy followed by chemoradiotherapy (INCT-CRT) (Aref and Abdalla, 2022; Garcia-Aguilar et al., 2022; Sütcüoğlu et al., 2023). However, survival outcomes between the two TNT regimens are not different; therefore, more in-depth and rigorous studies with reliable criteria are urgently needed to explain the pros and cons of CRT-CNCT and INCT-CRT.

Topical administration (HAIC, PIPAC, and HIPEC) may be a feasible and promising strategy to increase antitumor activity while reducing neurotoxicity due to its low systemic exposure and high local concentration (Yamashita, 2004; de Jong et al., 2021). However, it is worthwhile to be alert to the risks associated with topical administration procedures, such as pump pocket complications, catheter or arterial complications, toxic or ischemic complications (Strnad et al., 2021), bowel obstruction, bleeding, abdominal pain (Alyami et al., 2019), and complications related to postoperative management (Hübner et al., 2020). Significantly, heterogeneous standardization of topical administration trials was in the context of patient selection, chemotherapy regimens, doses, number of cycles, technical protocols, and whether to combine topical administration with systemic chemotherapy, which led to controversial differences in treatment efficacy. Thus, there is an urgent need to standardize topical administration trial reports and datasets. It is suggestive for clinical practice although further validation of the effectiveness and OIPN of topical administration is required.

A *post hoc* analysis revealed difficulties in deciding the timing for discontinuation or suspension of oxaliplatin in patients with grade 2 OIPN, because physician likely underestimated OIPN via the Common Terminology Criteria for Adverse Events (CTCAE) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) in patients with mCRC during early treatment (Miura et al., 2021). Perhaps, diagnostic microdosing and evaluation of multiple single nucleotide polymorphisms in oxaliplatin transporters may be a promising strategy to assess OIPN for treatment customization in CRC patients (Nichetti et al., 2019; Zimmermann et al., 2020). As a result, there is an increased need for more effective and standardized assessment methods.

An increasing number of Traditional Chinese Medicines exerted protective effects against OIPN, such as curcumin (Howells et al., 2019), forsythia viridissima (Yi et al., 2019a; Yi et al., 2019b), rutin, quercetin (Azevedo et al., 2013), Huangqi Guizhi Wuwu decoction (Cheng et al., 2017), and resveratrol (Donald et al., 2017), *etc.* Furthermore, laser acupuncture and ultrasound acupuncture significantly alleviated both oxaliplatin-induced cold and mechanical allodynia and also reduced the incidence and severity of neurotoxicity symptoms, which could be effective interventions for OIPN symptoms in patients with CRC (Hsieh et al., 2016; Chien et al., 2021).

Until now, the standard duration of adjuvant chemotherapy cycles for CRC has been between 3 and 6 months. However, efforts have been made to reduce treatment time in order to reduce toxicity. Recently developed strategies, such as chronomodulated infusion and chemoprotectants combination have been assessed to manage neurotoxicity. Further, more strategies to reduce toxicity based on pathophysiological mechanisms of neurotoxicity are necessary. Moreover, such studies should include long-term patient follow-up, and assess specific parameters such as quality of life, cost-benefit relationship, required resources, and racial disparities, among others (Kennedy et al., 2022).

Author contributions

FC: Conceptualization, Methodology, Visualization, Writing—original draft, Writing—review and editing. RZ: Conceptualization, Methodology, Writing—review and editing. CSu: Conceptualization, Methodology, Writing—review and editing. QR: Methodology, Writing—review and editing. CZ: Methodology, Writing—review and editing. CSh: Methodology, Writing—review and editing. ZY: Methodology, Writing—review

and editing. MW: Conceptualization, Methodology, Writing—review and editing. LS: Conceptualization, Methodology, Supervision, Writing—review and editing. CP: Conceptualization, Supervision, Writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Natural Science Foundation of Sichuan Province (2022NSFSC1349) and Xinglin Scholar Fund of CDUTCM (QJRC2022023).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Figure 1 was created by Figdraw (www.figdraw.com).

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1231401/full#supplementary-material

References

Albers, J. W., Chaudhry, V., Cavaletti, G., and Donehower, R. C. (2011). Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst. Rev.* 2, CD005228. doi:10.1002/14651858.CD005228.pub3

Alberti, P., Canta, A., Chiorazzi, A., Fumagalli, G., Meregalli, C., Monza, L., et al. (2020). Topiramate prevents oxaliplatin-related axonal hyperexcitability and oxaliplatin induced peripheral neurotoxicity. *Neuropharmacology* 164, 107905. doi:10.1016/j.neuropharm.2019.107905

Alyami, M., Hübner, M., Grass, F., Bakrin, N., Villeneuve, L., Laplace, N., et al. (2019). Pressurised intraperitoneal aerosol chemotherapy: Rationale, evidence, and potential indications. *Lancet Oncol.* 20 (7), e368–e377. doi:10.1016/S1470-2045(19)30318-3

Andoh, T., Kitamura, R., and Kuraishi, Y. (2015). Milnacipran inhibits oxaliplatin-induced mechanical allodynia through spinal action in mice. *Biol. Pharm. Bull.* 38 (1), 151–154. doi:10.1248/bpb.b14-00581

André, T., Bensmaine, M. A., Louvet, C., François, E., Lucas, V., Desseigne, F., et al. (1999). Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J. Clin. Oncol.* 17 (11), 3560–3568. doi:10.1200/JCO.1999.17.11.3560

André, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C., et al. (2009). Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J. Clin. Oncol.* 27 (19), 3109–3116. doi:10.1200/JCO.2008.20.6771

André, T., Louvet, C., Raymond, E., Tournigand, C., and de Gramont, A. (1998). Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. *Ann. Oncol.* 9 (11), 1251–1253. doi:10.1023/a:1008475122124

André, T., Meyerhardt, J., Iveson, T., Sobrero, A., Yoshino, T., Souglakos, I., et al. (2020). Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): Final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol.* 21 (12), 1620–1629. doi:10.1016/S1470-2045(20)30527-1

Arango, D., Wilson, A. J., Shi, Q., Corner, G. A., Arañes, M. J., Nicholas, C., et al. (2004). Molecular mechanisms of action and prediction of response to oxaliplatin in colorectal cancer cells. *Br. J. Cancer* 91 (11), 1931–1946. doi:10.1038/sj.bjc.6602215

Aref, A., and Abdalla, A. (2022). Total neoadjuvant therapy for locally advanced rectal cancer: Induction or consolidation chemotherapy? *J. Clin. Oncol.* 40 (23), 2515–2519. doi:10.1200/JCO.22.00506

Areti, A., Yerra, V. G., Naidu, V., and Kumar, A. (2014). Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy. *Redox Biol.* 2, 289–295. doi:10.1016/j.redox.2014.01.006

Argyriou, A. A., Antonacopoulou, A. G., Alberti, P., Briani, C., Bruna, J., Velasco, R., et al. (2019). Liability of the voltage-gated potassium channel KCNN3 repeat polymorphism to acute oxaliplatin-induced peripheral neurotoxicity. *J. Peripher Nerv. Syst.* 24 (4), 298–303. doi:10.1111/jns.12347

Argyriou, A. A., Cavaletti, G., Briani, C., Velasco, R., Bruna, J., Campagnolo, M., et al. (2013). Clinical pattern and associations of oxaliplatin acute neurotoxicity: A prospective study in 170 patients with colorectal cancer. *Cancer* 119 (2), 438–444. doi:10.1002/cncr.27732

Argyriou, A. A., Kalofonou, F., Litsardopoulos, P., Anastopoulou, G. G., and Kalofonos, H. P. (2021). Oxaliplatin rechallenge in metastatic colorectal cancer patients with clinically significant oxaliplatin-induced peripheral neurotoxicity. *J. Peripher Nerv. Syst.* 26 (1), 43–48. doi:10.1111/jns.12426

Argyriou, A. A., Polychronopoulos, P., Iconomou, G., Koutras, A., Makatsoris, T., Gerolymos, M. K., et al. (2007). Incidence and characteristics of peripheral neuropathy during oxaliplatin-based chemotherapy for metastatic colon cancer. *Acta Oncol.* 46 (8), 1131–1137. doi:10.1080/02841860701355055

Argyriou, A. A. (2015). Updates on oxaliplatin-induced peripheral neurotoxicity (OXAIPN). *Toxics* 3 (2), 187–197. PMID: 29056657; PMCID: PMC5634688. doi:10.3390/toxics3020187

Arnould, S., Hennebelle, I., Canal, P., Bugat, R., and Guichard, S. (2003). Cellular determinants of oxaliplatin sensitivity in colon cancer cell lines. *Eur. J. Cancer* 39 (1), 112–119. doi:10.1016/s0959-8049(02)00411-2

Avan, A., Postma, T. J., Ceresa, C., Cavaletti, G., and Giovannetti, E., (2015). Platinum-induced neurotoxicity and preventive strategies: Past, present, and future. *Oncologist* 20 (4), 411–432. doi:10.1634/theoncologist.2014-0044

Azevedo, M. I., Pereira, A. F., Nogueira, R. B., Rolim, F. E., Brito, G. A. C., Wong, D. V. T., et al. (2013). The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Mol. Pain* 9, 53. doi:10.1186/1744-8069-9-53

Ballarini, E., Malacrida, A., Rodriguez-Menendez, V., Pozzi, E., Canta, A., Chiorazzi, A., et al. (2022). Sodium-Calcium exchanger 2: A pivotal role in oxaliplatin induced peripheral neurotoxicity and axonal damage? *Int. J. Mol. Sci.* 23 (17), 10063. doi:10.3390/ijms231710063

Baptista-de-Souza, D., Di Cesare Mannelli, L., Zanardelli, M., Micheli, L., Nunes-de-Souza, R. L., Canto-de-Souza, A., et al. (2014). Serotonergic modulation in neuropathy induced by oxaliplatin: Effect on the 5HT2C receptor. *Eur. J. Pharmacol.* 735, 141–149. doi:10.1016/j.ejphar.2014.04.028

Bécouarn, Y., Ychou, M., Ducreux, M., Borel, C., Bertheault-Cvitkovic, F., Seitz, J. F., et al. (1998). Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. *J. Clin. Oncol.* 16 (8), 2739–2744. doi:10.1200/JCO.1998.16.8.2739

Besora, S., Santos, C., Izquierdo, C., Martinez-Villacampa, M. M., Bruna, J., and Velasco, R. (2018). Rechallenge with oxaliplatin and peripheral neuropathy in colorectal cancer patients. *J. Cancer Res. Clin. Oncol.* 144 (9), 1793–1801. doi:10.1007/s00432-018-2691-8

Boilève, A., De Cuyper, A., Larive, A., Mahjoubi, L., Najdawi, M., Tazdait, M., et al. (2020). Hepatic arterial infusion of oxaliplatin plus systemic chemotherapy and targeted therapy for unresectable colorectal liver metastases. *Eur. J. Cancer* 138, 89–98. doi:10.1016/j.ejca.2020.07.022

Boku, N., Ohtsu, A., Hyodo, I., Shirao, K., Miyata, Y., Nskagawa, K., et al. (2007). Phase II study of oxaliplatin in Japanese patients with metastatic colorectal cancer

refractory to fluoropyrimidines. *Jpn. J. Clin. Oncol.* 37 (6), 440–445. doi:10.1093/jjco/hym069

Bondad, N., Boostani, R., Barri, A., Elyasi, S., and Allahyari, A. (2020). Protective effect of N-acetylcysteine on oxaliplatin-induced neurotoxicity in patients with colorectal and gastric cancers: A randomized, double blind, placebo-controlled, clinical trial. *J. Oncol. Pharm. Pract.* 26 (7), 1575–1582. doi:10.1177/1078155219900788

Boyette-Davis, J., and Dougherty, P. M. (2011). Protection against oxaliplatin-induced mechanical hyperalgesia and intraepidermal nerve fiber loss by minocycline. *Exp. Neurol.* 229 (2), 353–357. doi:10.1016/j.expneurol.2011.02.019

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68 (6), 394–424. doi:10.3322/caac.21492

Brody, H. (2015). Colorectal cancer. *Nature* 521 (7551), S1. doi:10.1038/521S1a

Calls, A., Torres-Espin, A., Tormo, M., Martínez-Escardó, L., Bonet, N., Casals, F., et al. (2022). A transient inflammatory response contributes to oxaliplatin neurotoxicity in mice. *Ann. Clin. Transl. Neurol.* 9 (12), 1985–1998. doi:10.1002/acn3.51691

Canta, A., Chiorazzi, A., Pozzi, E., Fumagalli, G., Monza, L., Meregalli, C., et al. (2020). Calmangafodipir reduces sensory alterations and prevents intraepidermal nerve fibers loss in a mouse model of oxaliplatin induced peripheral neurotoxicity. *Antioxidants (Basel)* 9 (7), 594. doi:10.3390/antiox9070594

Canta, A., Pozzi, E., and Carozzi, V. A. (2015). Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN). *Toxics* 3 (2), 198–223. Published 2015 Jun 5. doi:10.3390/toxics3020198

Cascinu, S., Catalano, V., Cordella, L., Labianca, R., Giordani, P., Baldelli, A. M., et al. (2002). Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: A randomized, double-blind, placebo-controlled trial. *J. Clin. Oncol.* 20 (16), 3478–3483. doi:10.1200/JCO.2002.07.061

Cassidy, J., Tabernero, J., Twelves, C., Brunet, R., Butts, C., Conroy, T., et al. (2004). XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer. *J. Clin. Oncol.* 22 (11), 2084–2091. doi:10.1200/JCO.2004.11.069

Cattel, L., La Grotta, G., Infante, L., Passera, R., Arpicco, S., Brusa, P., et al. (2003). Pharmacokinetic study of oxaliplatin iv chronomodulated infusion combined with 5-fluorouracil iv continuous infusion in the treatment of advanced colorectal cancer. *Farmaco* 58 (12), 1333–1338. doi:10.1016/S0014-827X(03)00193-9

Cavaletti, G., and Marmiroli, P. (2020). Management of oxaliplatin-induced peripheral sensory neuropathy. *Cancers (Basel).* 12 (6), 1370. doi:10.3390/cancers12061370

Cecchin, E., D'Andrea, M., Lonardi, S., Zanusso, C., Pella, N., Errante, D., et al. (2013). A prospective validation pharmacogenomic study in the adjuvant setting of colorectal cancer patients treated with the 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) regimen. *Pharmacogenomics J.* 13 (5), 403–409. doi:10.1038/tpj.2012.31

Cerles, O., Benoit, E., Chéreau, C., Chouzenoux, S., Morin, F., Guillaumot, M. A., et al. (2017). Niclosamide inhibits oxaliplatin neurotoxicity while improving colorectal cancer therapeutic response. *Mol. cancer Ther.* 16 (2), 300–311. doi:10.1158/1535-7163.MCT-16-0326

Chen, S. J., Chen, L. H., Yeh, Y. M., Lin, C. C. K., Lin, P. C., Huang, H. W., et al. (2021). Targeting lysosomal cysteine protease cathepsin S reveals immunomodulatory therapeutic strategy for oxaliplatin-induced peripheral neuropathy. *Theranostics* 11 (10), 4672–4687. doi:10.7150/thno.54793

Cheng, X., Huo, J., Wang, D., Cai, X., Sun, X., Lu, W., et al. (2017). Herbal medicine AC591 prevents oxaliplatin-induced peripheral neuropathy in animal model and cancer patients. *Front. Pharmacol.* 8, 344. doi:10.3389/fphar.2017.00344

Chien, A., Yang, C. C., Chang, S. C., Jan, Y. M., Yang, C. H., and Hsieh, Y. L. (2021). Ultrasound acupuncture for oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer: A pilot study. *PM R.* 13 (1), 55–65. doi:10.1002/pmrj.12361

Cho, H. K., Lee, E. S., Lee, J. W., Park, J. K., Kang, J. H., Lee, K. S., et al. (2006). Clinical pharmacokinetics of oxaliplatin and 5-fluorouracil administered in combination with leucovorin in Korean patients with advanced colorectal cancer. *J. Cancer Res. Clin. Oncol.* 132 (5), 320–326. doi:10.1007/s00432-005-0072-6

Chukyo, A., Chiba, T., Kambe, T., Yamamoto, K., Kawakami, K., Taguchi, K., et al. (2018). Oxaliplatin-induced changes in expression of transient receptor potential channels in the dorsal root ganglion as a neuropathic mechanism for cold hypersensitivity. *Neuropeptides* 67, 95–101. doi:10.1016/j.npep.2017.12.002

Clamp, A. R., Schöffski, P., Valle, J. W., Wilson, R. H., Marreaud, S., Govaerts, A. S., et al. (2008). A phase I and pharmacokinetic study of OSI-7904L, a liposomal thymidylate synthase inhibitor in combination with oxaliplatin in patients with advanced colorectal cancer. *Cancer Chemother. Pharmacol.* 61 (4), 579–585. doi:10.1007/s00280-007-0509-5

Conroy, T., Bosset, J. F., Etienne, P. L., Rio, E., Éfrançois, E., Mesgouez-Nebout, N., et al. (2021). Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 22 (5), 702–715. doi:10.1016/S1470-2045(21)00079-6

Coriat, R., Alexandre, J., Nicco, C., Quinquis, L., Benoit, E., Chéreau, C., et al. (2014). Treatment of oxaliplatin-induced peripheral neuropathy by intravenous mangafodipir. *J. Clin. Invest.* 124 (1), 262–272. doi:10.1172/JCI68730

Cremolini, C., Antoniotti, C., Rossini, D., Lonardi, S., Loupakis, F., Pietrantonio, F., et al. (2020). Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): A multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol.* 21 (4), 497–507. doi:10.1016/S1470-2045(19)30862-9

Culy, C. R., Clemett, D., and Wiseman, L. R. (2000). Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 60 (4), 895–924. doi:10.2165/00003495-200060040-00005

Custodio, A., Moreno-Rubio, J., Aparicio, J., Gallego-Plazas, J., Yaya, R., Maurel, J., et al. (2014). Pharmacogenetic predictors of severe peripheral neuropathy in colon cancer patients treated with oxaliplatin-based adjuvant chemotherapy: A GEMCAD group study. *Ann. Oncol.* 25 (2), 398–403. doi:10.1093/annonc/mdt546

De Gramont, A., Figer, A., Seymour, M., Homerin, M., Hmissi, A., Cassidy, J., et al. (2000). Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J. Clin. Oncol.* 18 (16), 2938–2947. doi:10.1200/JCO.2000.18.16.2938

de Jong, L. A. W., van Erp, N. P., and Bijelic, L. (2021). Pressurized intraperitoneal aerosol chemotherapy: The road from promise to proof. *Clin. Cancer Res.* 27 (7), 1830–1832. doi:10.1158/1078-0432.CCR-20-4342

Delord, J. P., Umlil, A., Guimbaud, R., Grégoire, N., Lafont, T., CaNSl, P., et al. (2003). Population pharmacokinetics of oxaliplatin. *Cancer Chemother. Pharmacol.* 51 (2), 127–131. doi:10.1007/s00280-002-0550-3

Demtröder, C., Solass, W., Zieren, J., Strumberg, D., Giger-Pabst, U., and Reymond, M. A. (2016). Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis.* 18 (4), 364–371. doi:10.1111/codi.13130

Descoeur, J., Pereira, V., Pizzoccaro, A., Francois, A., Ling, B., Maffre, V., et al. (2011). Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. *EMBO Mol. Med.* 3 (5), 266–278. doi:10.1002/emmm.201100134

Díaz-Rubio, E., Sastre, J., Zaniboni, A., Labianca, R., Cortés-Funes, H., de Braud, F., et al. (1998). Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: A phase II multicentric study. *Ann. Oncol.* 9 (1), 105–108. doi:10.1023/a:1008200825886

Dionisi, M., Riva, B., Delconti, M., Meregalli, C., Chiorazzi, A., Canta, A., et al. (2023). Inhibition of NHE1 transport activity and gene transcription in DRG neurons in oxaliplatin-induced painful peripheral neurotoxicity. *Sci. Rep.* 13 (1), 3991. Published 2023 Mar 9. doi:10.1038/s41598-023-31095-9

Donald, E. L., Stojanovska, L., Apostolopoulos, V., and Nurgali, K. (2017). Resveratrol alleviates oxidative damage in enteric neurons and associated gastrointestinal dysfunction caused by chemotherapeutic agent oxaliplatin. *Maturitas* 105, 100–106. doi:10.1016/j.maturitas.2017.05.010

Dong, D., Yang, D., Lin, L., Wang, S., and Wu, B. (2020). Circadian rhythm in pharmacokinetics and its relevance to chronotherapy. *Biochem. Pharmacol.* 178, 114045. doi:10.1016/j.bcp.2020.114045

Dumont, F., Passot, C., Raoul, J. L., Kepenekian, V., Lelièvre, B., Boisdron-Celle, M., et al. (2020). A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic approach using pressurised intraperitoneal aerosol chemotherapy for advanced peritoneal metastases of gastrointestinal tract cancers. *Eur. J. Cancer* 140, 37–44. doi:10.1016/j.ejca.2020.09.010

Durand, J. P., Deplanque, G., Montheil, V., Gornet, J. M., Scotte, F., Mir, O., et al. (2012). Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: Results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Ann. Oncol.* 23 (1), 200–205. doi:10.1093/annonc/mdr045

Elias, D., Bonnay, M., Puizillou, J. M., Antoun, S., Demirdjian, S., El, O. A., et al. (2002). Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: Pharmacokinetics and tissue distribution. *Ann. Oncol.* 13 (2), 267–272. doi:10.1093/annonc/mdf019

Elias, D., Lefevre, J. H., Chevalier, J., Brouquet, A., Marchal, F., Classe, J. M., et al. (2009). Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J. Clin. Oncol.* 27 (5), 681–685. doi:10.1200/JCO.2008.19.7160

Elias, D., Matsuhisa, T., Sideris, L., Liberale, G., Drouard-Troalen, L., Raynard, B., et al. (2004). Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: Pharmacokinetics, tissue distribution and tolerance. *Ann. Oncol.* 15 (10), 1558–1565. doi:10.1093/annonc/mdh398

Erratum: Global cancer statistics (2020). Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 70 (4), 313. doi:10.3322/caac.21609

Falcone, A., Masi, G., Allegrini, G., Danesi, R., Pfanner, E., Brunetti, I. M., et al. (2002). Biweekly chemotherapy with oxaliplatin, irinotecan, infusional fluorouracil, and leucovorin: A pilot study in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 20 (19), 4006–4014. doi:10.1200/JCO.2002.12.075

Fornaro, L., Masi, G., Bursi, S., Loupakis, F., Vasile, E., Antonuzzo, A., et al. (2009). A dose finding and pharmacokinetic study of capecitabine in combination with oxaliplatin

and irinotecan in metastatic colorectal cancer. *Cancer Chemother. Pharmacol.* 63 (5), 965–969. doi:10.1007/s00280-008-0840-5

Fox, R. J., Coffey, C. S., Conwit, R., Cudkowicz, M. E., Gleason, T., Goodman, A., et al. (2018). Phase 2 trial of ibudilast in progressive multiple sclerosis. *N. Engl. J. Med.* 379 (9), 846–855. doi:10.1056/NEJMoa1803583

Gamelin, E., Bouil, A. L., Boisdron-Celle, M., Turcant, A., Delva, R., Cailleux, A., et al. (1997). Cumulative pharmacokinetic study of oxaliplatin, administered every three weeks, combined with 5-fluorouracil in colorectal cancer patients. *Clin. Cancer Res.* 3 (6), 891–899.

Gamelin, L., Boisdron-Celle, M., Delva, R., Guérin-Meyer, V., Ifrah, N., Morel, A., et al. (2004). Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: A retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin. Cancer Res.* 10 (12), 4055–4061. doi:10.1158/1078-0432.CCR-03-0666

Gamelin, L., Boisdron-Celle, M., Morel, A., Poirier, A. L., Berger, V., Gamelin, E., et al. (2008). Oxaliplatin-related neurotoxicity: Interest of calcium-magnesium infusion and no impact on its efficacy. *J. Clin. Oncol.* 26 (7), 1188–1189. doi:10.1200/JCO.2007.15.3767

Garcia-Aguilar, J., Patil, S., Gollub, M. J., Kim, J. K., Yuval, J. B., Thompson, H. M., et al. (2022). Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J. Clin. Oncol.* 40 (23), 2546–2556. doi:10.1200/JCO.22.00032

Gauchan, P., Andoh, T., Kato, A., and Kuraishi, Y. (2009). Involvement of increased expression of transient receptor potential melastatin 8 in oxaliplatin-induced cold allodynia in mice. *Neurosci. Lett.* 458 (2), 93–95. doi:10.1016/j.neulet.2009.04.029

Gewandter, J. S., Kleckner, A. S., Marshall, J. H., Brown, J. S., Curtis, L. H., Bautista, J., et al. (2020). Chemotherapy-induced peripheral neuropathy (CIPN) and its treatment: An NIH collaboratory study of claims data. *Support Care Cancer* 28 (6), 2553–2562. doi:10.1007/s00520-019-05063-x

Gil-Delgado, M. A., Bastian, G., Guinet, F., Spano, J. P., Taillibert, S., Rocher, M. A., et al. (2004). Oxaliplatin plus irinotecan and FU-FOL combination and pharmacokinetic analysis in advanced colorectal cancer patients. *Am. J. Clin. Oncol.* 27 (3), 294–298. doi:10.1097/01.coc.0000071383.39986.a4

Glehen, O., Mohamed, F., and Gilly, F. N. (2004). Peritoneal carcinomatosis from digestive tract cancer: New management by cytoreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol.* 5 (4), 219–228. doi:10.1016/S1470-2045(04)01425-1

Glimelius, B., Manojlovic, N., Pfeiffer, P., Mosidze, B., Kurteva, G., Karlberg, M., et al. (2018). Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx®): A placebo-controlled randomised phase II study (PLIANT). *Acta Oncol.* 57 (3), 393–402. doi:10.1080/0284186X.2017.1398836

Goéré, D., Glehen, O., Quenet, F., Guilloit, J. M., Bereder, J. M., Lorimier, G., et al. (2020). Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): A randomised, phase 3 study. *Lancet Oncol.* 21 (9), 1147–1154. doi:10.1016/S1470-2045(20)30322-3

Graham, M. A., Lockwood, G. F., Greenslade, D., Brienza, S., Bayssas, M., and Gamelin, E. (2000). Clinical pharmacokinetics of oxaliplatin: A critical review. *Clin. Cancer Res.* 6 (4), 1205–1218.

Grolleau, F., Gamelin, L., Boisdron-Celle, M., Lapied, B., Pelhate, M., and Gamelin, E. (2001). A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. *J. Neurophysiol.* 85 (5), 2293–2297. doi:10.1152/jn.2001.85.5.2293

Grothey, A., Nikcevich, D. A., Sloan, J. A., Kugler, J. W., Silberstein, P. T., Dentchev, T., et al. (2011). Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: Ncctg N04C7. *J. Clin. Oncol.* 29 (4), 421–427. doi:10.1200/JCO.2010.31.5911

Haller, D. G., Tabernero, J., Maroun, J., de Braud, F., Price, T., Van Cutsem, E., et al. (2011). Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J. Clin. Oncol.* 29 (11), 1465–1471. doi:10.1200/JCO.2010.33.6297

Han, C. H., Khwaounjoo, P., Kilfoyle, D. H., Hill, A., and McKeage, M. J. (2013). Phase I drug-interaction study of effects of calcium and magnesium infusions on oxaliplatin pharmacokinetics and acute neurotoxicity in colorectal cancer patients. *BMC Cancer* 13, 495. doi:10.1186/1471-2407-13-495

Hartmann, J. T., and Lipp, H. P. (2003). Toxicity of platinum compounds. *Expert Opin. Pharmacother.* 4 (6), 889–901. doi:10.1517/14656566.4.6.889

Hershman, D. L., Lacchetti, C., and Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American society of clinical Oncology clinical practice guideline summary. *J. Oncol. Pract.* 10 (6), e421–e424. doi:10.1200/JOP.2014.001776

Hochster, H. S., Grothey, A., Hart, L., Rowland, K., Ansari, R., Alberts, S., et al. (2014). Improved time to treatment failure with an intermittent oxaliplatin strategy: Results of CONcePT. *Ann. Oncol.* 25 (6), 1172–1178. doi:10.1093/annonc/mdu107

Howells, L. M., Iwuji, C. O. O., Irving, G. R. B., Barber, S., Walter, H., Sidat, Z., et al. (2019). Curcumin combined with FOLFOX chemotherapy is safe and tolerable in patients with metastatic colorectal cancer in a randomized phase IIa trial. *J. Nutr.* 149 (7), 1133–1139. doi:10.1093/jn/nxz029

Hsieh, Y. L., Chou, L. W., Hong, S. F., Chang, F. C., Tseng, S. W., Huang, C. C., et al. (2016). Laser acupuncture attenuates oxaliplatin-induced peripheral neuropathy in patients with gastrointestinal cancer: A pilot prospective cohort study. *Acupunct. Med.* 34 (5), 398–405. doi:10.1136/acupmed-2016-011112

Hu, S., Huang, K. M., Adams, E. J., Loprinzi, C. L., and Lustberg, M. B. (2019). Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy. *Clin. Cancer Res.* 25 (21), 6295–6301. doi:10.1158/1078-0432.CCR-18-2152

Huang, K. M., Leblanc, A. F., Uddin, M. E., Kim, J. Y., Chen, M., Eisenmann, E. D., et al. (2020). Neuronal uptake transporters contribute to oxaliplatin neurotoxicity in mice. *J. Clin. Invest.* 130 (9), 4601–4606. doi:10.1172/JCI136796

Hübner, M., Kusamura, S., Villeneuve, L., Al-Niaimi, A., Alyami, M., Balonov, K., et al. (2020). Guidelines for perioperative care in cytoreductive surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC): Enhanced recovery after surgery (ERAS®) society recommendations - Part II: Postoperative management and special considerations. *Eur. J. Surg. Oncol.* 46 (12), 2311–2323. doi:10.1016/j.ejso.2020.08.006

Iveson, T. J., Sobrero, A. F., Yoshino, T., Souglakos, I., Ou, F. S., Meyers, J. P., et al. (2021). Duration of adjuvant doublet chemotherapy (3 or 6 months) in patients with high-risk stage II colorectal cancer. *J. Clin. Oncol.* 39 (6), 631–641. doi:10.1200/JCO.20.01330

Jemnitz, K., Heredi-Szabo, K., Janossy, J., Ioja, E., Vereczkey, L., and Krajcsi, P. (2010). ABCC2/Abcc2: A multispecific transporter with dominant excretory functions. *Drug Metab. Rev.* 42 (3), 402–436. doi:10.3109/03602530903491741

Jong, N. N., Nakanishi, T., Liu, J. J., Tamai, I., and McKeage, M. J. (2011). Oxaliplatin transport mediated by organic cation/carnitine transporters OCTN1 and OCTN2 in overexpressing human embryonic kidney 293 cells and rat dorsal root ganglion neurons. *J. Pharmacol. Exp. Ther.* 338 (2), 537–547. Epub 2011 May 23. PMID: 21606177. doi:10.1124/jpet.111.181297

Kagiava, A., Tsingotjidou, A., Emmanouilides, C., and Theophilidis, G. (2008). The effects of oxaliplatin, an anticancer drug, on potassium channels of the peripheral myelinated nerve fibres of the adult rat. *Neurotoxicology* 29 (6), 1100–1106. doi:10.1016/j.neuro.2008.09.005

Kakchekeeva, T., Demtröder, C., Herath, N. I., Griffiths, D., Torkington, J., Solaß, W., et al. (2016). *In vivo* feasibility of electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy (ePIPAC). *Ann. Surg. Oncol.* 23 (5), 592–598. doi:10.1245/s10434-016-5108-4

Karlsson, J. O., Ignarro, L. J., Lundström, I., Jynge, P., and Almén, T. (2015). Calmangafodipir [Ca4Mn(DPDP)5], mangafodipir (MnDPDP) and MnPLED with special reference to their SOD mimetic and therapeutic properties. *Drug Discov. Today* 20 (4), 411–421. doi:10.1016/j.drudis.2014.11.008

Kato, S., Imai, H., Gamoh, M., Takahata, T., Ohori, H., Yasuda, K., et al. (2018). Intermittent withdrawal of oxaliplatin for alleviating neurotoxicity during oxaliplatin-based chemotherapy for Japanese patients with inoperable or metastatic colorectal cancer: A phase 2 multicenter study. *Tohoku J. Exp. Med.* 245 (1), 21–28. doi:10.1620/tjem.245.21

Kelley, M. R., Jiang, Y., Guo, C., Reed, A., Meng, H., and Vasko, M. R. (2014). Role of the DNA base excision repair protein, APE1 in cisplatin, oxaliplatin, or carboplatin induced sensory neuropathy. *PLoS One* 9 (9), e106485. doi:10.1371/journal.pone.0106485

Kelley, M. R., Wikel, J. H., Guo, C., Pollok, K. E., Bailey, B. J., Wireman, R., et al. (2016). Identification and characterization of new chemical entities targeting apurinic/apyrimidinic endonuclease 1 for the prevention of chemotherapy-induced peripheral neuropathy. *J. Pharmacol. Exp. Ther.* 359 (2), 300–309. doi:10.1124/jpet.116.235283

Kemeny, N., Tong, W., Gonen, M., Stockman, J., Di Lauro, C., Teitcher, J., et al. (2002). Phase I study of weekly oxaliplatin plus irinotecan in previously treated patients with metastatic colorectal cancer. *Ann. Oncol.* 13 (9), 1490–1496. doi:10.1093/annonc/mdf247

Kennedy, E., Zwaal, C., Asmis, T., Cho, C., Galica, J., Ginty, A., et al. (2022). An evidence-based guideline for surveillance of patients after curative treatment for colon and rectal cancer. *Curr. Oncol.* 29 (2), 724–740. doi:10.3390/curroncol29020062

Kern, W., Beckert, B., Lang, N., Stemmler, J., Beykirch, M., Stein, J., et al. (2001). Phase I and pharmacokinetic study of hepatic arterial infusion with oxaliplatin in combination with folinic acid and 5-fluorouracil in patients with hepatic metastases from colorectal cancer. *Ann. Oncol.* 12 (5), 599–603. doi:10.1023/a:1011186708754

Kern, W., Braess, J., Böttger, B., Kaufmann, C. C., Hiddemann, W., and Schleyer, E. (1999). Oxaliplatin pharmacokinetics during a four-hour infusion. *Clin. Cancer Res.* 5 (4), 761–765.

Kim, G., Tan, H. L., Sundar, R., Lieske, B., Chee, C. E., Ho, J., et al. (2021). PIPAC-OX: A phase I study of oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy in patients with peritoneal metastases. *Clin. Cancer Res.* 27 (7), 1875–1881. doi:10.1158/1078-0432.CCR-20-2152

Kim, J. J., Kang, J., Hong, Y. S., Kim, K. P., Kim, S. Y., Kim, T. W., et al. (2018). Oxaliplatin rechallenge in metastatic colorectal cancer patients after prior oxaliplatin treatment. *Med. Oncol.* 35 (5), 65. doi:10.1007/s12032-018-1124-5

Koury, M. J. (2014). Abnormal erythropoiesis and the pathophysiology of chronic anemia. *Blood Rev.* 28 (2), 49–66. doi:10.1016/j.blre.2014.01.002

Krukowski, K., Nijboer, C. H., Huo, X., Kavelaars, A., and Heijnen, C. J. (2015). Prevention of chemotherapy-induced peripheral neuropathy by the small-molecule inhibitor pifithrin-μ. *Pain* 156 (11), 2184–2192. doi:10.1097/j.pain.0000000000000290

Kuebler, J. P., Wieand, H. S., O'Connell, M. J., Smith, R. E., Colangelo, L. H., Yothers, G., et al. (2007). Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. *J. Clin. Oncol.* 25 (16), 2198–2204. doi:10.1200/JCO.2006.08.2974

Kupsch, P., Henning, B. F., Passarge, K., Richly, H., Wiesemann, K., Hilger, R. A., et al. (2005). Results of a phase I trial of sorafenib (BAY 43-9006) in combination with oxaliplatin in patients with refractory solid tumors, including colorectal cancer. *Clin. Colorectal Cancer* 5 (3), 188–196. doi:10.3816/ccc.2005.n.030

Kus, T., Aktas, G., Alpak, G., Kalender, M. E., Sevinc, A., Kul, S., et al. (2016). Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: A single-center retrospective case-control study. *Support Care Cancer* 24 (5), 2085–2091. doi:10.1007/s00520-015-3009-x

Lévi, F. (2001). Circadian chronotherapy for human cancers. *Lancet Oncol.* 2 (5), 307–315. doi:10.1016/S1470-2045(00)00326-0

Lévi, F., Karaboué, A., Etienne-Grimaldi, M. C., Paintaud, G., Focan, C., Innominato, P., et al. (2017). Pharmacokinetics of irinotecan, oxaliplatin and 5-fluorouracil during hepatic artery chronomodulated infusion: A translational European optiliv study. *Clin. Pharmacokinet.* 56 (2), 165–177. doi:10.1007/s40262-016-0431-2

Lévi, F., Metzger, G., Massari, C., and Milano, G. (2000). Oxaliplatin: Pharmacokinetics and chronopharmacological aspects. *Clin. Pharmacokinet.* 38 (1), 1–21. doi:10.2165/00003088-200038010-00001

Lévi, F., Misset, J. L., Brienza, S., Adam, R., Metzger, G., Itzakhi, M., et al. (1992). A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. *Cancer* 69 (4), 893–900. doi:10.1002/1097-0142(19920215)69:4<893:aid-cncr2820690410>3.0.co;2-x

Lévi, F. A., Zidani, R., Vannetzel, J. M., Perpoint, B., Focan, C., Faggiuolo, R., et al. (1994). Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: A randomized multi-institutional trial. *J. Natl. Cancer Inst.* 86 (21), 1608–1617. doi:10.1093/jnci/86.21.1608

Lim, A., Le Sourd, S., Senellart, H., Luet, D., Douane, F., Perret, C., et al. (2017). Hepatic arterial infusion chemotherapy for unresectable liver metastases of colorectal cancer: A multicenter retrospective study. *Clin. Colorectal Cancer* 16 (4), 308–315. doi:10.1016/j.clcc.2017.03.003

Lin, T., Hu, L., Hu, F., Li, K., Wang, C. Y., Zong, L. J., et al. (2022). NET-triggered NLRP3 activation and IL18 release drive oxaliplatin-induced peripheral neuropathy. *Cancer Immunol. Res.* 10 (12), 1542–1558. doi:10.1158/2326-6066.CIR-22-0197

Liu, J. J., Jamieson, S. M., Subramaniam, J., Ip, V., Jong, N. N., Mercer, J. F., et al. (2009). Neuronal expression of copper transporter 1 in rat dorsal root ganglia: Association with platinum neurotoxicity. *Cancer Chemother. Pharmacol.* 64 (4), 847–856. Epub 2009 May 24. PMID: 19466412. doi:10.1007/s00280-009-1017-6

Liu, J. J., Kim, Y., Yan, F., Ding, Q., Ip, V., Jong, N. N., et al. (2013). Contributions of rat Ctr1 to the uptake and toxicity of copper and platinum anticancer drugs in dorsal root ganglion neurons. *Biochem. Pharmacol.* 85 (2), 207–215. Epub 2012 Nov 1. PMID: 23123662. doi:10.1016/j.bcp.2012.10.023

Loprinzi, C. L., Lacchetti, C., Bleeker, J., Cavaletti, G., Chauhan, C., Hertz, D. L., et al. (2020). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. *J. Clin. Oncol.* 38 (28), 3325–3348. doi:10.1200/JCO.20.01399

Loupakis, F., Cremolini, C., Masi, G., Lonardi, S., Zagonel, V., Salvatore, L., et al. (2014). Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N. Engl. J. Med.* 371 (17), 1609–1618. doi:10.1056/NEJMoa1403108

Lurvink, R. J., Tajzai, R., Rovers, K. P., Wassenaar, E. C. E., Moes, D. A. R., Pluimakers, G., et al. (2021). Systemic pharmacokinetics of oxaliplatin after intraperitoneal administration by electrostatic pressurized intraperitoneal aerosol chemotherapy (ePIPAC) in patients with unresectable colorectal peritoneal metastases in the CRC-PIPAC trial. *Ann. Surg. Oncol.* 28 (1), 265–272. doi:10.1245/s10434-020-08743-9

Maindrault-Goebel, F., de Gramont, A., Louvet, C., André, T., Carola, E., Mabro, M., et al. (2001). High-dose intensity oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX 7). *Eur. J. Cancer* 37 (8), 1000–1005. doi:10.1016/s0959-8049(01)00068-5

Maindrault-Goebel, F., Louvet, C., André, T., Carola, E., Lotz, J. P., Molitor, J. L., et al. (1999). Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. *Eur. J. Cancer* 35 (9), 1338–1342. doi:10.1016/s0959-8049(99)00149-5

Martinez-Balibrea, E., Martínez-Cardús, A., Musulén, E., Ginés, A., Manzano, J. L., Aranda, E., et al. (2009). Increased levels of copper efflux transporter ATP7B are associated with poor outcome in colorectal cancer patients receiving oxaliplatin-based chemotherapy. *Int. J. Cancer* 124 (12), 2905–2910. doi:10.1002/ijc.24273

McDonald, E. S., and Windebank, A. J. (2002). Cisplatin-induced apoptosis of DRG neurons involves bax redistribution and cytochrome c release but not fas receptor signaling. *Neurobiol. Dis.* 9 (2), 220–233. doi:10.1006/nbdi.2001.0468

Merkel, U., Wedding, U., Roskos, M., Höffken, K., and Hoffmann, A. (2003). Pharmacokinetics of oxaliplatin during chronomodulated infusion in metastatic gastrointestinal cancer patients: A pilot investigation with preliminary results. *Exp. Toxicol. Pathol.* 54 (5-6), 475–479. doi:10.1078/0940-2993-00283

Micov, A. M., Tomić, M. A., Todorović, M. B., Vuković, M. J., Pecikoza, U. B., Jasnic, N. I., et al. (2020). Vortioxetine reduces pain hypersensitivity and associated depression-like behavior in mice with oxaliplatin-induced neuropathy. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 103, 109975. doi:10.1016/j.pnpbp.2020.109975

Miguel, C. Á., Noya-Riobó, M. V., Brumovsky, P. R., Villar, M. J., and Coronel, M. F. (2022). Sex-related differences in oxaliplatin-induced changes in the expression of transient receptor potential channels and their contribution to cold hypersensitivity. *Neurosci. Lett.* 788, 136863. doi:10.1016/j.neulet.2022.136863

Milla, P., Airoldi, M., Weber, G., Drescher, A., Jaehde, U., and Cattel, L. (2009). Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: Effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. *Anticancer Drugs* 20 (5), 396–402. doi:10.1097/CAD.0b013e32832a2dc1

Miltenburg, N. C., and Boogerd, W. (2014). Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treat. Rev.* 40 (7), 872–882. doi:10.1016/j.ctrv.2014.04.004

Miura, Y., Ando, M., Yamazaki, K., Hironaka, S., Boku, N., Muro, K., et al. (2021). Time-dependent discrepancies between physician-assessed and patient-reported oxaliplatin-induced peripheral neuropathy in patients with metastatic colorectal cancer who received mFOLFOX6 plus bevacizumab: A post hoc analysis (WJOG4407GSS2). *Support Care Cancer* 29 (7), 3715–3723. doi:10.1007/s00520-020-05891-2

Mizoguchi, S., Andoh, T., Yakura, T., and Kuraishi, Y. (2016). Involvement of c-Myc-mediated transient receptor potential melastatin 8 expression in oxaliplatin-induced cold allodynia in mice. *Pharmacol. Rep.* 68 (3), 645–648. doi:10.1016/j.pharep.2016.03.001

Myint, K., Biswas, R., Li, Y., Jong, N., Jamieson, S., Liu, J., et al. (2019). Identification of MRP2 as a targetable factor limiting oxaliplatin accumulation and response in gastrointestinal cancer. *Sci. Rep.* 9 (1), 2245. doi:10.1038/s41598-019-38667-8

Nichetti, F., Falvella, F. S., Miceli, R., Cheli, S., Gaetano, R., Fucà, G., et al. (2019). Is a pharmacogenomic panel useful to estimate the risk of oxaliplatin-related neurotoxicity in colorectal cancer patients? *Pharmacogenomics J.* 19 (5), 465–472. doi:10.1038/s41397-019-0078-0

Ohdo, S. (2003). Changes in toxicity and effectiveness with timing of drug administration: Implications for drug safety. *Drug Saf.* 26 (14), 999–1010. doi:10.2165/00002018-200326140-00002

Pachman, D. R., Qin, R., Seisler, D. K., Smith, E. M. L., and Beutler, A. S. (2015). Clinical course of oxaliplatin-induced neuropathy: Results from the randomized phase III trial N08CB (alliance). *J. Clin. Oncol.* 33 (30), 3416–3422. doi:10.1200/JCO.2014.58.8533

Park, S. B., Lin, C. S., Krishnan, A. V., Goldstein, D., Friedlander, M. L., and Kiernan, M. C. (2009). Oxaliplatin-induced neurotoxicity: Changes in axonal excitability precede development of neuropathy. *Brain* 132 (10), 2712–2723. doi:10.1093/brain/awp219

Petrelli, F., Labianca, R., Zaniboni, A., Lonardi, S., Galli, F., Rulli, E., et al. (2020). Assessment of duration and effects of 3 vs 6 Months of adjuvant chemotherapy in high-risk stage II colorectal cancer: A subgroup analysis of the tosca randomized clinical trial. *JAMA Oncol.* 6 (4), 547–551. doi:10.1001/jamaoncol.2019.6486

Pfeiffer, P., Sørbye, H., Ehrsson, H., Fokstuen, T., Mortensen, J. P., Baltesgard, L., et al. (2006). Short-time infusion of oxaliplatin in combination with capecitabine (XELOX30) as second-line therapy in patients with advanced colorectal cancer after failure to irinotecan and 5-fluorouracil. *Ann. Oncol.* 17 (2), 252–258. doi:10.1093/annonc/mdj060

Potenzieri, A., Riva, B., Rigolio, R., Chiorazzi, A., Pozzi, E., Ballarini, E., et al. (2020). Oxaliplatin-induced neuropathy occurs through impairment of haemoglobin proton buffering and is reversed by carbonic anhydrase inhibitors. *Pain* 161 (2), 405–415. doi:10.1097/j.pain.0000000000001722

Poupon, L., Lamoine, S., Pereira, V., Barriere, D. A., Lolignier, S., Giraudet, F., et al. (2018). Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. *Neuropharmacology* 140, 43–61. doi:10.1016/j.neuropharm.2018.07.026

Quénet, F., Elias, D., Roca, L., Goéré, D., Ghouti, L., Pocard, M., et al. (2021). Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 22 (2), 256–266. doi:10.1016/S1470-2045(20)30599-4

Quenet, F., Goéré, D., Mehta, S. S., Roca, L., Dumont, F., Hessissen, M., et al. (2011). Results of two bi-institutional prospective studies using intraperitoneal oxaliplatin with or without irinotecan during HIPEC after cytoreductive surgery for colorectal carcinomatosis. *Ann. Surg.* 254 (2), 294–301. doi:10.1097/SLA.0b013e3182263933

Rothenberg, M. L., Oza, A. M., Bigelow, R. H., Berlin, J. D., Marshall, J. L., Ramanathan, R. K., et al. (2003). Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive

colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. *J. Clin. Oncol.* 21 (11), 2059–2069. doi:10.1200/JCO.2003.11.126

Rovers, K. P., Lurvink, R. J., Wassenaar, E. C., Kootstra, T. J., Scholten, H. J., Tajzai, R., et al. (2019). Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: Protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC). *BMJ Open* 9 (7), e030408. doi:10.1136/bmjopen-2019-030408

Saarto, T., and Wiffen, P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database Syst. Rev.* 4, CD005454. doi:10.1002/14651858.CD005454.pub2

Sałat, K. (2020). Chemotherapy-induced peripheral neuropathy-part 2: Focus on the prevention of oxaliplatin-induced neurotoxicity. *Pharmacol. Rep.* 72 (3), 508–527. doi:10.1007/s43440-020-00106-1

Salehifar, E., Janbabaei, G., Hendouei, N., Alipour, A., Tabrizi, N., and Avan, R. (2020). Comparison of the efficacy and safety of pregabalin and duloxetine in taxane-induced sensory neuropathy: A randomized controlled trial. *Clin. Drug Investig.* 40 (3), 249–257. doi:10.1007/s40261-019-00882-6

Schultheis, B., Folprecht, G., Kuhlmann, J., Ehrenberg, R., Hacker, U. T., Köhne, C. H., et al. (2013). Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: Results of a multicenter, phase ib study. *Ann. Oncol.* 24 (6), 1560–1567. doi:10.1093/annonc/mdt056

Selvy, M., Pereira, B., Kerckhove, N., Busserolles, J., Farsi, F., Guastella, V., et al. (2021). Prevention, diagnosis and management of chemotherapy-induced peripheral neuropathy: A cross-sectional study of French oncologists' professional practices. *Support Care Cancer* 29 (7), 4033–4043. doi:10.1007/s00520-020-05928-6

Shin, S. J., Ahn, J. B., Park, K. S., Lee, Y. J., Hong, Y. S., Kim, T. W., et al. (2012). A Phase Ib pharmacokinetic study of the anti-angiogenic agent CKD-732 used in combination with capecitabine and oxaliplatin (XELOX) in metastatic colorectal cancer patients who progressed on irinotecan-based chemotherapy. *Invest. New Drugs* 30 (2), 672–680. doi:10.1007/s10637-010-9625-x

Shirao, K., Matsumura, Y., Yamada, Y., Muro, K., Gotoh, M., Boku, N., et al. (2006). Phase I study of single-dose oxaliplatin in Japanese patients with malignant tumors. *Jpn. J. Clin. Oncol.* 36 (5), 295–300. doi:10.1093/jjco/hyl016

Shirota, Y., Stoehlmacher, J., Brabender, J., Xiong, Y. P., Uetake, H., Danenberg, K. D., et al. (2001). ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. *J. Clin. Oncol.* 19 (23), 4298–4304. doi:10.1200/JCO.2001.19.23.4298

Sisignano, M., Baron, R., Scholich, K., and Geisslinger, G. (2014). Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. *Nat. Rev. Neurol.* 10 (12), 694–707. doi:10.1038/nrneurol.2014.211

Sittl, R., Carr, R. W., Fleckenstein, J., and Grafe, P. (2010). Enhancement of axonal potassium conductance reduces nerve hyperexcitability in an *in vitro* model of oxaliplatin-induced acute neuropathy. *Neurotoxicology* 31 (6), 694–700. doi:10.1016/j.neuro.2010.07.006

Smaaland, R., Laerum, O. D., Lote, K., Sletvold, O., Sothern, R. B., and Bjerknes, R. (1991). DNA synthesis in human bone marrow is circadian stage dependent. *Blood* 77 (12), 2603–2611. doi:10.1182/blood.v77.12.2603.2603

Smith, E. M., Pang, H., Cirrincione, C., Fleishman, S., Paskett, E. D., Ahles, T., et al. (2013). Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA* 309 (13), 1359–1367. doi:10.1001/jama.2013.2813

Sprowl, J. A., Ciarimboli, G., Lancaster, C. S., Giovinazzo, H., Gibson, A. A., Du, G., et al. (2013b). Oxaliplatin-induced neurotoxicity is dependent on the organic cation transporter OCT2. *Proc. Natl. Acad. Sci. U. S. A.* 110 (27), 11199–11204. doi:10.1073/pnas.1305321110

Sprowl, J. A., Ness, R. A., and Sparreboom, A. (2013a). Polymorphic transporters and platinum pharmacodynamics. *Drug metabolism Pharmacokinet.* 28 (1), 19–27. doi:10.2133/dmpk.dmpk-12-rv-073

Sprowl, J. A., Gibson, A. A., Hu, S., Du, G., and Lin, W. (2016). A phosphotyrosine switch regulates organic cation transporters. *Nat. Commun.* 7, 10880. doi:10.1038/ncomms10880

Staff, N. P., Cavaletti, G., Islam, B., Lustberg, M., Psimaras, D., and Tamburin, S. (2019). Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. *J. Peripher Nerv. Syst.* 24 (2), S26–S39. doi:10.1111/jns.12335

Strnad, B. S., Ludwig, D. R., Gilcrease-Garcia, B., Fraum, T. J., Shetty, A. S., Doyle, M. B. M., et al. (2021). Contemporary imaging of the surgically placed hepatic arterial infusion chemotherapy pump. *AJR Am. J. Roentgenol.* 217 (3), 633–643. doi:10.2214/AJR.20.24437

Sun, T., Li, K., Xu, G., Zhu, K., Wang, Q., Dang, C., et al. (2021). Postoperative oxaliplatin-based hyperthermic intraperitoneal chemotherapy: An effective and safe palliative treatment option for colorectal cancer with peritoneal metastasis. *World J. Surg. Oncol.* 19 (1), 200. Published 2021 Jul 6. doi:10.1186/s12957-021-02320-4

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71 (3), 209–249. doi:10.3322/caac.21660

Sütcüoğlu, O., Rustamova Cennet, N., Özet, A., Özdemir, N., and Yazıcı, O. (2023). Interpretation of the OPRA study: Are our criteria reliable enough to recommend watch and wait? *J. Clin. Oncol.* 41 (2), 416–417. doi:10.1200/JCO.22.01260

Ta, L E., Espeset, L., Podratz, J., and Windebank, A. J. (2006). Neurotoxicity of oxaliplatin and cisplatin for dorsal root ganglion neurons correlates with platinum-DNA binding. *Neurotoxicology* 27 (6), 992–1002. doi:10.1016/j.neuro.2006.04.010

Teng, C., Reuter, S. E., Blinman, P. L., Dhillon, H. M., Galettis, P., Proschogo, N., et al. (2020). Ibudilast for prevention of oxaliplatin-induced acute neurotoxicity: A pilot study assessing preliminary efficacy, tolerability and pharmacokinetic interactions in patients with metastatic gastrointestinal cancer. *Cancer Chemother. Pharmacol.* 86 (4), 547–558. doi:10.1007/s00280-020-04143-8

Tournigand, C., Cervantes, A., Figer, A., Lledo, G., Flesch, M., Buyse, M., et al. (2006). OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer-a GERCOR study. *J. Clin. Oncol.* 24 (3), 394–400. doi:10.1200/JCO.2005.03.0106

Van Cutsem, E., Prenen, H., D'Haens, G., Bennouna, J., Carrato, A., Ducreux, M., et al. (2015). A phase I/II, open-label, randomised study of nintedanib plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 in first-line metastatic colorectal cancer patients. *Ann. Oncol.* 26 (10), 2085–2091. doi:10.1093/annonc/mdv286

Van Cutsem, E., Verslype, C., Beale, P., Clarke, S., Bugat, R., Rakhit, A., et al. (2008). A phase Ib dose-escalation study of erlotinib, capecitabine and oxaliplatin in metastatic colorectal cancer patients. *Ann. Oncol.* 19 (2), 332–339. doi:10.1093/annonc/mdm452

Wang, D. S., Wang, Z. Q., Chen, G., Peng, J. W., Wang, W., Deng, Y. H., et al. (2020). Phase III randomized, placebo-controlled, double-blind study of monosialotetrahexosylganglioside for the prevention of oxaliplatin-induced peripheral neurotoxicity in stage II/III colorectal cancer. *Cancer Med.* 9 (1), 151–159. doi:10.1002/cam4.2693

Wasserman, E., Cuvier, C., Lokiec, F., Goldwasser, F., Kalla, S., Méry-Mignard, D., et al. (1999). Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: Results of two independent phase I studies with pharmacokinetics. *J. Clin. Oncol.* 17 (6), 1751–1759. doi:10.1200/JCO.1999.17.6.1751

Wu, Z., Ouyang, J., He, Z., and Zhang, S. (2012). Infusion of calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in colorectal cancer: A systematic review and meta-analysis. *Eur. J. Cancer* 48 (12), 1791–1798. doi:10.1016/j.ejca.2012.03.018

Xiao, W. H., and Bennett, G. J. (2012). Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. *Pain* 153 (3), 704–709. doi:10.1016/j.pain.2011.12.011

Yamashita, T. (2004). Chemotherapy for advanced hepatocellular carcinoma: Systemic chemotherapy or hepatic arterial infusion chemotherapy? *J. Gastroenterol.* 39 (4), 404–406. doi:10.1007/s00535-004-1330-0

Yehia, R., Saleh, S., El Abhar, H., Saad, A. S., and Schaalan, M. (2019). L-carnosine protects against oxaliplatin-induced peripheral neuropathy in colorectal cancer patients: A perspective on targeting nrf-2 and NF-κB pathways. *Toxicol. Appl. Pharmacol.* 365, 41–50. doi:10.1016/j.taap.2018.12.015

Yi, J. M., Shin, S., Kim, N. S., and Bang, O. S. (2019b). Ameliorative effects of aqueous extract of Forsythiae suspensa fruits on oxaliplatin-induced neurotoxicity *in vitro* and *in vivo*. *BMC Complement. Altern. Med.* 19 (1), 339. doi:10.1186/s12906-019-2761-8

Yi, J. M., Shin, S., Kim, N. S., and Bang, O. S. (2019a). Neuroprotective effects of an aqueous extract of *Forsythia viridissima* and its major constituents on oxaliplatin-induced peripheral neuropathy. *Molecules* 24 (6), 1177. doi:10.3390/molecules24061177

Yonezawa, A., Masuda, S., Yokoo, S., Katsura, T., and Inui, K. (2006). Cisplatin and oxaliplatin, but not carboplatin and nedaplatin, are substrates for human organic cation transporters (SLC22A1-3 and multidrug and toxin extrusion family). *J. Pharmacol. Exp. Ther.* 319 (2), 879–886. doi:10.1124/jpet.106.110346

Yoshino, T., Oki, E., Misumi, T., Kotaka, M., Manaka, D., Eto, T., et al. (2022). Final analysis of 3 versus 6 Months of adjuvant oxaliplatin and fluoropyrimidine-based therapy in patients with stage III colon cancer: The randomized phase III ACHIEVE trial. *J. Clin. Oncol.* 40 (29), 3419–3429. doi:10.1200/JCO.21.02628

Yoshino, T., Yamanaka, T., Oki, E., Kotaka, M., Manaka, D., Eto, T., et al. (2019). Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 Months of oxaliplatin-based adjuvant chemotherapy for colon cancer: The ACHIEVE phase 3 randomized clinical trial. *JAMA Oncol.* 5 (11), 1574–1581. doi:10.1001/jamaoncol.2019.2572

Zheng, H., Xiao, W. H., and Bennett, G. J. (2011). Functional deficits in peripheral nerve mitochondria in rats with paclitaxel- and oxaliplatin-evoked painful peripheral neuropathy. *Exp. Neurol.* 232 (2), 154–161. doi:10.1016/j.expneurol.2011.08.016

Zhou, L., Liu, R., Huang, D., Li, H., Ning, T., Zhang, L., et al. (2021). Monosialotetrahexosylganglioside in the treatment of chronic oxaliplatin-induced peripheral neurotoxicity: TJMUCH-GI-001, a randomised controlled trial. *EClinicalMedicine* 41, 101157. doi:10.1016/j.eclinm.2021.101157

Zimmermann, M., Li, T., Semrad, T. J., Wu, C. Y., Yu, A., Cimino, G., et al. (2020). Oxaliplatin-DNA adducts as predictive biomarkers of FOLFOX response in colorectal cancer: A potential treatment optimization strategy. *Mol. Cancer Ther.* 19 (4), 1070–1079. doi:10.1158/1535-7163.MCT-19-0133

Glossary

5-FU	Fluorouracil
APE1	Apyrimidinic endonuclease/redox factor-1
AUC	Exposure/area under the curve
CL	Clearance
Cmax	Maximum concentration
CR	Complete response
CRC	Colorectal cancer
CRT-CNCT	Chemoradiotherapy followed by consolidation chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTSS	Cathepsin S
DRG	Dorsal root ganglion
ePIPAC	Electrostatic PIPAC
FACT/ GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
GM1	Monosialotetrahexosylganglioside
GSH	Reduced glutathione
HAIC	Hepatic arterial infusion chemotherapy
HIPEC	Hyperthermic intraperitoneal chemotherapy
INCT-CRT	Induction chemotherapy followed by chemoradiotherapy
IV	Intravenous infusion
MATE	Multidrug and toxin extrusion
mCRC	Metastatic CRC
MRP2	Multidrug resistance-associated protein 2
NHE1	Na/H exchanger isoform-1
OCT	Organic cation transporter
OIPN	Oxaliplatin-induced peripheral neurotoxicity
PC	Peritoneal carcinomatosis
PD	Progressive disease
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
PR	Partial response
RBCs	Red blood cells
rCTR1	Rat copper transporter 1
ROS	Reactive oxygen species
SD	Stable disease
$t_{1/2}$	Half-life
TRP	Transient receptor potential
TRPM8	TRP melastatin 8
Vd	Apparent volume of distribution

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 August 2023
DOI 10.3389/fphar.2023.1200254

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Hitoshi Ando,
Kanazawa University, Japan
Bin Zhao,
Peking Union Medical College Hospital (CAMS), China

*CORRESPONDENCE
Jing Zhang,
3415340@zju.edu.cn

RECEIVED 04 April 2023
ACCEPTED 09 August 2023
PUBLISHED 17 August 2023

CITATION
Wu Y, Wei M and Zhang J (2023), A real-world pharmacovigilance analysis of FDA adverse event reporting system database for upadacitinib.
Front. Pharmacol. 14:1200254.
doi: 10.3389/fphar.2023.1200254

A real-world pharmacovigilance analysis of FDA adverse event reporting system database for upadacitinib

Yan Wu, Meihao Wei and Jing Zhang*

Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Objective: To mine the adverse drug event (ADE) signals of upadacitinib based on the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to provide a reference for the safe clinical use of the drug.

Methods: The ADE data for upadacitinib from Q1 2004 to Q1 2023 in the FAERS database were retrieved, and data mining was performed using the reporting odds ratio and proportional reporting ratio.

Results: A total of 21,213 ADE reports for the primary suspect drug upadacitinib were obtained, involving 444 ADEs. Patients aged ≥60 years (21.48%) and female (70.11%) patients were at a higher risk of ADEs with upadacitinib. After data cleaning, 182 ADE signals from 19 system organ classes (SOCs) were obtained. Six of these SOCs that occurred more frequently and were not mentioned in the drug labeling information included renal and urinary system (1.09%), reproductive and breast diseases (1.14%), ear and labyrinth disorders (0.57%), psychiatric disease (0.57%), blood and lymphatic system disorders (0.57%), and endocrine disorders (0.57%). The top ten most frequent ADE signals reported for upadacitinib were mainly related to: infections and infestations (7), investigations (2), and skin and subcutaneous tissue disorders (1). The top 10 ADEs in signal intensity ranking were lip neoplasm, ureteral neoplasm, eczema herpeticum, vulvar dysplasia, mediastinum neoplasm, eosinopenia, herpes zoster cutaneous disseminated, eye ulcer, acne cystic, and *Moraxella* infection. The top 10 high-frequency events leading to serious adverse events were urinary tract infection (2.74%), herpes zoster (1.63%), diverticulitis (1.19%), bronchitis (0.68%), nasopharyngitis (0.68%), localised infection (0.66%), nephrolithiasis (0.66%), pulmonary thrombosis (0.66%), blood cholesterol increased (0.55%), and *Pneumocystis jirovecii* pneumonia (0.53%).

Conclusion: Clinicians should be vigilant to upadacitinib-induced events in systems not covered in the drug labeling information and to new and highly signaled ADEs to ensure the safe and effective use of upadacitinib.

KEYWORDS

adverse event, FAERS database, upadacitinib, therapeutic drug monitoring, pharmacovigilance

1 Introduction

Janus kinase (JAK) inhibitors are small-molecule compounds that can block the signal transduction of the JAK/STAT (signal transducers and activators of transcription) signaling pathway (Clark et al., 2014). JAK inhibitors block the synthesis and secretion of various inflammatory factors, thus exerting anti-inflammatory and immunomodulatory effects (Xin et al., 2020). This finding provides an opportunity for treating primary immune deficiency diseases, hereditary autoimmune diseases, auto-inflammatory diseases, and hematological and oncological disorders (McInnes and Gravallese, 2021). Currently, upadacitinib has received much attention as the world's first highly selective JAK inhibitor. Upadacitinib was launched in the United States on August 16, 2019 and is approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis, atopic dermatitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis. The drug entered the Chinese market on February 24, 2022.

In addition to affecting pathogenic pathways, the JAK/STAT pathway is critical for normal signal transduction in the body (Banerjee et al., 2017). Therefore, while inhibiting the JAK/STAT pathway may alleviate certain inflammatory symptoms, it is also likely to inhibit the normal transmission of essential cytokines in the body (Clarke et al., 2021). In particular, when JAK inhibitors are unable to selectively inhibit specific disease-related signaling pathways, they will inevitably have an impact on overall cytokine expression in the body. Non-selective JAK inhibitors, such as tofacitinib, have been found to have a high incidence of adverse events such as infections, cardiovascular disease, tumors, and liver injury in clinical trials (Ytterberg et al., 2022). Upadacitinib selectively inhibits the JAK1 pathway, and the compound is 60 and 100 times more selective for JAK1 over JAK2 and JAK3, respectively, at the cellular level (Parmentier et al., 2018). Disinhibition of JAK2 may lead to thrombocytopenia and anemia, and disinhibition of JAK3 may lead to a lack of T and B cell activity, which can lead to immunodeficiency and infections (Choy, 2019).

However, the adverse effects of upadacitinib should not be ignored. In a systematic review and network meta-analysis, Lasa et al. (2022) found that upadacitinib ranked highest in adverse effects compared to other biologics and small molecules used to treat patients with moderate-to-severe ulcerative colitis. In recent years, more attention has been paid to the adverse effects of JAK inhibitors in terms of thrombosis (Setyawan et al., 2021; Dong et al., 2022). There is, however, a lack of data on other side effects of upadacitinib. To this end, we study aimed to analyze the real-world safety of upadacitinib by mining the latest data in the FDA Adverse Event Reporting System (FAERS) database.

2 Materials and methods

2.1 Data source

The data used in this study were obtained from the FAERS database, which has been open to the public since 2004 and collects adverse drug events (ADEs) from the world. The data are spontaneously reported by medical professionals, patients, and pharmaceutical companies from different regions, and are extremely voluminous and not limited by space and time, allowing for the early detection of ADE signals and providing a basis for the safe clinical use of drugs (Zhai et al., 2019). In this study, the FAERS database was accessed through the OpenVigil 2.1 data platform. This platform is a pharmacovigilance tool validated by scholars such as Bohm, University of Kiel, Germany (Bohm et al., 2016). Due to spontaneous reporting, the FAERS database has flaws like inadequate reporting data, irregular reporting, and duplicate reporting. In contrast, this platform only loads reports with complete case information from the FAERS database and performs subsequent cleaning, so the total number of ADE frequencies may be slightly less than that of the FAERS database. However, the quality of data and results based on this platform analysis is more reliable due to the exclusion of incomplete reports. This study was conducted using the FAERS database. "Upadacitinib", "Rinvoq", and "ABT-494" were used as search terms, choosing "primary suspect" as the drug role, and the search period was from Q1 2004 to Q1 2023.

2.2 Data mining and cleaning

Frequency methods were used to detect ADE signals of upadacitinib, including the reporting odds ratio (ROR) and proportional reporting ratio (PRR) in the proportional imbalance method. In this method, the target ADE occurrence ratio of the target drug is compared with that of all other drugs. If the target ADE occurrence ratio is greater than the set threshold, it is considered as imbalance, which indicates the generation of potential ADE signal. Both methods are based on the disproportionality fourfold table (Supplementary Table S1). The ROR value, PRR value, and the corresponding 95% confidence interval (95% CI) were calculated according to the formulae (Sakaeda et al., 2013; Bohm et al., 2021). The formulae and thresholds for the ROR and PRR methods are shown in Supplementary Table S2. ADEs that met both the above ROR and PRR signal requirements were included and analyzed in this study. The internationally used methods for signal mining of ADEs are proportional imbalance analysis, including the PRR method, ROR method, Bayesian Confidence Propagation Neural Network (BCPNN), and Gamma Poisson Shrinker (GPS) (Kubota et al., 2004). The frequency method is simple to calculate and highly sensitive, but the possibility of false positives is high when the number of adverse events is very small; the Bayesian method is stable, but the calculation is complex and the signal detection time is relatively lagging. Therefore, both the PRR method and the ROR method were used in this study to improve the sensitivity and specificity of ADE signal detection. The higher the ROR and PRR, the stronger the ADE signal and the stronger the statistical relationship between the target drug and the target ADE (Sakaeda et al., 2013).

OpenVigil 2.1 data platform cleanses two files based on demographic information and drug information, retaining only those cases where all drugs in the report are accurately identified. After removing the duplicate individual safety reports, to reduce the

10.3389/fphar.2023.1200254

TABLE 1 Basic information of upadacitinib ADE reports.

	N. Of reported ADEs	Ratio (%)
Gender		
Male	5043	23.77
Female	14872	70.11
Unknown	1298	6.12
Age group, (y)		
<18	89	0.42
18–59	4085	19.26
≥60	4557	21.48
Unknown	12482	58.84
Reported Countries		
United States	15134	71.34
Canada	779	3.67
Japan	393	1.85
Germany	383	1.81
Brazil	222	1.05

"indication bias", we screened excluded the indication-related signals and system organ classes (SOCs) not related to drug therapy, such as injury, poisoning, and procedural complications, product issues, surgical and medical procedures, and social circumstances.

2.3 Statistical analysis

The ADEs were categorized and described according to the preferred term (PT) and SOC in the International Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 (Tieu and Breder, 2018). R language version 4.2.1 and Microsoft Excel 2019 were used to process the data.

3 Results

3.1 Descriptive results

After data cleaning, a total of 21213 adverse drug event (ADE) reports for upadacitinib were retrieved from Q1 2004 to Q1 2023, and 444 ADE signals were detected. In terms of gender composition, the number of females (14872 cases) was higher than that of males (5043 cases). Excluding 58.84% of patients of unknown age, fewer than 1% of the patients were under the age of 18 (0.42%), 19.26% were between the ages of 18 and 59, and 21.48% were over the age of 60. Reports originated from 51 countries, among which the top five countries were the United States, Canada, Japan, Germany, and Brazil, accounting for 79.72% of the total reports. Basic information regarding ADE reports concerning upadacitinib is presented in Table 1.

3.2 ADE signals and organs involved in upadacitinib

Using the PRR and ROR methods, 444 ADE signals for upadacitinib were filtered according to the threshold value. After data cleaning, 182 signals remained, involving 19 SOCs, with a cumulative ADE frequency of 6100. The results showed that the SOCs with a high number of signals were infections and infestations (42.31%), neoplasms benign, malignant and unspecified (incl cysts and polyps) (9.89%), investigations (9.34%), and skin and subcutaneous tissue disorders (7.69%). Six of these SOCs identified were not mentioned in the drug labeling information for upadacitinib: renal and urinary system (1.09%), reproductive and breast diseases (1.14%), ear and labyrinth disorders (0.57%), psychiatric disease (0.57%), blood and lymphatic system disorders (0.57%), and endocrine disorders (0.57%).

3.3 ADE frequency of upadacitinib

Sorted by frequency, the top ten most frequent ADE signals reported for upadacitinib were mainly related to: infections and infestations (7), investigations (2), and skin and subcutaneous tissue disorders (1) as detailed in Table 2.

3.4 Signal strength of ADEs of upadacitinib

The 182 upadacitinib ADE signals obtained were analyzed using the PRR method and the ROR method. The results of sorting by the PRR and the ROR methods are consistent. The top ten ADEs in the signal intensity ranking were all closely correlated with upadacitinib: lip neoplasm, ureteral neoplasm, eczema herpeticum, vulvar dysplasia, mediastinum neoplasm, eosinopenia, herpes zoster cutaneous disseminated, eye ulcer, acne cystic, and *Moraxella* infection, as shown in Table 3. Except for unknown age, 92.3% of all malignancies occurred in older patients (≥53 years).

3.5 Signals of serious adverse events with upadacitinib

After removing ADEs that did not specify the outcome of the adverse event, the clinical outcomes were analyzed and the frequency of serious adverse event (SAE) signals leading to death, life-threatening events, hospitalization or prolongation of the patient's hospital stay, disability, and teratogenicity were collected and ranked. Overall, 22.2% of upadacitinib reports were associated with serious outcomes. The top ten most frequent occurrences were urinary tract infection (2.74%), herpes zoster (1.63%), diverticulitis (1.19%), bronchitis (0.68%), nasopharyngitis (0.68%), localised infection (0.66%), nephrolithiasis (0.66%), pulmonary thrombosis (0.66%), blood cholesterol increased (0.55%), and *Pneumocystis jirovecii* pneumonia (0.53%). Among them, nephrolithiasis (0.66%) was not mentioned in the drug labeling information.

TABLE 2 Top 10 ADE frequency of upadacitinib

PT	SOC	Frequency	PRR (χ2)	ROR (95%CI)
Nasopharyngitis	Infections and infestations	465	2.946 (597.479)	2.99 (2.727–3.278)
Urinary tract infection	Infections and infestations	439	3.016 (590.619)	3.058 (2.782–3.362)
Acne	Skin and subcutaneous tissue disorders	407	12.867 (4356.46)	13.099 (11.863–14.464)
Infection	Infections and infestations	304	2.446 (258.89)	2.467 (2.202–2.763)
Herpes zoster	Infections and infestations	304	5.858 (1211.036)	5.928 (5.291–6.643)
Sinusitis	Infections and infestations	278	3.166 (409.242)	3.194 (2.837–3.597)
Blood cholesterol increased	Investigations	189	3.919 (406.277)	3.945 (3.417–4.555)
Bronchitis	Infections and infestations	144	2.123 (84.351)	2.13
				(1.808–2.51)
Hepatic enzyme increased	Investigations	137	2.323 (101.801)	2.332
				(1.97–2.759)
Upper respiratory tract infection	Infections and infestations	133	3.305 (210.802)	3.32
				(2.798–3.939)

TABLE 3 Top 10 signal strength of ADEs of upadacitinib

PT	SOC	N.	PRR (χ2)	ROR (95%CI)
Lip neoplasm	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	47.631 (87.335)	47.637 (14.704–154.335)
Ureteral neoplasm	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	47.631 (87.335)	47.637 (14.704–154.335)
Eczema herpeticum	Infections and infestations	16	46.188 (615.686)	46.222 (27.795–76.864)
Vulvar dysplasia	Reproductive system and breast disorders	4	36.565 (99.037)	36.572 (13.329–100.346)
Mediastinum neoplasm	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	30.94 (83.555)	30.945 (11.328–84.532)
Eosinopenia	Blood and lymphatic system disorders	3	26.231 (47.657)	26.235 (8.257–83.356)
Herpes zoster cutaneous disseminated	Infections and infestations	4	20.985 (55.499)	20.989 (7.745–56.882)
Eye ulcer	Eye disorders	6	14.308 (60.112)	14.312 (6.369–32.162)
acne cystic	Skin and subcutaneous tissue disorders	19	13.696 (206.396)	13.707 (8.697–21.603)
Moraxella infection	Infections and infestations	3	13.116 (22.057)	13.117 (4.179–41.176)

4 Discussion

This study discovered that there were more ADE reports from female patients than from male patients for upadacitinib (14,872 and 5,043,respectively). Hunter T M et al. found a 1:4 ratio of the incidence of male-to-female patients with RA in the United States (Hunter et al., 2017), consistent with our findings with the ratio of ADE reports. In terms of age, the frequency of adverse reactions was higher in older individuals (≥60 years). Approximately 45% of the patients with RA are older than 65 years (Hunter et al., 2017), which is a patient group that may be associated with an increased risk of serious infections (Peng et al., 2020).

In this study, 182 signals involving 19 SOCs were mined. SOCs with a higher frequency of occurrence and more signals mainly focus on infections and infestations, investigations, neoplasms benign, malignant and unspecified (incl cysts and polyps), gastrointestinal disorders, vascular disorders, pneumonia, infection, herpes zoster, sinusitis, thrombosis, localised infection, and skin cancer. These ADEs are frequently reported, and are stated in the drug labeling information. Specific ADEs mentioned in the instructions, such as severe infection, tuberculosis, opportunistic infection, malignancy, gastrointestinal perforation, thrombosis, elevated hepatic transaminases, elevated lipids, and anemia were all detected in this study, which further verified the reliability of the current study.

It can be seen from the results of this study that most ADEs were concentrated in the infections and infestations SOC, both in terms of signal percentage (42.13%), frequency of occurrence (55.62%), and leading to SAEs, which is consistent with the results of previous safety trials of upadacitinib (Sandborn et al.,

2020; McInnes et al., 2021; Reich et al., 2021). McInnes et al. (2021) found that the incidence of infection with upadacitinib was 39.4%–43.3%, and in this study, the real-world incidence of infection slightly higher than in clinical trials, which may be related to real-world patient diversity. Urinary tract infections, which were the second most frequently reported, have been reported in a previous phase III clinical trial report (Cohen et al., 2021). The sites of infection were not specified in the infections section in the drug labeling information.

In addition to common ADEs, data from this study uncovered renal and urinary system, reproductive and breast diseases, ear and labyrinth disorders, psychiatric disease, blood and lymphatic system disorders, and endocrine disorders. Such ADEs not mentioned in the drug labeling information, warranting further study to determine the causal relationship between ADEs and the drug. In the top 10 ranking of upadacitinib ADEs in terms of signal strength, both tumors and infections had strong signal intensities, suggesting a high correlation. Inhibition of the JAK/STAT pathway leads to loss of immune cell function, which induces malignancy. Except for unknown age, 92.3% of all malignancies occurred in older patients (≥53 years), consistent with clinical trial results (Fleischmann et al., 2022). Older patients need more attention for tumorigenesis. Among the top ten signals leading to serious adverse reactions, nephrolithiasis was not mentioned in the drug labeling information. Liang et al. (2019) found that some long-noncoding RNAs (lncRNA), microRNAs (miRNA), and messenger RNAs (mRNA) in the urine of patients with kidney stones were significantly different from those of normal subjects. These RNAs play a key role in the JAK/STAT pathway, which may be potentially related to kidney stones. As upadacitinib has only been on the market for a short time, no case reports or studies of these ADE-related adverse reactions exist, however, a total of 31 such ADE reports can be found in the FAERS database. We believe that the present study provides additional information for clinical practice and suggests that physicians should be highly vigilant to the possibility of such ADEs as early as possible.

This study had some limitations: 1) due to upadacitinib only being approved for use for a relatively short time and considering that the FAERS database is spontaneously presented, there may be problems of missing reports and under-reporting of ADEs, resulting in a bias in the results of signal analysis; 2) the FAERS database does not provide the baseline conditions of patients, in terms of preexisting conditions and liver and kidney function, so it is impossible to determine the influence of these factors on the occurrence of ADE; 3) OpenVigil 2.1 data platform does not grab the information about the reporter from the FAERS database, and our results would have been more complete if this part of the information had been made available; 4) the ROR and PRR methods can only indicate the existence of a statistical correlation between the target drug and the target ADE and cannot indicate the causal relationship between them. The ADE signals that differ from the drug labeling information obtained in this study need to be further explored by reviewing new clinical data and research methods.

5 Conclusion

In conclusion, this study used the OpenVigil 2.1 data platform based on the FAERS database to mine the ADE signals of upadacitinib, eliminate incomplete information, and make the data analysis completer and more reliable, which can provide a reference for the safe use of upadacitinib in patients. Clinicians should be vigilant to the possibility of new ADEs identified in this study that are not detailed in the drug labeling information. Safety monitoring should be reinforced to effectively reduce the incidence of upadacitinib-related ADEs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

JZ designed the study. YW contributed to the data acquisition, analyses, and drafting of the manuscript. MW contributed to data acquisition and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Zhejiang Medical and Health Science and Technology project grant 2022KY839.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1200254/full#supplementary-material

References

Banerjee, S., Biehl, A., Gadina, M., Hasni, S., and Schwartz, D. M. (2017). JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *J. Drugs* 77 (5), 521–546. doi:10.1007/s40265-017-0701-9

Bohm, R., Bulin, C., Waetzig, V., Cascorbi, I., Klein, H. J., and Herdegen, T. (2021). Pharmacovigilance-based drug repurposing: the search for inverse signals via OpenVigil identifies putative drugs against viral respiratory infections. *Br. J. Clin. Pharmacol.* 87 (11), 4421–4431. doi:10.1111/bcp.14868

Bohm, R., von Hehn, L., Herdegen, T., Klein, H. J., Bruhn, O., Petri, H., et al. (2016). OpenVigil FDA - inspection of U.S. American adverse drug events pharmacovigilance data and novel clinical applications. *PLoS One* 11 (6), e0157753. doi:10.1371/journal.pone.0157753

Choy, E. H. (2019). Clinical significance of Janus Kinase inhibitor selectivity. *Rheumatol. Oxf.* 58 (6), 953–962. doi:10.1093/rheumatology/key339

Clark, J. D., Flanagan, M. E., and Telliez, J. B. (2014). Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J. Med. Chem.* 57 (12), 5023–5038. doi:10.1021/jm401490p

Clarke, B., Yates, M., Adas, M., Bechman, K., and Galloway, J. (2021). The safety of JAK-1 inhibitors. *Rheumatol. Oxf.* 60 (2), ii24–ii30. doi:10.1093/rheumatology/keaa895

Cohen, S. B., van Vollenhoven, R. F., Winthrop, K. L., Zerbini, C. A. F., Tanaka, Y., Bessette, L., et al. (2021). Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann. Rheum. Dis.* 80 (3), 304–311. doi:10.1136/annrheumdis-2020-218510

Dong, Z., Ye, X., Chen, C., Wang, R., Liu, D., Xu, X., et al. (2022). Thromboembolic events in janus kinase inhibitors: A pharmacovigilance study from 2012 to 2021 based on the Food and drug administration's adverse event reporting system. *Br. J. Clin. Pharmacol.* 88 (9), 4180–4190. doi:10.1111/bcp.15361

Fleischmann, R., Mysler, E., Bessette, L., Peterfy, C. G., Durez, P., Tanaka, Y., et al. (2022). Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. *RMD Open* 8 (1), e002012. doi:10.1136/rmdopen-2021-002012

Hunter, T. M., Boytsov, N. N., Zhang, X., Schroeder, K., Michaud, K., and Araujo, A. B. (2017). Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. *Rheumatol. Int.* 37 (9), 1551–1557. doi:10.1007/s00296-017-3726-1

Kubota, K., Koide, D., and Hirai, T. (2004). Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiol Drug Saf.* 13 (6), 387–394. doi:10.1002/pds.964

Lasa, J. S., Olivera, P. A., Danese, S., and Peyrin-Biroulet, L. (2022). Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: A systematic review and network meta-analysis. *Lancet Gastroenterol. Hepatol.* 7 (2), 161–170. doi:10.1016/S2468-1253(21)00377-0

Liang, X., Lai, Y., Wu, W., Chen, D., Zhong, F., Huang, J., et al. (2019). LncRNA-miRNA-mRNA expression variation profile in the urine of calcium oxalate stone patients. *BMC Med. Genomics* 12 (1), 57. doi:10.1186/s12920-019-0502-y

McInnes, I. B., Anderson, J. K., Magrey, M., Merola, J. F., Liu, Y., Kishimoto, M., et al. (2021). Trial of upadacitinib and adalimumab for psoriatic arthritis. *N. Engl. J. Med.* 384 (13), 1227–1239. doi:10.1056/NEJMoa2022516

McInnes, I. B., and Gravallese, E. M. (2021). Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat. Rev. Immunol.* 21 (10), 680–686. doi:10.1038/s41577-021-00603-1

Parmentier, J. M., Voss, J., Graff, C., Schwartz, A., Argiriadi, M., Friedman, M., et al. (2018). *In vitro* and *in vivo* characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol.* 2, 23. doi:10.1186/s41927-018-0031-x

Peng, L., Xiao, K., Ottaviani, S., Stebbing, J., and Wang, Y. J. (2020). A real-world disproportionality analysis of FDA Adverse Event Reporting System (FAERS) events for baricitinib. *Expert Opin. Drug Saf.* 19 (11), 1505–1511. doi:10.1080/14740338.2020.1799975

Reich, K., Teixeira, H. D., de Bruin-Weller, M., Bieber, T., Soong, W., Kabashima, K., et al. (2021). Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 397 (10290), 2169–2181. doi:10.1016/S0140-6736(21)00589-4

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Sandborn, W. J., Ghosh, S., Panes, J., Schreiber, S., D'Haens, G., Tanida, S., et al. (2020). Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. *Gastroenterology* 158 (8), 2139–2149. doi:10.1053/j.gastro.2020.02.030

Setyawan, J., Azimi, N., Strand, V., Yarur, A., and Fridman, M. (2021). Reporting of thromboembolic events with JAK inhibitors: analysis of the FAERS database 2010-2019. *Drug Saf.* 44 (8), 889–897. doi:10.1007/s40264-021-01082-y

Tieu, C., and Breder, C. D. (2018). A critical evaluation of safety signal analysis using algorithmic standardised MedDRA queries. *Drug Saf.* 41 (12), 1375–1385. doi:10.1007/s40264-018-0706-7

Xin, P., Xu, X., Deng, C., Liu, S., Wang, Y., Zhou, X., et al. (2020). The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int. Immunopharmacol.* 80, 106210. doi:10.1016/j.intimp.2020.106210

Ytterberg, S. R., Bhatt, D. L., Mikuls, T. R., Koch, G. G., Fleischmann, R., Rivas, J. L., et al. (2022). Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N. Engl. J. Med.* 386 (4), 316–326. doi:10.1056/NEJMoa2109927

Zhai, Y., Ye, X., Hu, F., Xu, J., Guo, X., Zhuang, Y., et al. (2019). Endocrine toxicity of immune checkpoint inhibitors: A real-world study leveraging US Food and drug administration adverse events reporting system. *J. Immunother. Cancer* 7 (1), 286. doi:10.1186/s40425-019-0754-2

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 August 2023
DOI 10.3389/fphar.2023.1205062

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Yuzheng Zhuge,
Nanjing Drum Tower Hospital, China
Ning Zhang,
Fudan University, China

*CORRESPONDENCE
Liu Xiao-Dong,
liuxd@sj-hospital.org

RECEIVED 13 April 2023
ACCEPTED 11 August 2023
PUBLISHED 24 August 2023

CITATION
Jing-Lun Z, Shuang C, Li-Mei Z and Xiao-Dong L (2023), YKL-40 promotes chemokine expression following drug-induced liver injury via TF-PAR1 pathway in mice.
Front. Pharmacol. 14:1205062.
doi: 10.3389/fphar.2023.1205062

YKL-40 promotes chemokine expression following drug-induced liver injury via TF-PAR1 pathway in mice

Zhan Jing-Lun[1,2], Chai Shuang[1,2], Zhao Li-Mei[1,2] and Liu Xiao-Dong[1,2]*

[1]Department of Pharmacy, Shengjing Hospital of China Medical University, Shenyan, China, [2]Department of the Second Clinical Pharmacy, School of Pharmacy, China Medical University, Shenyang, China

Background: The inflammatory factor YKL-40 is associated with various inflammatory diseases and is key to remodeling inflammatory cells and tissues. YKL-40 (Chi3l1) promotes the activation of tissue factor (TF), leading to intrahepatic vascular coagulation (IAOC) and liver injury. TF is a key promoter of the exogenous coagulation cascade and is also involved in several signaling involving cell proliferation, apoptosis, charring, migration and inflammatory diseases pathways. However, the effect of YKL-40-induced TF-PAR1 pathway on the expression of downstream chemokines remains unknown.

Methods: We established a liver injury model using Concanavalin A (ConA) in C57 BL/6 mice. By adopting various experimental techniques, the effect of YKL-40 induced TF-PAR1 pathway on the expression of downstream chemokine ligand 2 (CCL2) and IP-10 was verified.

Results: We found that overexpression of YKL-40 increased the expression of TF, protease-activated receptor 1 (PAR1), CCL2 and IP-10 in mice and exacerbated the severity of liver injury. However, blocking the expression of TF significantly reversed the extent of liver injury.

Conclusion: We found that YKL-40 promotes the expression of downstream chemokines ligand 2 (CCL2) and IP-10 by activating the TF-PAR1 pathway, leading to increased recruitment of inflammatory cells and exacerbating the progression of liver injury. This provides a new approach for the clinical treatment of drug-induced liver injury.

KEYWORDS

YKL-40, TF-PAR1 pathway, inflammation, liver injury, CCL2, IP-10

Abbreviations: TF, Tissue factor; IAOC, intrahepatic vascular coagulation; ConA, concanavalin A; PAR1, protein kinase 1; Chi3l1, inflammatory factor YKL-40; DILI, drug-induced liver injury; CCL2, Chemokine ligand 2; HCV, Hepatitis C.

1 Introduction

Drug-induced liver injury (DILI) is the primary cause of acute liver failure and poor outcomes of transplantation. The annual incidence rate of DILI has increased recently, outpacing fatty liver disease and viral hepatitis (Katarey and Verma, 2016). Several studies have revealed that intrahepatic vascular coagulation (IAOC) is a major cause of the onset and progression of liver fibrosis, cirrhosis, and liver cancer (Ganey et al., 2007; Sullivan et al., 2013; Miyakawa et al., 2015), and the inflammatory factor YKL-40 (Chi3l1) is associated with various inflammatory diseases. YKL-40 levels are increased to varying degrees in infectious diseases, such as respiratory, kidney, liver, cardiovascular, and skin inflammatory diseases (Montgomery et al., 2017; Ma et al., 2018; Shan et al., 2018; Arain et al., 2020; Ebrahim et al., 2020), and it has diagnostic as well as prognostic value as an inflammatory marker.

YKL-40 is a member of the 18-glycosyl hydrolase family without chitinase activity. It is expressed in several cells, including megaphage/monocytes, neutrophils, fibroblasts, vascular smooth muscle cells, and chondrocytes (Johansen, 2006; Lee et al., 2011). Overexpression of YKL-40 is linked to the pathogenesis and prognosis of several inflammatory diseases. YKL-40 affects angiogenic activity, inflammatory microenvironment, and epithelial-mesenchymal transformation, by promoting the release of inflammatory factors, resulting in the activation of corresponding signal transduction pathways (Montgomery et al., 2017; Ma et al., 2018; Shan et al., 2018; Arain et al., 2020; Ebrahim et al., 2020). Studies in murine model of concanavalin (ConA)-induced liver injury have revealed that YKL-40 (Chi3l1) promotes the activation of tissue factor (TF), thereby inducing IAOC and eventually leading to liver injury (Shan et al., 2018). However, the mechanism underlying TF-mediated activation of IAOC that exacerbates liver disease is not fully understood.

Coagulation dysfunction caused by liver injury is frequently associated with upregulated TF expression (Hisada et al., 2016; Henderson et al., 2021). The dysregulated coagulation cascade has been the main pathophysiological manifestation of TF activation. Furthermore, TF activity impacts procoagulant events and inflammatory non-coagulation signaling pathways transmitted through specific receptors, such as PARs (protease-activated receptors) pathway. During an inflammatory disease, inflammatory factors induce TF release into the blood, where it causes coagulation cascade reaction, forming a vicious circle of "coagulation-inflammation network," exacerbating the disease (Witkowski et al., 2016). The histological grade of the illness and the TF levels are strongly correlated. The elevated TF expression significantly impacts patient prognosis and survival rate. Mounting evidence suggests that the TF-PARs pathway can promote the progression of inflammatory diseases, cancer, and other diseases. However, the specific mechanism underlying TF-PARs pathway and its target recognition remain largely unknown. Protein kinase 1 (PAR1), PAR2, PAR3, and PAR4 are members of the PARs family and TF affects cell proliferation, apoptosis, scorching, migration, and the onset and development of inflammatory diseases through the TF-PAR1 pathway (Reinhardt et al., 2012; Feng et al., 2020).

Chemokines play an important role in the pathophysiology of autoimmune hepatitis, development of liver inflammation, and subsequent wound healing response. Chemokines regulate the movement and activity of liver cells including Kupffer cells and hepatic stellate cells, endothelial cells, and circulating immune cells and guide the movement and positioning of inflammatory and immune cells in the liver (Zimmermann and Tacke, 2011). Studies have revealed that hepatitis is directly related to abnormal chemokine production (Fahey et al., 2014). Chemokine ligand 2 (CCL2) and chemokine IP-10 (also known as CXCL10) are inflammatory chemokines that play a key role in recruiting neutrophils and promoting the secretion of various other cytokines, thereby aggravating disease occurrence and progression (Mascia et al., 2017; Tacke, 2017). Notably, CCL2 is one of the chemokines involved in liver fibrosis. Chronic chemokine production may result in a continuous assemblage of inflammatory cells in the liver, causing persistent inflammation and liver damage (Kang and Shin, 2011).

Here, we used a mouse model of ConA-induced liver injury to investigate how YKL-40 promotes TF activation and influences the occurrence and progression of DILI. We show that YKL-40 promotes the expression of CCL2 and IP-10 by inducing the TF-PAR1 pathway in the liver, leading to an increase in inflammatory cell recruitment, thus sparking the onset and progression of liver injury. Furthermore, TF and PAR1 expression levels positively correlated with YKL-40 expression levels following the ConA induction in our study. Thus, YKL-40 is the potential key upstream effector of the TF-PAR1 pathway and promotes the progression of liver injury.

2 Materials and methods

2.1 Animal experiments

Male C57/BL6 mice (8–12 weeks old) were used in the study. Mice were obtained from Beijing Huafukang Biotechnology Co., Ltd. (Beijing, China) and housed in a temperature-and light-controlled laboratory with *ad libitum* access to food and water. Animal experiments were carried out in accordance with the national standard of the People's Republic of China, Guidelines for Ethical Review of Laboratory Animal Welfare (GB/T35892-

Gene	Primer sequences
TF	Forward:AACCCACCAACTATACCTACACT
	Reverse:GTCTGTGAGGTCGCACTCG
PAR1	Forward:GGCGCTTGCTGATCGTC
	Rreverse:CGTAGCATCTGTCCTCTCTGA
CCL2/MCP-1	Forward:TTAAAAACCTGGACTGGAACCAA
	Reverse:GCATTAGCTTCAGATTTACGGGT
CXCL10/IP-10	Forward:TGAATCCGGAATCTAAGACCATCAA
	Reverse:AGGACTAGCCATCCACTGGGTAAAG
GAPDH	Forward:GCTACACTGAGGACCAGGTTGTC
	Reverse:AGCCGTATTCATTGTCATACCAGG

2018) and the guidelines of the Animal Protection and Use Committee of China Medical University. Briefly, C57/BL6 mice were divided into 4 experimental groups. To establish a mouse model of DILI, 15 mg/kg ConA (Solarbio, C8110) was injected into the tail vein of mice. In the experimental groups, mice were immediately injected with recombinant Chi3l1 (500 ng, Sino Biological, 50929-M08H), anti-Chi3l1 antibody (500 ng, Sino Biological, 50929-RP01), or anti-TF antibody (1/1,000, 500 μg, Bioss, bs-4690R) after receiving ConA (Shan et al., 2018). Finally, mice were anesthetized with phenobarbital, their livers were collected, and subjected to further analysis.

2.2 ELISA

The experiment was performed using a mouse YKL-40 ELISA kit (Shanghai Shuangying Biotechnology Co., Ltd., SY-M06, 294, China) per manufacturer's protocol.

2.3 Real-time PCR

RIPA lysis buffer (TransGen Biotech, AU341, China) was used to extract RNA from real-time PCR. Quantitative real-time PCR was used to analyze gene expression using QuantiStudio 1. The following primers were used.

2.4 Western blot analysis

We weighed liver tissues and extracted the protein according to the standard protocol. Protein samples were resolved by performing SDS-polyacrylamide gel electrophoresis and transferred to a membrane. The membrane was then blocked with a rapid blocking solution and incubated with the specific primary antibodies against TF (Bioss, bs-4690R, 1/1,000), PAR1 (Solarbio, K009690P, 1/1,500), CCL2/MCP-1 (ProteinTech, 25542-1-AP, 1/2,000), and CXCL10/IP-10 (ProteinTech, 10937-1-AP, 1/500). GAPDH (ProteinTech, 10494-1-AP, 1/6000) was used as the control. This was followed by incubation with the secondary antibody (goat anti-rabbit IgG (H+L); ProteinTech, SA00001-2, 1:6,000). Finally, immunoreactive bands were visualized using a chemiluminescent solution and chemiluminescence imaging system. The immunoreactive bands were quantified using ImageJ software.

2.5 Immunohistochemical (IHC) staining

Liver tissue samples were fixed in 4% paraformaldehyde, embedded in paraffin (KEDEE,KD-BM,China), and sectioned (HistoCore AUTOCUT, China). Slice thickness is 5 um. The primary antibodies against TF (ProteinTech, 17435-1-AP, 1: 3,000), PAR1 (Solarbio, K009690P, 1/1500), CCL2/MCP-1 (ProteinTech, 25542-1-AP, 1/2000), and CXCL10/IP-10 (ProteinTech, 10937-1-AP, 1/500) were used and signals were quantified.

2.6 Hematoxylin & eosin (H&E) staining

The embedded liver tissue sections were dewaxed and stained with H&E staining kit (Solarbio, G1120, China). The slices were stained with eosin for 1 min and after 10 min of hematoxylin staining, they were subjected to 1 min of differentiation using the differentiation solution. The slices were then dried in a series of graded alcohol and treated with xylene twice for 1 min each. The slides were sealed with neutral gum and examined under a microscope.

2.7 Statistical analysis

The data is presented as the mean ± SEM. GraphPad Prism (GraphPad Software) was used for statistical analysis. The unpaired Student's t-test was used to evaluate the differences between the two groups. A one-way analysis of variance was used to examine the results from several groups. Results with $p < 0.05$ were considered statistically significant.

3 Results

3.1 YKL-40 exacerbates the progression of liver injury

Firstly, we induced high and low expression of YKL40 to elucidate the relationship between YKL-40 expression and the course of drug-related liver injury, and further clarify the degree of liver injury in each experimental group. We use ELISA and HE staining techniques. The ELISA results showed that after ConA induction, TF and PAR1 levels were positively correlated with YKL-40 levels (Figure 1A). Then, we examined the tissue damage at the histological level. It should be noted that in Con group, complete Lobules of liver structure was shown in HE staining. On the contrary, in ConA group, the structure of Lobules of liver was destroyed and disordered, and Vasodilation was observed, there was obvious red blood cell sludge in hepatic sinuses, liver edema, especially in the portal vein area, and a large number of lymphocytes. More importantly, more serious liver injury was observed in the YKL-40 overexpression group, which was manifested as structural destruction of the Lobules of liver, large and deeply stained liver nuclei, dual nuclei, diffuse cytoplasm, obvious inflammation in the portal vein area, liver edema, and severe congestion of the hepatic sinuses around the central vein with patchy or lamellar necrosis. On the contrary, when YKL-40 is low expressed, Lobules of liver structure damage, hepatic cord disorder and hepatic tissue congestion are relatively less (Figures 1B,C). In summary, it can be seen that the degree of liver injury often increases with the increase of YKL-40 expression.

3.2 YKL-40 induces TF-PAR1 pathway and promotes CCL2 and IP-10 expression

PAR1 is the main receptor for thrombin, closely related to TF expression, and involved in liver inflammation and fibrosis (Gutiérrez-Rodríguez and Herranz, 2015; Flaumenhaft and De

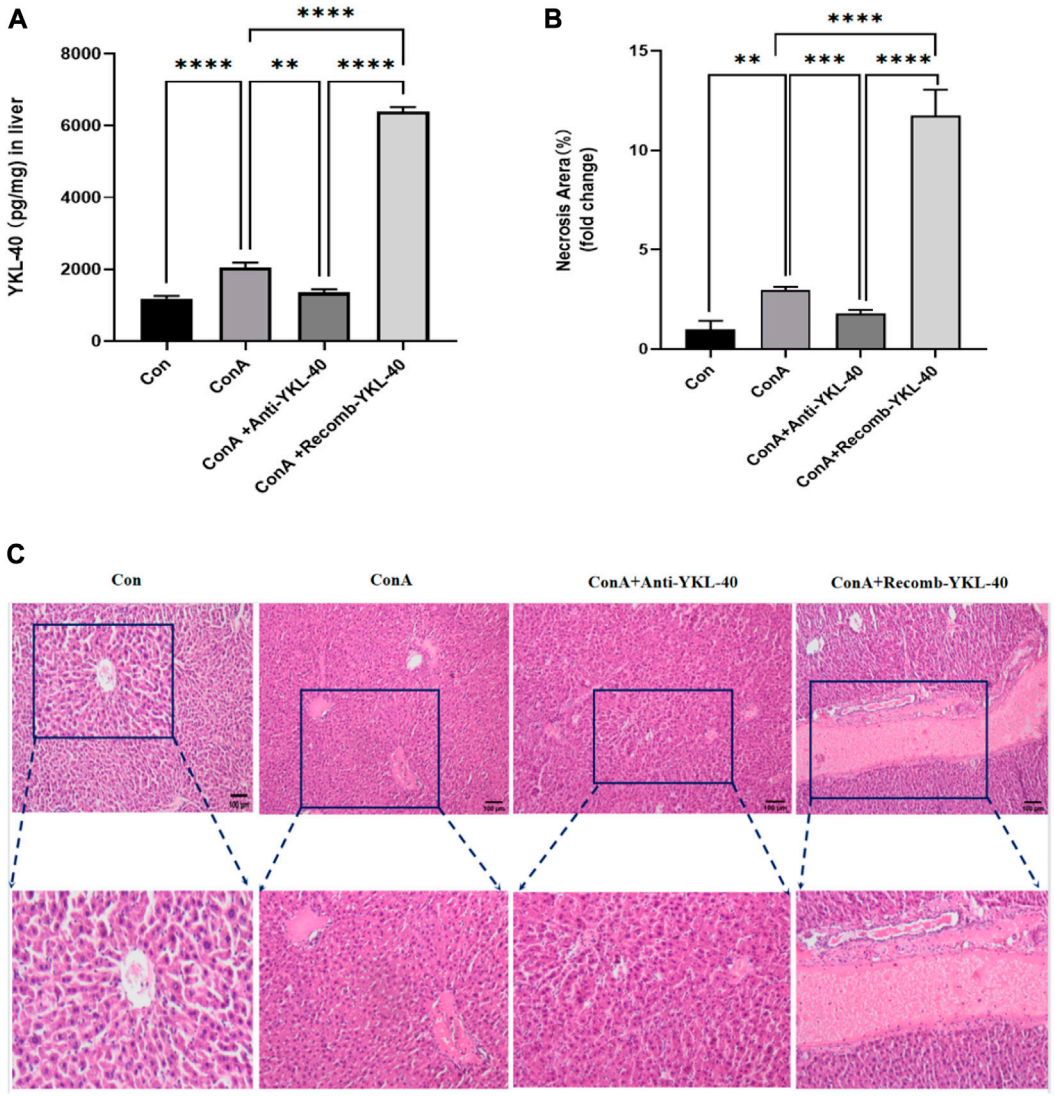


FIGURE 1
YKL-40 exacerbates the progression of liver injury. **(A)** The expression of YKL40 in liver tissue; **(B)** Hematoxylin and Eosin staining (magnification×100) showing YKL-40-mediated induction of TF-PAR1 pathway and aggravation of drug-induced liver injury. **(C)** Necrotic areas as quantified by ImageJ software. Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

Ceunynck, 2017). Thrombin activates PAR1 in endothelial cells, upregulates adhesion molecules on the surface of endothelial cells, and promotes the production of cytokines and chemokines, thus activating neutrophils and Monocyte. Our real-time PCR data shows that an increase in TF, PAR1, CCL2, and IP-10 levels is associated with an increase in YKL-40 expression level (Figures 2A–D). The results of immunoblotting are consistent with these findings (Figure 3).

3.3 YKL-40-mediated induction of TF-PAR1 pathway aggravates DILI progression

CCL2 is involved in the pathogenesis of many liver diseases, such as hepatitis, fibrosis, and cancer. Research has found that the PAR1 signaling pathway affects the expression of CCL2, which in turn promotes the recruitment of neutrophils in inflammatory diseases. In severe acute hepatitis mice that experience necrotizing inflammation and acute Liver failure, IP-10 may be important for lymphocyte recruitment (Reiberger et al., 2008). Here, we conducted histological examination to investigate the role of YKL-40 mediated TF-PAR1 pathway in the progression of DILI. Immunohistochemical and other experimental results showed that the expression of TF, PAR1, CCL2, and IP-10 in the liver of drug-induced liver injury mice in the ConA group was higher than that in the untreated group and the YKL-40 low expression group. However, when YKL-40 was overexpressed, the expression was significantly higher than the other three groups. Therefore, YKL-40 induces the TF-PAR1 pathway, significantly increasing the expression of downstream chemokines CCL2 and IP-10 (Figure 4).

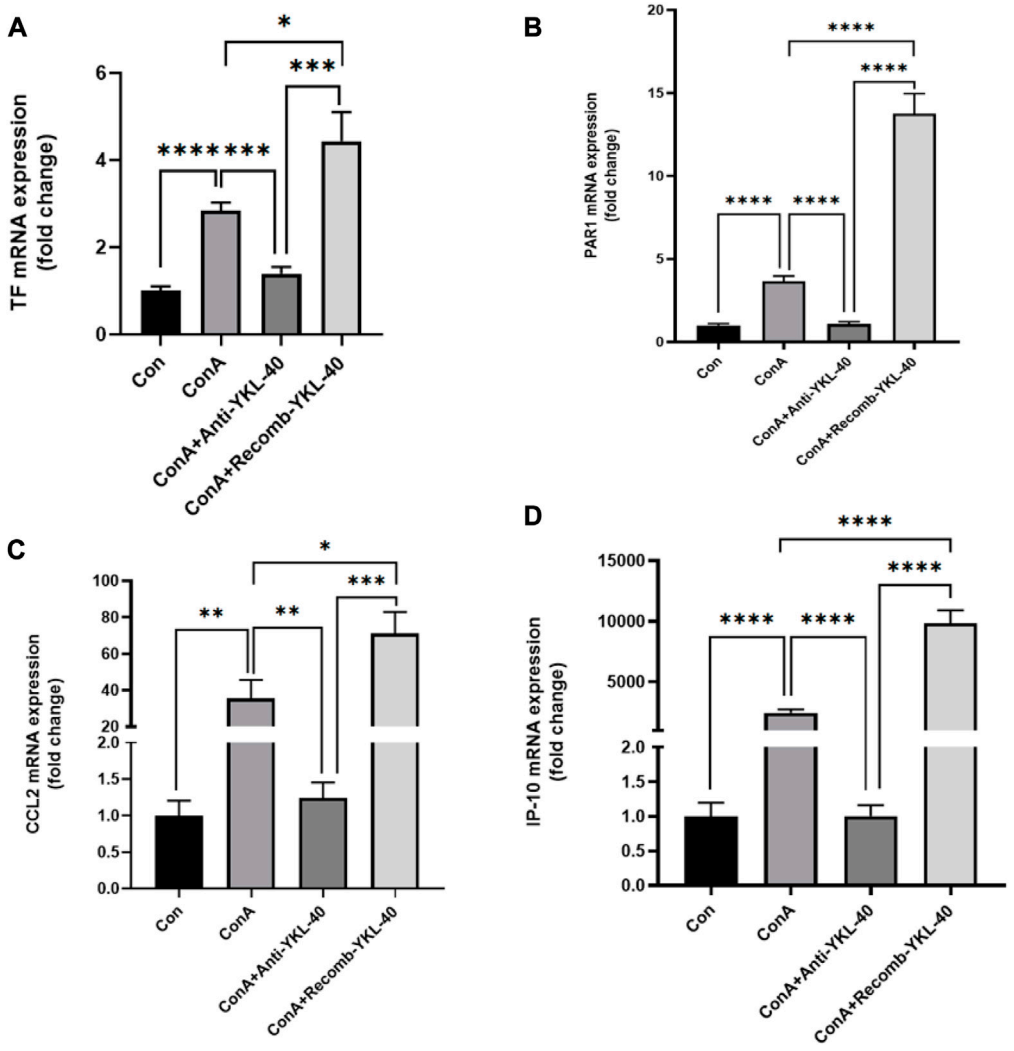


FIGURE 2
YKL-40 induces TF-PAR1 pathway, promoting the expression of chemokines CCL2 and IP10. **(A)** TF mRNA expression in mouse liver; **(B)** PAR1 mRNA expression in mouse liver; **(C)** CCL2 mRNA expression in mouse liver; **(D)** IP-10 mRNA expression in mouse liver. *p* values were determined using one-way ANOVA or an unpaired *t*-test. Data are expressed as mean ± SEM (n = 6). $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, ns means no statistical difference.

3.4 YKL-40-mediated TF-PAR1 pathway can effectively alleviate the progression of DILI after being blocked

To investigate the effect of the TF-PAR1 pathway on the expression of CCL2 and IP-10, we used anti TF antibodies to inhibit endogenous TF proteins. Use ELISA to detect the expression of YKL-40 in each group. Research has found that when the TF-PAR1 pathway is blocked, there is no statistically significant difference in the expression of YKL-40 compared to the drug-induced liver injury group caused by ConA. It is worth noting that even in the medium, the expression of YKL-40 was not affected and remained in a high expression state ($p < 0.001$), indicating that YKL-40 acts as an upstream of the TF-PAR1 pathway and is not affected by blocking the TF-PAR1 pathway (Figure 5A). Then, we used H&E stain to explore and study the histological examination method. The results showed that the structure of Lobules of liver in Con group was intact; In ConA group, the structure of Lobules of liver was damaged, hepatic cord was disordered, hepatocytes were edematous, and there was obvious red cell sludge and inflammatory cell infiltration in hepatic sinuses; In the liver tissue of ConA+Anti TF and ConA+RecombYKL-40+Anti TF groups, the structure of Lobules of liver was slightly damaged, the arrangement of hepatic cords was slightly disordered, a small amount of congestion was found in the liver tissue, and the hepatic sinuses around the central vein were congested (Figures 5B,C). In summary, blocking TF expression can effectively alleviate the progression of DILI.

3.5 YKL-40-mediated induction of TF-PAR1 pathway affects the course of DILI by regulating TF expression

When TF was blocked, even with high expression of YKL-40, the mRNA levels of TF, PAR1, CCL2, and IP-10 did not show significant differences compared to untreated normal mice.

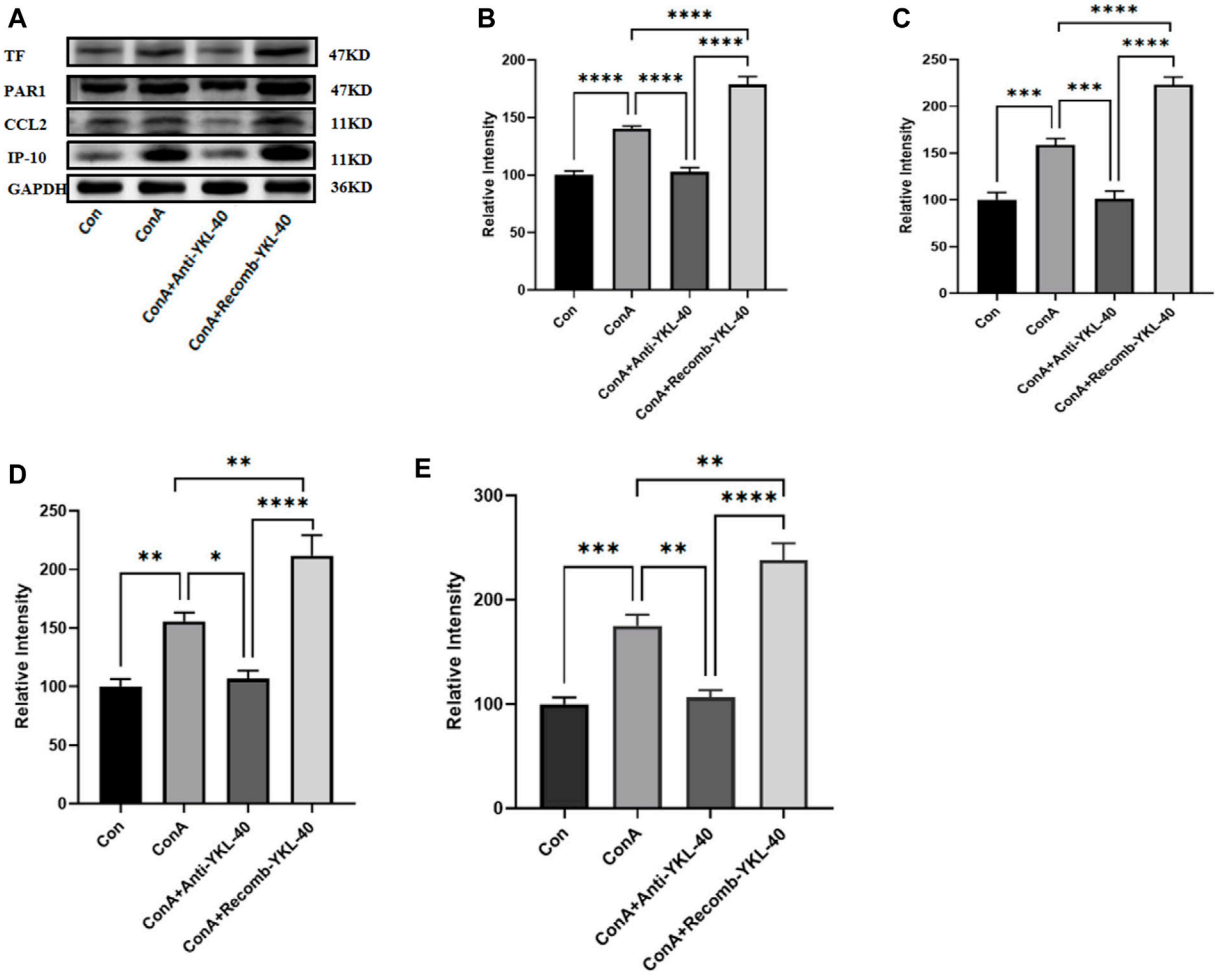


FIGURE 3
YKL-40 induces TF-PAR1 pathway and affects liver pathogenesis. **(A)** The levels of TF-PAR1 pathway proteins induced by YKL-40 in the liver and CCL2 and IP-10 were measured; **(B)** TF protein expression in mouse liver; **(C)** PAR1 protein expression in mouse liver; **(D)** CCL2 protein expression in mouse liver; **(E)** IP-10 protein expression in mouse liver. *p* values were determined using one-way ANOVA or an unpaired t-test. Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

However, the mRNA levels of TF, PAR1, CCL2, and IP-10 in the drug-induced liver injury group mice induced by ConA were significantly higher than those in the other three groups (Figure 6). The results of protein expression analysis are consistent with those of mRNA expression analysis (Figure 7). In summary, these findings suggest that blocking the TF-PAR1 pathway inhibits the release of downstream chemokines CCL2 and IP-10 mediated by YKL-40, thereby affecting the process of DILI.

3.6 Blocking TF-PAR1 pathway alleviates DILI progression

Inflammation and coagulopathy have been linked in several systemic inflammatory diseases such as sepsis and acute respiratory infections. Interleukin-1 (IL-1), IL-6, C-reactive protein and other inflammatory mediators stimulate TF expression on the surface of endothelial cells under inflammatory conditions such as sepsis and acute lung injury, leading to hypercoagulability (Abraham, 2000; Lou et al., 2019). At the same time, TF acts on endothelial cells via the PAR1 pathway to produce pro-inflammatory effects (Chen et al., 2004; Lou et al., 2019). Thus, highly expressed TF can play a dual role in promoting inflammation and coagulation. To verify whether inhibition of the TF-PAR1 pathway could inhibit the YKL-40-induced inflammatory immune response and attenuate the extent of liver injury in DILI by blocking the expression of downstream chemokines CCL2 and IP-10, we injected anti-TF antibodies in the model group and the corresponding YKL-40 high expression group blocked the expression of endogenous TF protein, and further histological examination was performed. Compared to the control group, blocking TF expression did not result in significantly increased expression of TF, PAR1, CCL2, and IP-10 even when YKL-40 was overexpressed; the model group (ConA group) had higher expression levels of all four markers in the liver than the other two groups that blocked TF and the control group (Figure 8). In conclusion, these findings suggest that blocking TF expression suppresses YKL-40-mediated expression of CCL2 and IP-10 through inhibition of the TF-PAR1 pathway.

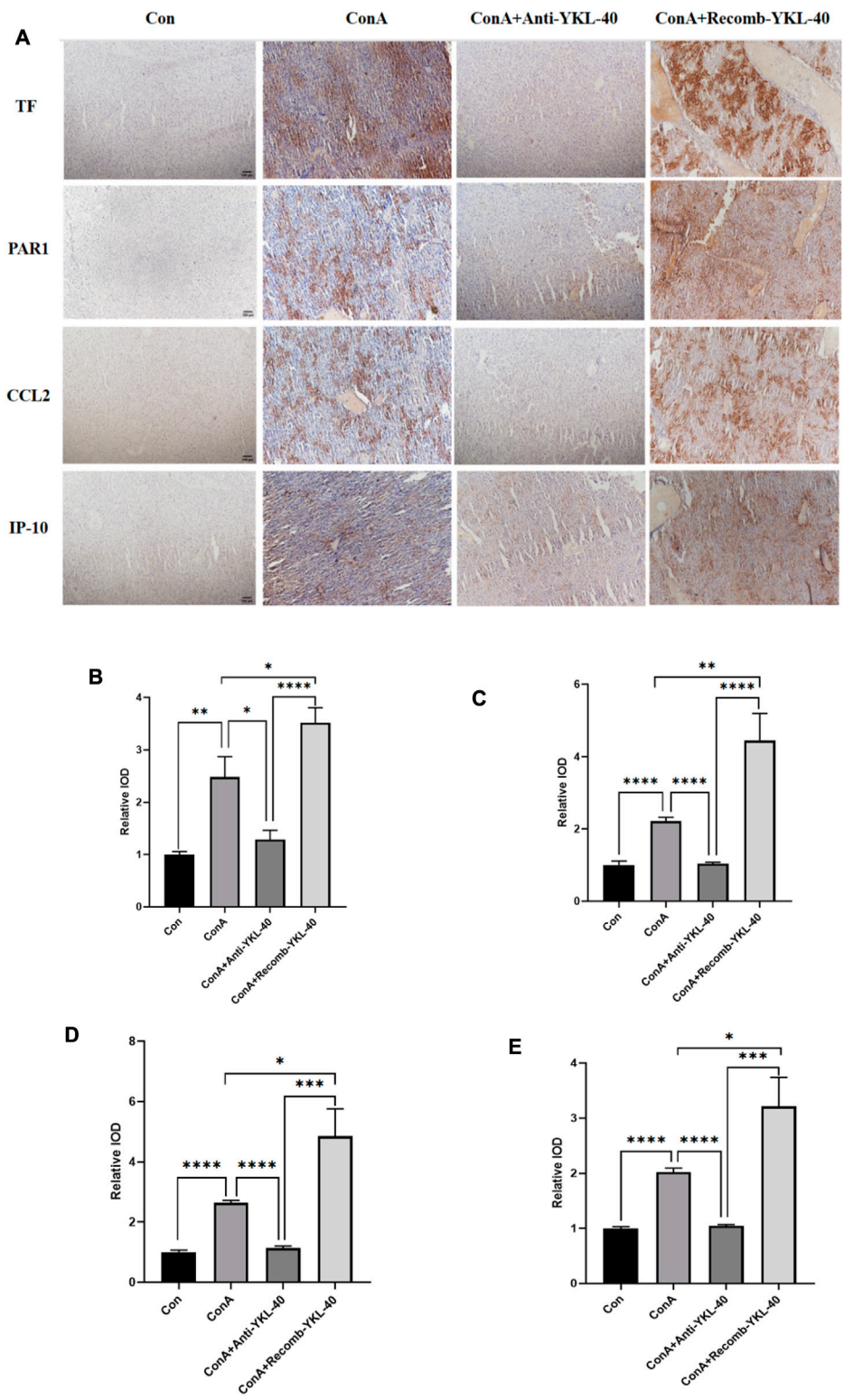


FIGURE 4
YKL-40-mediated induction of TF-PAR1 pathway aggravates DILI progression. **(A)** Immunohistochemistry (IHC) (magnification×100) was performed to determine whether YKL-40 induced TF-PAR1 pathway and aggravated drug-induced liver injury; **(B)** Immunohistochemical statistics of TF; **(C)** Immunohistochemical statistics of PAR1; **(D)** Immunohistochemical statistics of CCL2; **(E)** Immunohistochemical statistics of IP-10. *p* values were determined using one-way ANOVA or an unpaired *t*-test. Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

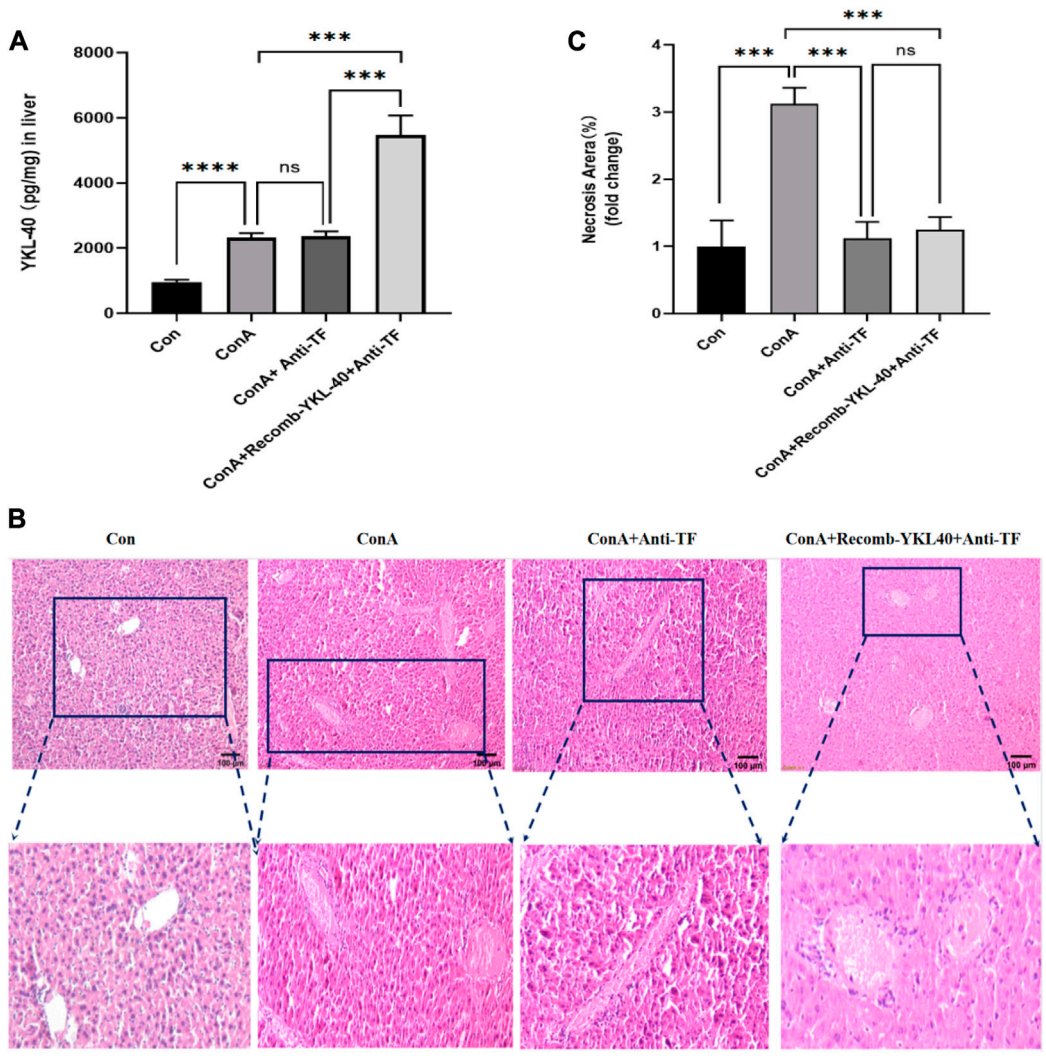


FIGURE 5
YKL-40-mediated TF-PAR1 pathway can effectively alleviate the progression of DILI after being blocked. **(A)** After the endogenous TF protein expression was blocked YKL-40 expression in liver tissue; **(B)** Blocking TF suppressed YKL-40-induced TF-PAR1 pathway and mitigated drug-induced liver injury (magnificationx100). **(C)** Necrotic areas as quantified by ImageJ software. Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

4 Discussion

Drug-induced liver injury (DILI) is a liver injury caused by the drug itself and its metabolites during drug use. Drug specific heterogeneous reactions are currently a hot research topic. Drug-induced liver injury through direct toxic effects is often predictable, and its diagnosis of liver injury is relatively easy. However, drugs can cause liver damage through specific heterogeneous reactions, both in terms of mechanism and symptoms, which are particularly complex. Among them, allergic specific DILI works together with the body's immune system, also known as immune mediated DILI. Due to its independence from dosage, unpredictability, and uncertain incubation period, diagnosis is even more difficult. The pathological process of the liver injury model established by Concanavalin A (ConA) is similar to that of many known acute and chronic liver diseases, especially it can better simulate the pathogenesis of human autoimmune liver diseases. Intrahepatic vascular coagulation plays an important role in the occurrence and development of liver diseases such as fibrosis, cirrhosis, and liver cancer. Therefore, in the context of relevant research, further exploration of the pathogenesis of DILI from the perspective of coagulation can contribute to a deeper understanding of immune mediated DILI.

The study revealed the relationship between inflammatory reaction and blood coagulation in systemic inflammatory diseases (including Sinusitis, acne vulgaris and acute hepatitis) (Montgomery et al., 2017; Shan et al., 2018; Ebrahim et al., 2020). More and more evidence suggests that after the coagulation system is activated in liver disease, some coagulation related proteins act as liver inflammatory factors. IAOC plays a crucial role in acute liver injury (Ganey et al., 2007; Sullivan et al., 2013; Miyakawa et al., 2015). In the ConA induced acute liver injury model, YKL-40 induced TF to participate in IAOC; It is worth noting that this process may be related to the activation of the MAPK pathway

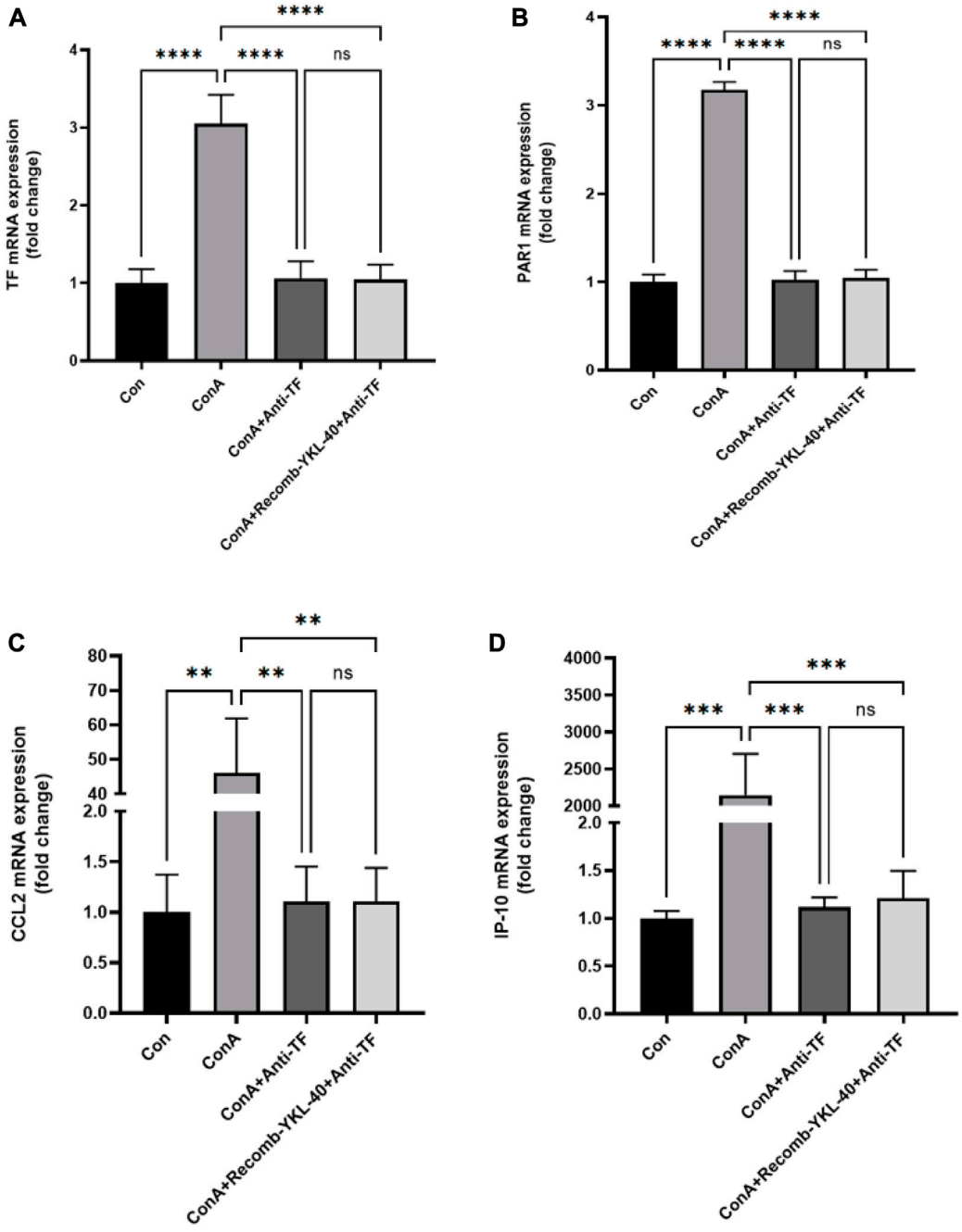


FIGURE 6
YKL-40-induced TF-PAR1 pathway influences the course of DILI by regulating TF expression. **(A)** After blocking the endogenous TF protein expression, TF mRNA expression was measured in mouse liver; **(B)** After blocking the endogenous TF protein expression, PAR1 mRNA was measured in mouse liver; **(C)** After blocking the endogenous TF protein expression, CCL2 expression was measured in mouse liver; **(D)** After blocking the endogenous TF protein expression, IP-10 expression was measured in mouse liver. *p* values were determined using one-way ANOVA or an unpaired *t*-test. Data are expressed as mean ± SEM (n = 6).*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

(Shan et al., 2018). Although the relationship between YKL-40 and TF has been elucidated, the mechanism by which YKL-40 regulates the downstream deterioration of liver diseases caused by TF is still unknown. Clarifying the interaction between the coagulation system and liver inflammation will provide new therapeutic targets for DILI. Therefore, in this study, we investigated YKL-40 mediated TF induction and its impact on the liver.

TF expression is often upregulated in inflammatory liver disease (Hisada et al., 2016; Henderson et al., 2021). The role of TF in initiating coagulation and thrombosis has been fully demonstrated. TF promotes coagulation cascade reactions by binding and activating coagulation factor VIIa (FVIIa) (Toschi et al., 1997). Secondly, in inflammatory diseases, TF exposure to the blood affects cell proliferation, apoptosis, scorching,

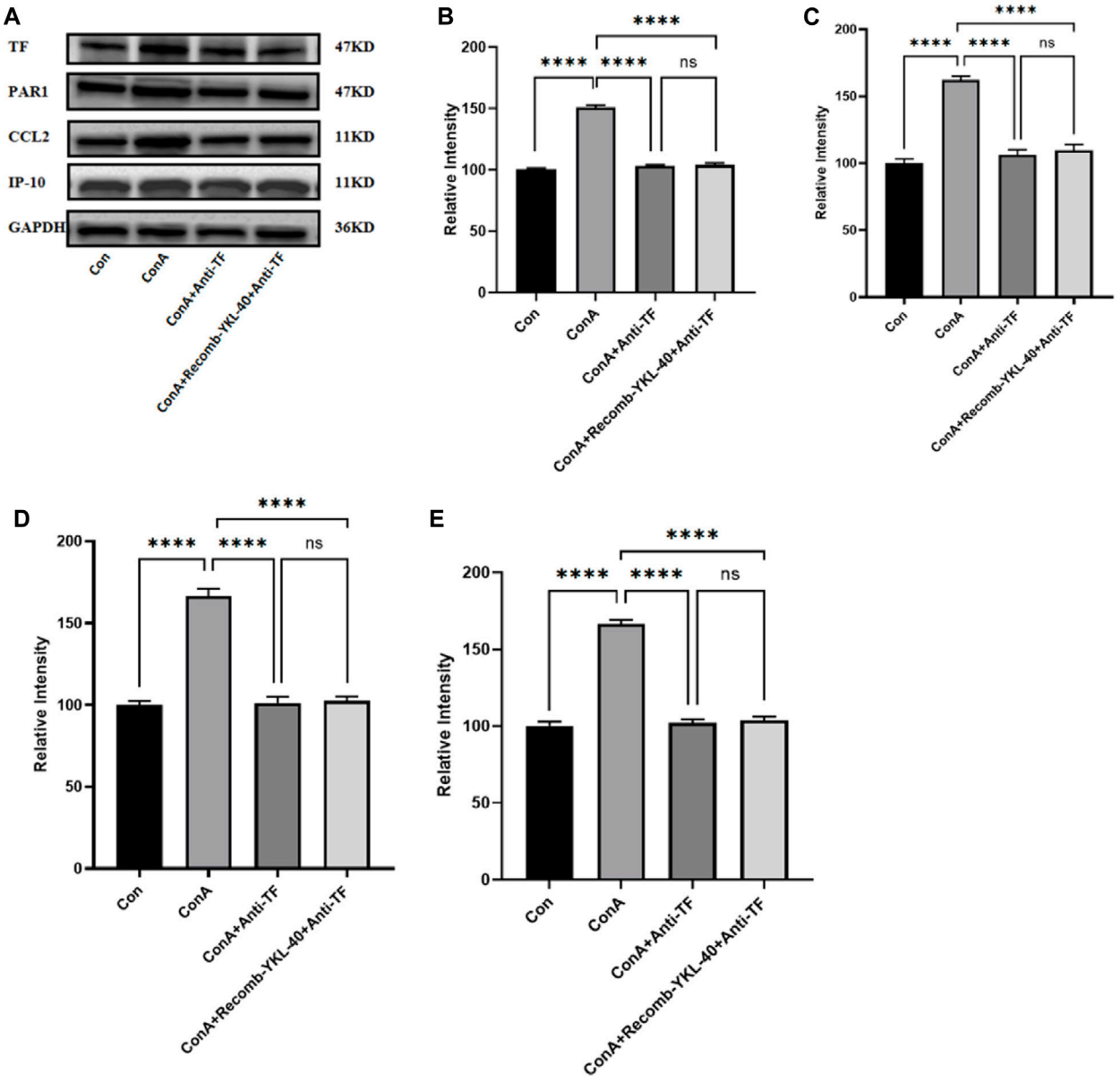


FIGURE 7
Effect of blocking TF-PAR1 pathway on liver pathogenesis. After the endogenous TF protein expression was blocked, **(A)** the expression of TF-PAR1 pathway proteins in the liver following YKL-40 induction and the levels of downstream chemokines CCL2 and IP-10 were determined; **(B)** TF protein expression in mouse liver; **(C)** PAR1 protein expression in mouse liver; **(D)** CCL2 protein expression in mouse liver; **(E)** Expression of IP-10 protein in mouse liver. *p* values were determined using one-way ANOVA or an unpaired t-test. Data are expressed as mean ± SEM (n = 6). $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, ns means no statistical difference.

migration, and aggregation of inflammatory factors through the TF-PAR1 pathway, ultimately exacerbating the vicious cycle of the "coagulation inflammation network" (Witkowski et al., 2016), thereby exacerbating the disease. PAR1, as the main thrombin receptor, is closely related to TF expression and plays a key role in liver fibrosis (Gutiérrez-Rodríguez and Herranz, 2015; Flaumenhaft and De Ceunynck, 2017). In recent years, it has been considered a new therapeutic target for inflammatory diseases. For example, after injecting PAR1 activating peptide into mice, thrombin can produce pro-inflammatory effects, manifested as edema and increased vascular permeability (Cirino et al., 1996). The formation of TF-FVIIa complex produces thrombin, which can activate cells through PAR1, thereby exacerbating the disease (Ganey et al., 2007). For example, PAR1 deficient mice have a significant response to Paracetamol (APAP) induced acute Liver failure after 6 h, which is manifested by liver injury and decreased liver fibrin deposition. Similarly, our findings suggest that YKL-40 activates the TF-PAR1 pathway and plays a crucial role in the progression of DILI. In addition, overexpression of YKL-40 is positively correlated with the expression levels of TF and PAR1, which can lead to intrahepatic coagulation and

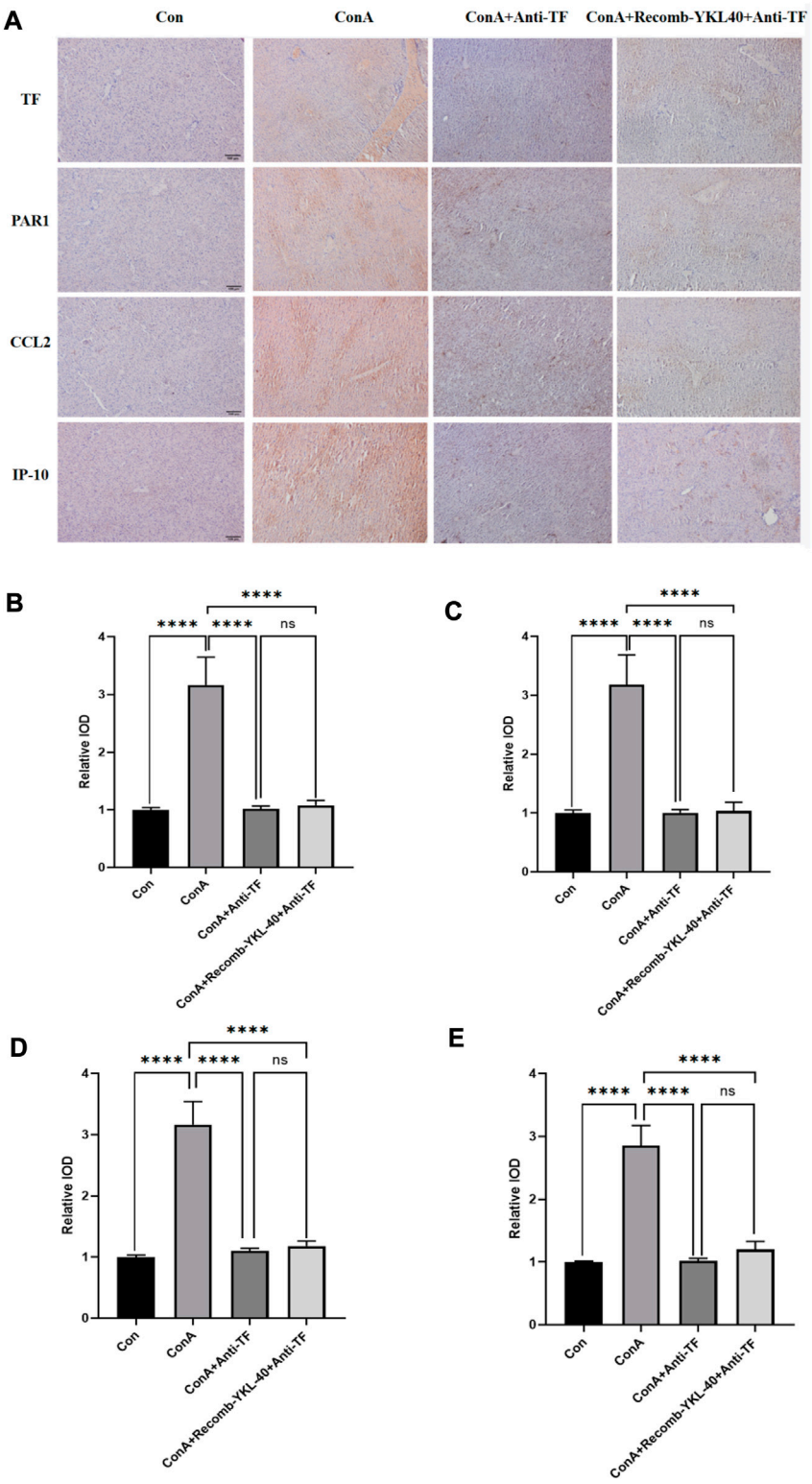


FIGURE 8
Blocking TF-PAR1 pathway alleviates DILI progression. **(A)** Blocking TF-PAR1 pathway alleviated drug-induced liver injury (DILI) as determined by immunohistochemistry (magnification×100) (n = 6). **(B)** Immunohistochemical statistics of TF; **(C)** Immunohistochemical statistics of PAR1; **(D)** Immunohistochemical statistics of CCL2; **(E)** Immunohistochemical statistics of IP-10. *p* values were determined using one-way ANOVA or an unpaired *t*-test. Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns means no statistical difference.

exacerbation of the condition. On the contrary, blocking the endogenous TF pathway will significantly reduce the mRNA and protein levels of TF and PAR1, as well as alleviate liver injury, even when YKL-40 is overexpressed. Similarly, we know that the increased expression of the inflammatory factor YKL-40 is significantly correlated with the severity of inflammatory diseases (Arain et al., 2020; Ebrahim et al., 2020). Our research results indicate that YKL-40 in the liver can aggravate liver injury and affect the progression of DILI by activating the TF-PAR1 pathway.

Chemokines are important inflammatory mediators that mobilize, guide, and locate effector cells in immune system mediated liver diseases. They also play a crucial role in controlling viral infections (Czaja, 2014). In addition, overexpression of chemokines can exacerbate the inflammatory response and increase the degree of liver damage. If its expression is effectively controlled, it will help regulate immune response and inflammation, thereby improving clinical symptoms and prognosis. In recent years, research has shown that chemokines CCL2 and IP-10 are closely related to liver diseases such as hepatitis, fibrosis, and cancer, which has attracted widespread attention. Among them, CCL2, as one of the key chemokines involved in liver inflammation and fibrosis, plays a crucial role in liver diseases (Mascia et al., 2017; Tacke, 2017). It has been widely validated in the hepatitis experimental model of $CCL2^{-/-}$ mice (Karlmark et al., 2009; Galastri et al., 2012). CCL2 accumulation in murine model of liver fibrosis significantly increases the local inflammatory cell pool, inducing chronic inflammation that leads to further liver cell damage and stress responses, such as extracellular matrix deposition, steatosis, enhanced angiogenesis and the formation of an inflammatory microenvironment (Karlmark et al., 2009; Baeck et al., 2012; Baeck et al., 2014; Shao et al., 2022). IP-10/CXCL10 is a newly discovered chemokine that can combine with chemokine receptors expressed on NK cells and T cells to induce their migration to specific tissues. Its serum level is intimately related to the extent of necrotizing liver inflammation and fibrosis (Tacke et al., 2011; Elemam et al., 2022). For example, Hepatitis C (HCV) virus infection and intrahepatic INF-γ drive increased CXCL10 expression through the sinus endothelium and liver cells.

This induces T cell recruitment into the liver and aggravates the degree of necrotizing inflammation and fibrosis (Ferrari et al., 2019). IP-10 is also involved in immune system-mediated liver injury as observed in severe hepatitis. Its abnormally high expression drives the infiltration of several inflammatory cells into the liver tissue and initiates liver tissue necrosis (Karin and Razon, 2018). For instance, in humans, acute hepatitis B virus infection is accompanied by systemic cytokine and chemokine responses combined with increased serum CXCL10 level, which attracts more inflammatory cells to the liver and aggravates liver injury (Moroz et al., 2019). The interaction of the core protein and globular C1q receptor in HCV can induce macrophages to secrete CCL2 and CXCL10 through the NF-κB signaling pathway, thereby influencing the course of HCV (Song et al., 2021). CCL2 and IP-10 activation is reportedly regulated by the PAR1 pathway. In our study, YKL-40 overexpression following drug-induced injury activated the TF-PAR1 pathway, which in turn increased the expression of downstream chemokines CCL2 and IP-10 and aggravated liver injury. Suppressing TF-PAR1 pathway via blocking endogenous TF alleviates liver pathogenesis, even if YKL-40 is overexpressed. Therefore, TF-PAR1 pathway, which can be induced by YKL-40, plays a critical role in DILI. An in-depth investigation of the relationship between these pathways and chemokines can help us understand how leukocytes enter the liver and aggravate the immune response. This can also facilitate identification of therapeutic targets for liver inflammation. The various pathogenic mechanisms underlying liver diseases are not mutually exclusive, and in fact, may even be synergistic. Thus, further research is needed to determine the interaction among these pathways, their influence, and if they play unique roles at different stages of DILI.

5 Conclusion

This study revealed that YKL-40 promotes the expression of CCL2 and IP-10 in ConA-induced DILI in wild-type mice by inducing the TF-PAR1 pathway. This causes increased inflammatory cell recruitment, thus sparking the onset and progression of liver injury. This is a potential mechanism underlying the aggravation of liver inflammation and injury and presents novel targets for therapeutic intervention in DILI.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by China Medical University Application for Laboratory Animal Welfare and Ethical review Issue N IACUC: CMU2021491.

Author contributions

ZJ-L conducted mouse experiments, aided in experiment design and drafted the manuscript. CS participated in drafting the manuscript preparation. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the 2020 40 Project, 345 Talent Program, Shengjing Hospital of China Medical University (Project No. M0723) and Outstanding Scientific Fund of Shengjing Hospital of China Medical University (Project No. M0779).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abraham, E. (2000). Coagulation abnormalities in acute lung injury and sepsis. *Am. J. Respir. Cell. Mol. Biol.* 22 (4), 401–404. doi:10.1165/ajrcmb.22.4.f184

Arain, F., Abraityte, A., Bogdanova, M., Solberg, O. G., Michelsen, A. E., Lekva, T., et al. (2020). YKL-40 (Chitinase-3-Like protein 1) serum levels in aortic stenosis. *Circ. Heart Fail* 13 (10), e006643. doi:10.1161/CIRCHEARTFAILURE.119.006643

Baeck, C., Wehr, A., Karlmark, K. R., Heymann, F., Vucur, M., Gassler, N., et al. (2012). Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury. *Gut* 61 (3), 416–426. doi:10.1136/gutjnl-2011-300304

Baeck, C., Wei, X., Bartneck, M., Fech, V., Heymann, F., Gassler, N., et al. (2014). Pharmacological inhibition of the chemokine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C(+) macrophage infiltration in mice. *Hepatology* 59 (3), 1060–1072. doi:10.1002/hep.26783

Chen, D., Giannopoulos, K., Shiels, P. G., Webster, Z., McVey, J. H., Kemball-Cook, G., et al. (2004). Inhibition of intravascular thrombosis in murine endotoxemia by targeted expression of hirudin and tissue factor pathway inhibitor analogs to activated endothelium. *Blood* 104 (5), 1344–1349. doi:10.1182/blood-2003-12-4365

Cirino, G., Cicala, C., Bucci, M. R., Sorrentino, L., Maraganore, J. M., and Stone, S. R. (1996). Thrombin functions as an inflammatory mediator through activation of its receptor. *J. Exp. Med.* 183 (3), 821–827. doi:10.1084/jem.183.3.821

Czaja, A. J. (2014). Review article: chemokines as orchestrators of autoimmune hepatitis and potential therapeutic targets. *Aliment. Pharmacol. Ther.* 40 (3), 261–279. doi:10.1111/apt.12825

Ebrahim, A., Mustafa, A. I., El-Shimi, O. S., and Fathy, M. A. (2020). Serum YKL40: A novel potential link between inflammation and dyslipidemia in acne vulgaris. *J. Cosmet. Dermatol* 19 (5), 1219–1223. doi:10.1111/jocd.13124

Elemam, N. M., Talaat, I. M., and Maghazachi, A. A. (2022). CXCL10 chemokine: A critical player in RNA and dna viral infections. *Viruses* 14 (11), 2445. doi:10.3390/v14112445

Fahey, S., Dempsey, E., and Long, A. (2014). The role of chemokines in acute and chronic hepatitis C infection. *Cell. Mol. Immunol.* 11 (1), 25–40. doi:10.1038/cmi.2013.37

Feng, L., Ning, R., Liu, J., Liang, S., Xu, Q., Liu, Y., et al. (2020). Silica nanoparticles induce JNK-mediated inflammation and myocardial contractile dysfunction. *J. Hazard Mater* 391, 122206. doi:10.1016/j.jhazmat.2020.122206

Ferrari, S. M., Fallahi, P., Ruffilli, I., Elia, G., Ragusa, F., Paparo, S. R., et al. (2019). Immunomodulation of CXCL10 secretion by hepatitis C virus: could CXCL10 Be a prognostic marker of chronic hepatitis C? *J. Immunol. Res.* 2019, 5878960. doi:10.1155/2019/5878960

Flaumenhaft, R., and De Ceunynck, K. (2017). Targeting PAR1: now what? *Trends Pharmacol. Sci.* 38 (8), 701–716. doi:10.1016/j.tips.2017.05.001

Galastri, S., Zamara, E., Milani, S., Novo, E., Provenzano, A., Delogu, W., et al. (2012). Lack of CC chemokine ligand 2 differentially affects inflammation and fibrosis according to the genetic background in a murine model of steatohepatitis. *Clin. Sci. (Lond)* 123 (7), 459–471. doi:10.1042/CS20110515

Ganey, P. E., Luyendyk, J. P., Newport, S. W., Eagle, T. M., Maddox, J. F., Mackman, N., et al. (2007). Role of the coagulation system in acetaminophen-induced hepatotoxicity in mice. *Hepatology* 46 (4), 1177–1186. doi:10.1002/hep.21779

Gutiérrez-Rodríguez, M., and Herranz, R. (2015). From multiple PAR1 receptor/protein interactions to their multiple therapeutic implications. *Curr. Top. Med. Chem.* 15 (20), 2080–2114. doi:10.2174/1568026615666150519103911

Henderson, M. W., Sparkenbaugh, E. M., Wang, S., Ilich, A., Noubouossie, D. F., Mailer, R., et al. (2021). Plasmin-mediated cleavage of high-molecular-weight kininogen contributes to acetaminophen-induced acute liver failure. *Blood* 138 (3), 259–272. doi:10.1182/blood.2020006198

Hisada, Y., Alexander, W., Kasthuri, R., Voorhees, P., Mobarrez, F., Taylor, A., et al. (2016). Measurement of microparticle tissue factor activity in clinical samples: A summary of two tissue factor-dependent FXa generation assays. *Thromb. Res.* 139, 90–97. doi:10.1016/j.thromres.2016.01.011

Johansen, J. S. (2006). Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. *Dan. Med. Bull.* 53 (2), 172–209.

Kang, W., and Shin, E. C. (2011). Clinical implications of chemokines in acute and chronic hepatitis C virus infection. *Yonsei Med. J.* 52 (6), 871–878. doi:10.3349/ymj.2011.52.6.871

Karin, N., and Razon, H. (2018). Chemokines beyond chemo-attraction: CXCL10 and its significant role in cancer and autoimmunity. *Cytokine* 109, 24–28. doi:10.1016/j.cyto.2018.02.012

Karlmark, K. R., Weiskirchen, R., Zimmermann, H. W., Gassler, N., Ginhoux, F., Weber, C., et al. (2009). Hepatic recruitment of the inflammatory Gr1+ monocyte subset upon liver injury promotes hepatic fibrosis. *Hepatology* 50 (1), 261–274. doi:10.1002/hep.22950

Katarey, D., and Verma, S. (2016). Drug-induced liver injury. *Clin. Med. (Lond)* 16 (6), s104–s109. doi:10.7861/clinmedicine.16-6-s104

Lee, C. G., Da Silva, C. A., Dela Cruz, C. S., Ahangari, F., Ma, B., Kang, M. J., et al. (2011). Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. *Annu. Rev. Physiol.* 73, 479–501. doi:10.1146/annurev-physiol-012110-142250

Lou, J., Hu, Y., Wu, M. D., Che, L. Q., and Zhao, Y. (2019). Endothelial cell-specific anticoagulation reduces inflammation in a mouse model of acute lung injury. *Acta Pharmacol. Sin.* 40 (6), 769–780. doi:10.1038/s41401-018-0175-7

Ma, Y., Zheng, C., and Shi, L. (2018). The role of YKL40 in the pathogenesis of CRS with nasal polyps. *Eur. Arch. Otorhinolaryngol.* 275 (2), 431–438. doi:10.1007/s00405-017-4859-2

Mascia, C., Lichtner, M., Zuccalà, P., Vita, S., Tieghi, T., Marocco, R., et al. (2017). Active HCV infection is associated with increased circulating levels of interferon-gamma (IFN-γ)-inducible protein-10 (IP-10), soluble CD163 and inflammatory monocytes regardless of liver fibrosis and HIV coinfection. *Clin. Res. Hepatol. Gastroenterol.* 41 (6), 644–655. doi:10.1016/j.clinre.2017.04.007

Miyakawa, K., Joshi, N., Sullivan, B. P., Albee, R., Brandenberger, C., Jaeschke, H., et al. (2015). Platelets and protease-activated receptor-4 contribute to acetaminophen-induced liver injury in mice. *Blood* 126 (15), 1835–1843. doi:10.1182/blood-2014-09-598656

Montgomery, T. A., Xu, L., Mason, S., Chinnadurai, A., Lee, C. G., Elias, J. A., et al. (2017). Breast regression protein-39/chitinase 3-like 1 promotes renal fibrosis after kidney injury via activation of myofibroblasts. *J. Am. Soc. Nephrol.* 28 (11), 3218–3226. doi:10.1681/ASN.2017010110

Moroz, L., Soni, S., Dudnyk, V., and Zaichko, N. (2019). Predictive value of serum IL-17A and IP-10 for evaluation of liver fibrosis progression in patients with HBV/HIV CO-infection. *Georgian Med. News* 290, 73–77.

Reiberger, T., Aberle, J. H., Kundi, M., Kohrgruber, N., Rieger, A., Gangl, A., et al. (2008). IP-10 correlates with hepatitis C viral load, hepatic inflammation and fibrosis and predicts hepatitis C virus relapse or non-response in HIV-HCV coinfection. *Antivir. Ther.* 13 (8), 969–976. doi:10.1177/135965350801300815

Reinhardt, C., Bergentall, M., Greiner, T. U., Schaffner, F., Ostergren-Lundén, G., Petersen, L. C., et al. (2012). Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling. *Nature* 483 (7391), 627–631. doi:10.1038/nature10893

Shan, Z., Liu, X., Chen, Y., Wang, M., Gao, Y. R., Xu, L., et al. (2018). Chitinase 3-like-1 promotes intrahepatic activation of coagulation through induction of tissue factor in mice. *Hepatology* 67 (6), 2384–2396. doi:10.1002/hep.29733

Shao, L. N., Zhou, S. H., Wang, N., Zhang, S. T., and Liu, M. (2022). Association between the genetic polymorphisms of *CCL2, CCL5, CCL8, CCR2*, and *CCR5* with chronic hepatitis C virus infection in the Chinese han population. *Immunol. Invest.* 51 (5), 1182–1197. doi:10.1080/08820139.2021.1916524

Song, X., Gao, X., Wang, Y., Raja, R., Zhang, Y., Yang, S., et al. (2021). HCV core protein induces chemokine CCL2 and CXCL10 expression through NF-κB signaling pathway in macrophages. *Front. Immunol.* 12, 654998. doi:10.3389/fimmu.2021.654998

Sullivan, B. P., Kopec, A. K., Joshi, N., Cline, H., Brown, J. A., Bishop, S. C., et al. (2013). Hepatocyte tissue factor activates the coagulation cascade in mice. *Blood* 121 (10), 1868–1874. doi:10.1182/blood-2012-09-455436

Tacke, F. (2017). Targeting hepatic macrophages to treat liver diseases. *J. Hepatol.* 66 (6), 1300–1312. doi:10.1016/j.jhep.2017.02.026

Tacke, F., Zimmermann, H. W., Berres, M. L., Trautwein, C., and Wasmuth, H. E. (2011). Serum chemokine receptor CXCR3 ligands are associated with progression, organ dysfunction and complications of chronic liver diseases. *J. Liver Int.* 31 (6), 840–849. doi:10.1111/j.1478-3231.2011.02504.x

Toschi, V., Gallo, R., Lettino, M., Fallon, J. T., Gertz, S. D., Fernández-Ortiz, A., et al. (1997). Tissue factor modulates the thrombogenicity of human atherosclerotic plaques. *Circulation* 95 (3), 594–599. doi:10.1161/01.cir.95.3.594

Witkowski, M., Landmesser, U., and Rauch, U. (2016). Tissue factor as a link between inflammation and coagulation. *Trends Cardiovasc Med.* 26 (4), 297–303. doi:10.1016/j.tcm.2015.12.001

Zimmermann, H. W., and Tacke, F. (2011). Modification of chemokine pathways and immune cell infiltration as a novel therapeutic approach in liver inflammation and fibrosis. *Inflamm. Allergy Drug Targets* 10 (6), 509–536. doi:10.2174/187152811798104890

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 25 August 2023
DOI 10.3389/fphar.2023.1244400

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Prince Kasongo Mwila,
University of the Witwatersrand, South Africa
Xiao Li,
Shandong Provincial Qianfoshan Hospital, China
Helge Waldum,
Norwegian University of Science and Technology, Norway

*CORRESPONDENCE
Zeyi Zheng,
zzy798343105@outlook.com

RECEIVED 22 June 2023
ACCEPTED 14 August 2023
PUBLISHED 25 August 2023

CITATION
Zheng Z, Lu Z and Song Y (2023), Long-term proton pump inhibitors use and its association with premalignant gastric lesions: a systematic review and meta-analysis.
Front. Pharmacol. 14:1244400.
doi: 10.3389/fphar.2023.1244400

Long-term proton pump inhibitors use and its association with premalignant gastric lesions: a systematic review and meta-analysis

Zeyi Zheng[1]*, Ziyu Lu[2] and Yani Song[3]

[1]School of Traditional Chinese Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia, China, [2]School of Basic Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia, China, [3]School of Water Resources and Hydropower Engineering, Wuhan University, Wuhan, Hubei, China

Background: Long-term maintenance therapy with proton pump inhibitors (PPIs) is a common treatment strategy for acid-related gastrointestinal diseases. However, concerns have been raised about the potential increased risk of gastric cancer and related precancerous lesions with long-term PPI use. This systematic review and meta-analysis aimed to evaluate this potential risk.

Methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published before 1 March 2023, with no language restrictions. The primary endpoint was the occurrence and progression of gastric mucosal atrophy, intestinal metaplasia, Enterochromaffin-like (ECL) cell hyperplasia, gastric polyps, and gastric cancer during the trial and follow-up. Data were analysed using a random effects model.

Results: Of the 4,868 identified studies, 10 met the inclusion criteria and were included in our analysis, comprising 27,283 participants. Compared with other treatments, PPI maintenance therapy for more than 6 months was associated with an increased risk of ECL cell hyperplasia (OR 3.01; 95% CI 1.29 to 7.04; p = 0.01). However, no significant increase was found in the risk of gastric mucosal atrophy (OR 1.01; 95% CI 0.55 to 1.85; p = 0.97), intestinal metaplasia (OR 1.14; 95% CI 0.49 to 2.68; p = 0.76), gastric polyps (OR 1.13; 95% CI 0.68 to 1.89; p = 0.64), or gastric cancer (OR 1.06; 95% CI 0.79 to 1.43; p = 0.71).

Conclusion: This systematic review and meta-analysis does not support an increased risk of gastric cancer or related precancerous lesions with long-term PPI maintenance therapy. However, long-term PPI use should be monitored for potential complications such as ECL cell hyperplasia. Further studies are needed to confirm these findings and evaluate the safety of PPI maintenance therapy for acid-related gastrointestinal diseases.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, Identifier: PROSPERO (CRD42022379692).

KEYWORDS

proton pump inhibitors, gastric cancer, meta-analysis, gastric mucosal atrophy, intestinal metaplasia, enterochromaffin-like cell, gastric polyps

1 Introduction

Gastric cancer is among the top five causes of death globally (Colquhoun et al., 2015), with a 5-year survival rate of 25%–30% (Allemani et al., 2015). The primary reason for this unfavourable prognosis is the late-stage diagnosis of most gastric cancer patients. Therefore, reducing gastric cancer mortality requires significant attention to managing its pathogenic factors and early signs.

The progression from normal gastric mucosa to early intestinal gastric cancer is typically a sequence of "normal gastric mucosa → chronic gastritis → atrophy → intestinal metaplasia → dysplasia → early gastric cancer" (Correa et al., 1975; Correa, 1992). Atrophy, intestinal metaplasia, and dysplasia are broadly referred to as gastric precancerous lesions due to their potential malignant risk (Piazuelo et al., 2021). Gastric polyps are limited epithelial protrusions of the epithelial mucosa, with fundus glandular polyps (FGPs) and hyperplastic polyps (HPs) being the most common pathological types (Ren et al., 2018). Adenomatous polyps have a high malignant potential and are often associated with gastric adenocarcinoma (Park and Lauwers, 2008). Molecular studies have shown that gastric polyps, excluding adenomatous polyps, also exhibit molecular changes that may lead to tumour progression and may have unknown risks of malignant transformation (Carmack et al., 2009).

Proton pump inhibitors (PPIs), widely used globally for treating acid-related diseases such as gastroesophageal reflux disease (Dilaghi et al., 2022) and peptic ulcer (Malfertheiner et al., 2017), are often used as maintenance therapy to prevent symptom recurrence. Long-term PPI use often results in increased circulating gastrin levels, which can affect gastrointestinal tissue. However, sustained high levels of circulating gastrin can lead to hyperplasia of gastric parietal cells and enterochromaffin-like cells in the gastric mucosa (Lundell et al., 2015), potentially inducing the development of fundic gland polyps (Kim, 2021) and other histopathological changes that may increase the risk of gastric cancer. (Hagiwara et al., 2011). The safety and adverse effects of long-term PPI use are becoming a concern.

The impact of long-term PPI use on gastric cancer-related lesions has been extensively studied, but the results have been inconsistent, leading to controversy about the safety of PPI maintenance therapy (Yadlapati and Kahrilas, 2018). Therefore, a meta-analysis is needed to comprehensively evaluate the association between long-term PPI use and gastric cancer and its related lesions. We conducted a systematic review and meta-analysis of existing randomized controlled trials to assess the adverse effects of long-term PPI use on gastric cancer, gastric mucosal atrophy, intestinal metaplasia, ECL cell hyperplasia, and gastric polyps to elucidate and improve the safety of PPI maintenance therapy.

Previous meta-analyses have shown varying results. Song's meta-analysis found no clear evidence of an increased risk of gastric mucosal atrophy and intestinal metaplasia but a more significant association with ECL cell hyperplasia (Song et al., 2014). Tran-Duy (Tran-Duy et al., 2016) and Martin (Martin et al., 2016)'s showed an association with an increased risk of fundic gland polyps and possibly an increased risk of gastric cancer. Three recent meta-analyses by Segna (Segna et al., 2021), Guo (Guo et al., 2023) and Peng (Peng et al., 2023) showed that PPI use was significantly associated with gastric cancer, but no duration-dependent effects of PPI with gastric cancer risk were found at < 1 year, 1–3 years, and more than 3 years. This meta-analysis includes more recent high-quality studies related to PPI maintenance therapy and reduced heterogeneity, allowing for a more comprehensive evaluation of the adverse effects on gastric cancer-related lesions.

2 Materials and methods

2.1 Search strategy

We conducted a literature search in PUBMED, EMBASE, and the Cochrane Central Register of Controlled Trials electronic databases to identify all published and unpublished randomised controlled trials up to 1 March 2023. An additional manual search of conference abstracts was performed to ascertain experimental details. Bibliographies of relevant studies were also manually searched. Two investigators independently conducted searches using the keywords "Stomach Neoplasms" and "proton pump inhibitor." The specific search strategy is detailed in the attached table.

2.2 Selection criteria

The inclusion criteria encompassed randomised controlled trials (RCTs) examining the long-term use of PPIs in adult patients. The study necessitated one group of participants on maintenance therapy with PPIs and a control group using other treatment strategies for an intervention period exceeding 6 months. Participants in both groups underwent upper gastrointestinal endoscopy at the start and conclusion of the trial. They reported the number or proportion of participants with gastric mucosal lesions such as gastric cancer, atrophy, intestinal metaplasia, ECL cell hyperplasia, and gastric polyps. The primary outcome was the study's ability to provide sufficient data to estimate the odds ratio (OR) between the occurrence and progression of each gastric cancer-related lesion and the use of PPI.

Articles without original data, studies that did not report data related to "gastric cancer, atrophy, intestinal metaplasia, ECL cell hyperplasia, and gastric polyps," and studies with duplicate reports were excluded.

Two independent investigators screened titles and abstracts to include all potential studies in the search results. They independently screened them in full text to identify eligible studies and document reasons for exclusion. In cases of uncertainty regarding study inclusion, the two review authors discussed to reach a resolution, and if necessary, a third expert was consulted.

This section was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Page et al., 2021), and registered at the International Prospective Register of Systematic Reviews (number CRD42022379692) (Figure 1. PRISMA flowchart illustrating the process of screening and selection of studies).

2.3 Data extraction and quality assessment

Two independent investigators extracted data from each study using a pre-designed data extraction form. Extracted data included

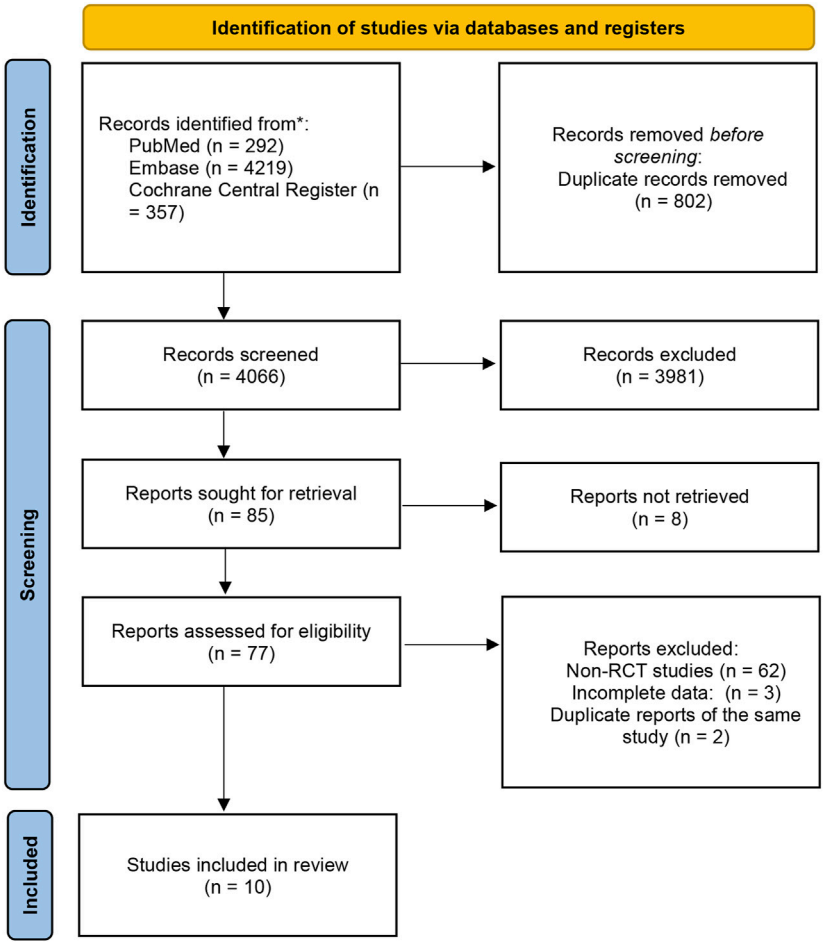


FIGURE 1
PRISMA flowchart illustrating the process of screening and selection of studies.

the first author's surname, year of publication, type of experiment, number of participants, age, sex, baseline diagnosis, inclusion and exclusion criteria, treatment and experimental interventions, duration of intervention, primary outcome, and number of events. For unpublished studies, we referred to their practical design article (Uemura et al., 2018) and extracted data from their most recent conference presentation (Kushima et al., 2022). Two independent investigators assessed the quality of each study using the Cochrane risk of bias tool (Higgins et al., 2011), with any discrepancies resolved by a third investigator.

2.4 Statistical analysis

For dichotomous variables, we assumed that patients who discontinued were negative and that data reporting only the change in the number of events and the possibility of repeated reporting were positive. We used Stata16 software to generate meta-analysis and forest plots. Binary data were analysed into odds ratio (OR) with a 95% confidence interval (CI) using the DerSimonian-Laird random effects model to evaluate the overall sensitivity and specificity of the model, thereby fully accounting for the additional uncertainty related to inter-study differences in the effects of different interventions. We calculated the parameters Q, I^2, I^2 (≥50%), and P (<0.05) (Higgins and Thompson, 2002; Higgins et al., 2003) to assess heterogeneity of values. If feasible, we planned to conduct a subgroup analysis to evaluate the potential impact of the incident location, *Helicobacter pylori* infection, PPI dose, and exposure time. In cases of high heterogeneity in the main results, we would conduct a sensitivity analysis to assess the impact of individual studies on aggregate statistics, by excluding one study at a time from the meta-analysis. If the number of included studies was sufficient (≥ 10), we would explore potential publication bias by constructing a funnel plot of the effect size of each trial relative to the standard error, and evaluate the asymmetry of the funnel plot using Begg and Egger tests, defining significant publication bias as a *p*-value <0.1.

3 Result

Initially, we identified a total of 4,868 studies from electronic databases. Out of these, 802 were duplicates. After screening by title and abstract, we selected 85 studies for further evaluation. However,

10.3389/fphar.2023.1244400

TABLE 1 Summary of study characteristics.

Study	Year	Treatment in both study groups	Duration of interventions	PPI users/ PPI none users	Outcome	Events in PPI users/ PPI none users	Age	Male	Countries/ Regions
Lundell et al.	1999	omeprazole (20–40 mg once daily) vs. antireflux surgery	up to 3 years	155/143	Worsening atrophic gastritis scores	10/11	18–77	OME 75% ARS 76%	Nordic countries
					Worsening intestinal metaplasia scores	2/3			
					ECL cell hyperplasia (diffuse/liner/ micronodular)	7/2			
Genta et al.	2003	esomeprazole (10,20,40 mg once daily) vs. placebo	up to 6 months	519/169	Changes From Baseline in Gastritis atrophy at Antral and Corporal Biopsy Sites	11/1	18–75	no mentioned	United States
					Changes From Baseline in intestinal metaplasia at Antral and Corporal Biopsy Sites	7/4			
					ECL Cell Scores at Baseline and Final Biopsies	27/1			
Howden et al.	2009	Dexlansoprazole (60,90 mg once daily) vs. placebo	up to 6 months	311/140	Improvement of intestinal metaplasia scores	10/5	≥18	MR90: 82 MR60: 83 Placebo:70	United States
					Prevalence of enterochromaffin-like cell hyperplasia or adenocarcinoma	0/0			
Peura et al.	2009	Dexlansoprazole (30,60,90 mg qd) vs. lansoprazole (30 mg qd) vs. placebo	276.2 ± 134.67 days	5633/896	The number of patients with gastric polyps	19/1	18–90	DLAS 46% LAS 53% Placebo 34%	United States
					The number of patients with intestinal metaplasia	5/0			
					The number of patients with enterochromaffin-like cell hyperplasia	0/0			
Fiocca et al.	2012	Esomeprazole (20 mg once daily) vs. laparoscopic surgery	up to 5 years	158/180	The number of atrophy at each time point (antrum/corpus)	4/6	18–70	LARS 72% ESO 82%	Europe
					The number of intestinal metaplasia at each time point (antrum/corpus)	11/12			
					The histogram of ECL cell hyperplasia at each time point	14/3			
Sugano et al.	2013	Esomeprazole (20 mg daily) vs. Placebo.	up to 72 weeks	214/213	The number of participants with gastric polyps at summary of adverse events	2/1	≥20	ESO 80.8% Placebo 79.1%	Japan
		Low-dose acetylsalicylic acid (81–324 mg/day for ≤5 of 7 days each week) and Gefarnate (50 mg twice daily)							Korea
									Taiwan

(Continued on following page)

TABLE 1 (*Continued*) **Summary of study characteristics.**

Study	Year	Treatment in both study groups	Duration of interventions	PPI users/ PPI none users	Outcome	Events in PPI users/ PPI none users	Age	Male	Countries/ Regions
Fujishiro et al.	2015	Rabeprazole (10 mg daily) vs. Rabeprazole (5 mg daily)	up to 76 weeks	204/201	Number of participants with Gastric cancer	4/1	35–90	10 mg 74.5% 5 mg 76.1%	Japan
Moayyedi et al.	2019	Pantoprazole (40 mg once daily) vs. placebo	up to 3 years	8,791/ 8,807	The number of patients with atrophy	19/26	mean 67.6 ± 8.1	PAT 78% Placebo 79%	America
					The number of patients with gastric cancer	86/83			Europe
									Asia Pacific and other
Haruma et al.	2022	Lansoprazole (15 or 30 mg once daily) vs. Vonoprazan (10 or 20 mg once daily)	up to 5 years	67/135	The number of patients with ECL cell hyperplasia	1/2	≥ 20	LPZ 61% VPZ 72%	Japan
Cho et al.	2023	lansoprazole 15 mg or tegoprazan 25 mg once daily	up to 24 weeks	174/173	The number of participants with gastric polyps at summary of adverse events	3/4	20–75	LPZ 110 TPZ 114	Korean

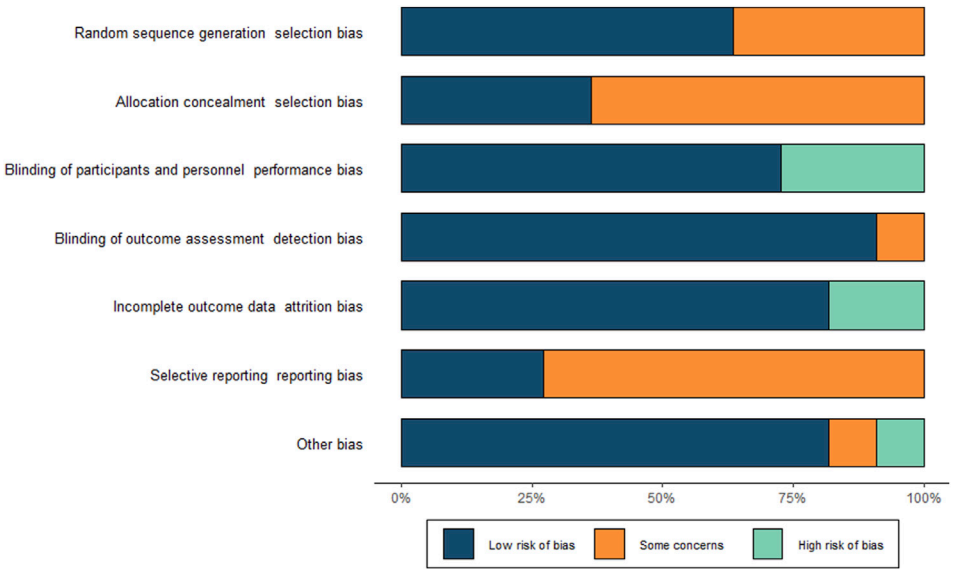


FIGURE 2
Risk of bias graph.

we could not retrieve 8 reports. Out of the remaining 77 studies, 62 were non-randomized controlled trials (RCTs) or review articles. Additionally, we found 2 reports to be duplicates of the same study, while 3 studies were excluded due to incomplete data. Among the remaining nine studies, one of them (Genta et al., 2003) reported adverse reaction results of two studies (Johnson et al., 2001; Vakil et al., 2001) with identical designs. We found the original texts of these two studies for quality analysis. One study (Haruma et al., 2021) is a meeting abstract for a study that is still in progress. We retrieved the study design (Uemura et al., 2018) for this study and the 4-year study data presented at the meeting in May 2022 (Kushima et al., 2022).

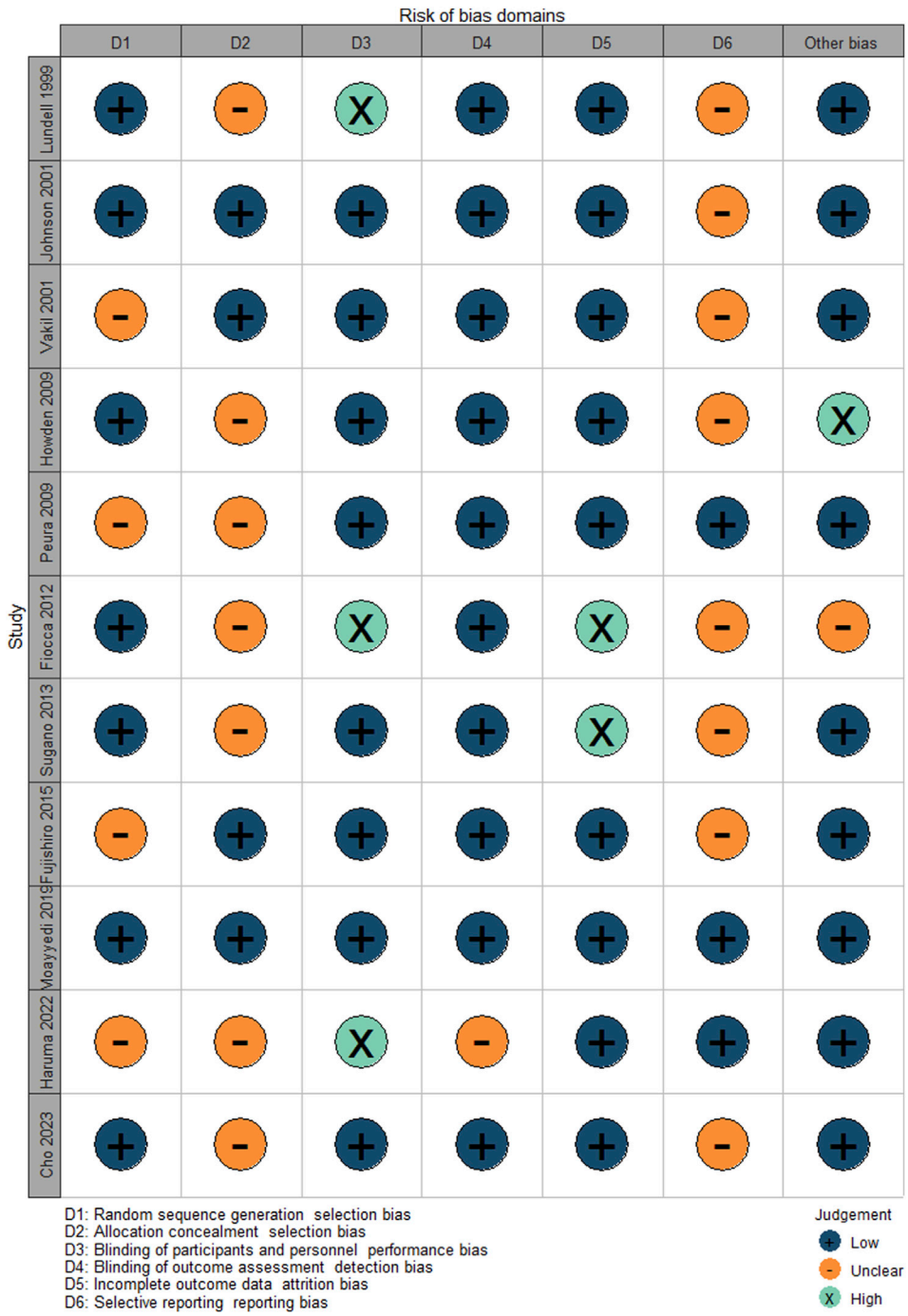


FIGURE 3
Risk of bias summary.

We included ten randomised controlled studies for the effect of proton pump inhibitors on gastric cancer-related lesions, comprising 27,283 subjects (Table 1. Summary of study characteristics) (Figure 2. Risk of bias Figure 3. Risk of bias summary.).

Gastric mucosal atrophy and intestinal metaplasia: Four studies evaluated gastric mucosal atrophy. One study reported the changes in the number of participants with gastric mucosal atrophy and intestinal metaplasia at the endpoint compared to the baseline for each degree of progression (Lundell et al., 1999). Another study reported only the endpoint number of occurrences of gastric mucosal atrophy (Moayyedi et al., 2019). A pooled set (Genta et al., 2003) of adverse effects of two studies (Johnson et al., 2001; Vakil et al., 2001) reported the number of participants whose gastric mucosal atrophy and intestinal metaplasia aggravated and decreased in the antrum and gastric corpus, respectively, compared to the baseline. One study also reported atrophy and intestinal metaplasia at each follow-up time point by dividing the gastric antrum and gastric corpus (Fiocca et al., 2012).

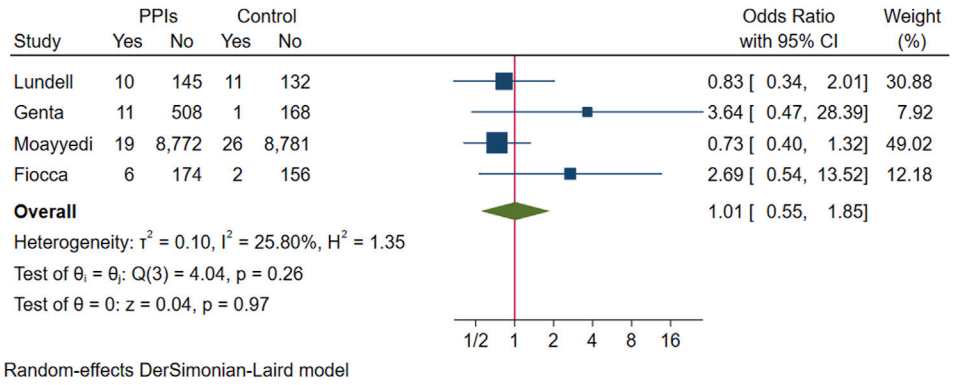


FIGURE 4
Forest plots of odds ratios for atrophy in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.

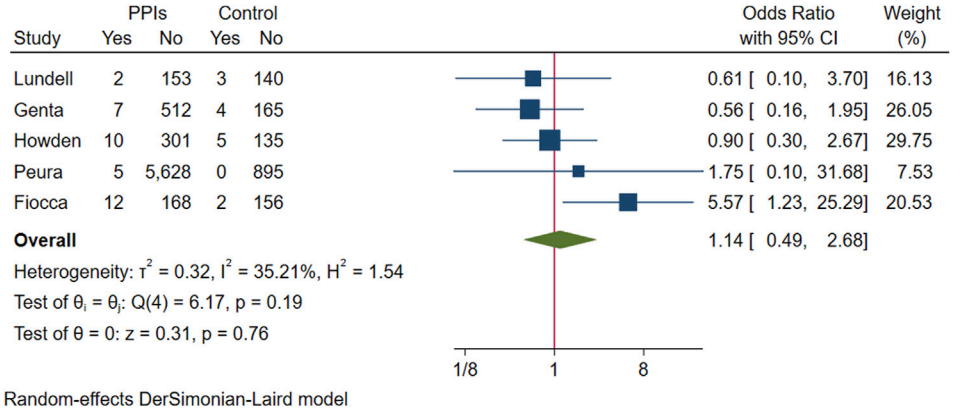


FIGURE 5
Forest plots of odds ratios for intestinal metaplasia in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.

However, we could not obtain trends from this study, and we had no way of knowing whether the participants with events in the antrum and gastric corpus overlapped. We first assume that the experimental group using PPI has the most events and the control group has the least events as a premise for including the data in this study. To avoid bias, we subsequently excluded this study and conducted an analysis again to observe whether the direction of the meta-analysis results after exclusion is consistent with that under this extreme condition.

In a pooled analysis of the above four studies, progressive worsening of gastric mucosal atrophy was found in 46 of 9,645 participants treated with PPI maintenance for more than 6 months and in 40 of 9,277 participants in the control group. No statistical difference was found between the groups (OR 1.01; 95% CI 0.55 to 1.85; *p*-value = 0.97), indicating that most participants showed improvement or no change in the degree of gastric mucosal atrophy (Figure 4. Forest plots of odds ratios for atrophy in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.). When re-analysed after excluding studies assuming extreme cases of Fiocca (Fiocca et al., 2012), the results of the meta-analysis were in the same direction (OR 0.84; 95% CI 0.5 to 1.41; *p*-value = 0.51) and the I^2 decreased from 25.8% to 7.48%.

We pooled five RCTs evaluating 8,303 participants, in which one study reported the incidence of intestinal metaplasia in participants with endpoint gastric biopsies (Howden et al., 2009), and another study reported the number of participants who had intestinal metaplasia in gastric biopsies (Peura et al., 2009). Intestinal metaplasia was present on endpoint gastric biopsies in 36 participants in the PPI group and 14 in the control group, with no evidence that intestinal metaplasia was associated with exacerbation and long-term use of PPIs (OR 1.14; 95% CI 0.49 to 2.68; *p*-value = 0.76) (Figure 5. Forest plots of odds ratios for intestinal metaplasia in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.). Likewise, after excluding studies that assumed extreme cases of Fiocca and conducting a subsequent analysis, the meta-analysis results were consistent in direction (OR 0.75; 95% CI 0.36 to 1.55; *p*-value = 0.44), and I^2 decreased from 35.21% to 0.

Enterochromaffin-like cell hyperplasia: Six studies evaluated changes in ECL cells. Two studies reported no occurrences of

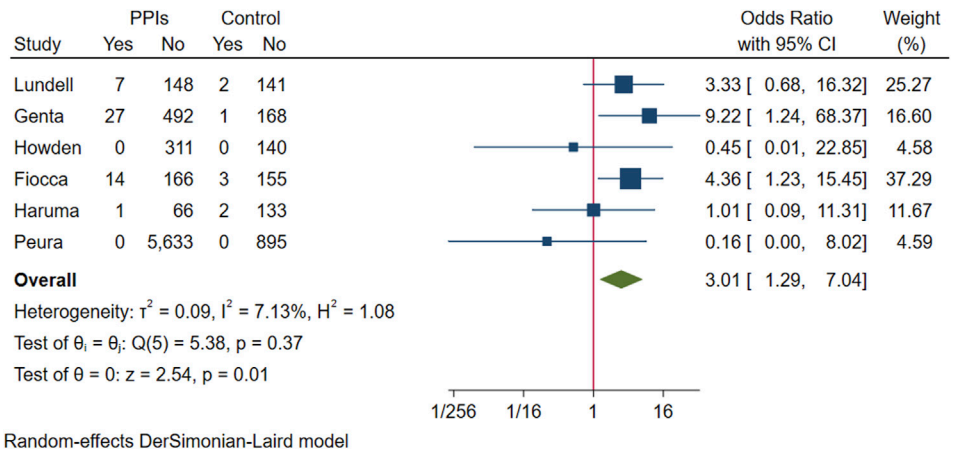


FIGURE 6
Forest plots of odds ratios for ECL cell hyperplastic in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.

ECL cell hyperplasia during the study period (Howden et al., 2009; Peura et al., 2009). One study reported changes in each level of ECL cell abnormalities in participants from baseline to endpoint (Lundell et al., 1999). Another study provided a histogram representation of the number of patients with ECL cell hyperplasia, which we manually entered for measurement (Fiocca et al., 2012). Additionally, one study reported the number of participants with ECL cell hyperplasia on gastric tissue biopsy at the endpoint and the proportion of these participants with participants whose ECL cell scores worsened (Genta et al., 2003). We also retrieved data from one ongoing study with a 5-year duration (Kushima et al., 2022) which presented its fourth-year gastric biopsy data at a conference in May 2022.

The above six studies were pooled and analysed. Among the 6,865 participants who used PPI maintenance therapy for more than 6 months, 49 had deterioration of ECL cell score, and only 8 of the 1,640 participants in the control group had a breakdown of ECL score. This meta-analysis showed that long-term PPI maintenance therapy users had an increased risk of worsening ECL cell scores relative to non-PPI users (OR 3.01; 95% CI 1.29 to 7.04; *p*-value = 0.01) (Figure 6. Forest plots of odds ratios for ECL cell hyperplastic in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.). On this basis, we performed a subgroup analysis regarding the duration of observation and the type of PPI, and the results showed that the negative effect of PPI maintenance treatment on ECL cell proliferation did not seem to be dependent on the duration of observation (<1 year: OR 3.33; 95% CI 0.2 to 54.59; *p*-value = 0.4, 1–3 years: OR 1.26; 95% CI 0.08 to 20.36; *p*-value = 0.87, >3 years: OR 3.06; 95% CI 0.89 to 10.45; *p*-value = 0.07), no trend was observed (Figure 7. Forest plots of the odds of ECL cell proliferation in participants who received proton pump inhibitors compared to those who did not receive proton pump inhibitors by different observation duration.), but it seemed to be related to the type of PPI, and the studies with Esomeprazole (OR 5.4; 95% CI 1.85 to 15.74; *p*-value = 0) were more significant than those with Lansoprazole (OR 0.9; 95% CI 0.11 to 7.01; *p*-value = 0.92) or Dexlansoprazole (OR 0.31; 95% CI 0.02 to 4.92; *p*-value = 0.4) (Figure 8. Forest plots of the odds of ECL cell proliferation in participants who received proton pump inhibitors compared to those who did not receive proton pump inhibitors by using different types of PPIs.).

Gastric polyps and Cancers: Four studies evaluated participants for gastric polyps over the course of the study. One study recorded the number of patients with endoscopic fundic gland polyps at baseline and during each follow-up period (Fiocca et al., 2012). Four other studies reported the number of participants who developed gastric polyps during the study as adverse reactions (Peura et al., 2009; Sugano et al., 2014; Kushima et al., 2022; Cho et al., 2023), but the location of the gastric polyp was not indicated. Three studies clearly described participants with gastrointestinal cancers; one research stated that no patients were found to have cancer during the study (Lundell et al., 1999), and another showed the number of participants with cancer in the adverse effect table (Moayyedi et al., 2019). Two groups of patients in one study used 10 mg and 5 mg of rabeprazole once daily (Fujishiro et al., 2015), respectively, which we included as the experimental and control groups were included in the study.

Pooling the above five studies, 55 of 6,268 participants who received PPI maintenance therapy for more than 6 months developed gastric polyps, gastric polyps were detected in 62 of the 1,575 participants in the control group, and there was no evidence that the presence of gastric polyps was associated with long-term PPI use (OR 1.13; 95% CI 0.68 to 1.89; *p*-value = 0.64) (Figure 9. Forest plots of odds ratios for gastric polyps in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.).

In a pooled analysis of three studies with gastric cancer statistics, 90 of the 9,306 participants in the experimental group developed to gastric cancer, and 84 of the 9,148 participants in the control group were found to have gastric cancer. The difference in prevalence between the two groups was not statistically significant (OR 1.06; 95% CI 0.79 to 1.43; *p*-value = 0.71) (Figure 10. Forest plots of odds ratios for gastric cancer in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.).

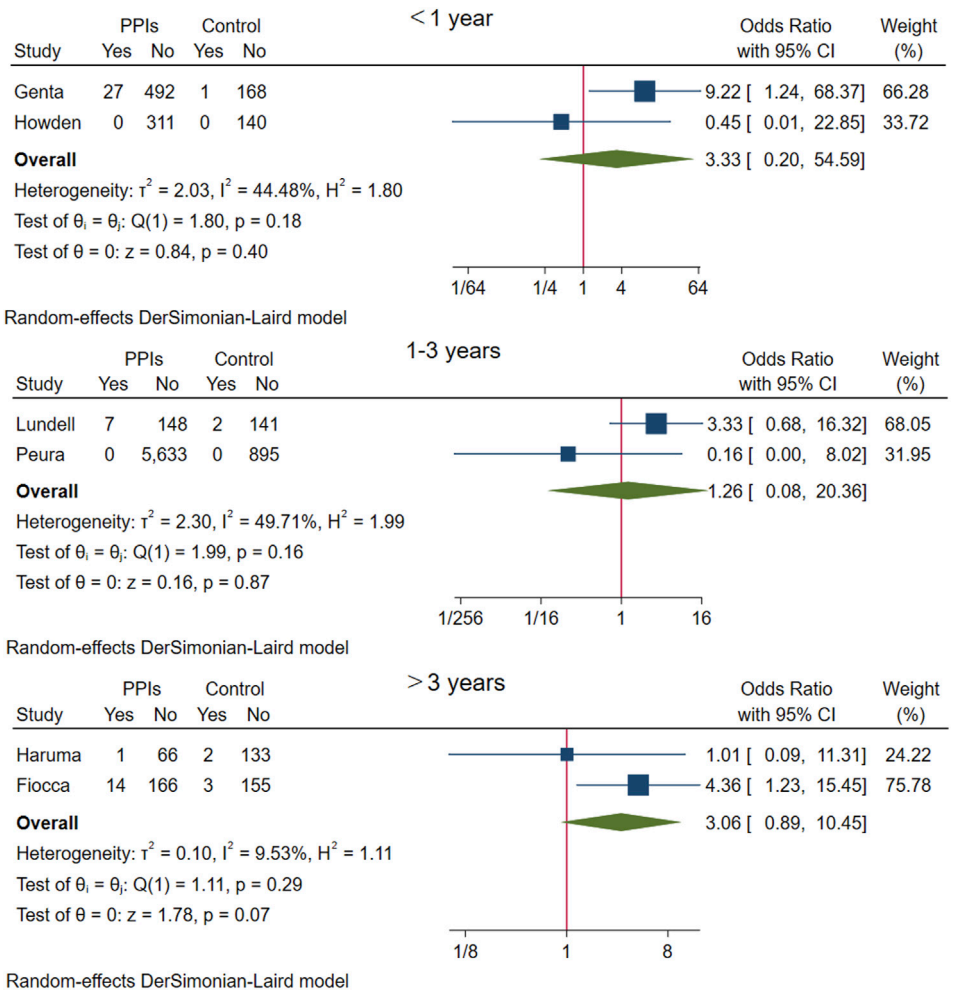


FIGURE 7
Forest plots of the odds of ECL cell proliferation in participants who received proton pump inhibitors compared to those who did not receive proton pump inhibitors by different observation duration.

4 Discussion

Our analysis found no evidence that long-term maintenance therapy with PPIs causes or exacerbates gastric mucosal atrophy, intestinal metaplasia, gastric polyps, or gastric cancer in users compared to other treatments. However, we did find a correlation between PPI use and ECL cell proliferation, which may depend on the type of PPI used rather than the duration of use. Our results are consistent with Song's analysis (Song et al., 2014), but incorporate more recent RCT studies to improve the analysis's quality and minimise bias. Overall, these findings suggest that long-term maintenance therapy with PPIs can be safely used as a therapeutic strategy in clinical practice. However, the potential risk of ECL cell proliferation associated with high gastrin levels over a long time must be considered.

In recent years, concerns have arisen that long-term use of PPIs may increase the risk of gastric cancer-related disease (Salvo et al., 2021), and various hypotheses have been proposed regarding its causes and mechanisms. One hypothesis is that prolonged acid suppression therapy may alter the stomach's acid environment, allowing colonisation by various bacteria (Yang and Metz, 2010), including *H. pylori*, which can damage the gastric oxidative glands (Parsons et al., 2017) and potentially trigger malignant transformation, possibly accompanied by a targeted transfer of gastric flora due to profound acid suppression (Malfertheiner et al., 2017). However, two studies (Lundell et al., 1999; Fiocca et al., 2012) found no significant increase in gastric atrophy and intestinal metaplasia in H. pylori-positive patients on long-term PPI maintenance therapy, and the difference in lesions in the gastric body and sinus in the two studies (Genta et al., 2003; Fiocca et al., 2012) was not significant. Although we initially planned to perform a subgroup analysis regarding *H. pylori* and lesion site, we were unable to do so due to the limited number of relevant trials. Based on the available studies, it appears that acid suppression alone is unlikely to have adverse effects on the human gastric mucosa. Nonetheless, the dysbiosis of the gastrointestinal flora caused by long-term PPI use (Sanduleanu et al., 2001; Lo and Chan, 2013) and the association of *H. pylori* with gastrointestinal cancers remain areas of concern (Lee et al., 2013; Mera et al., 2018; Yan et al., 2022). Further research is needed to determine the best approach to managing these risks.

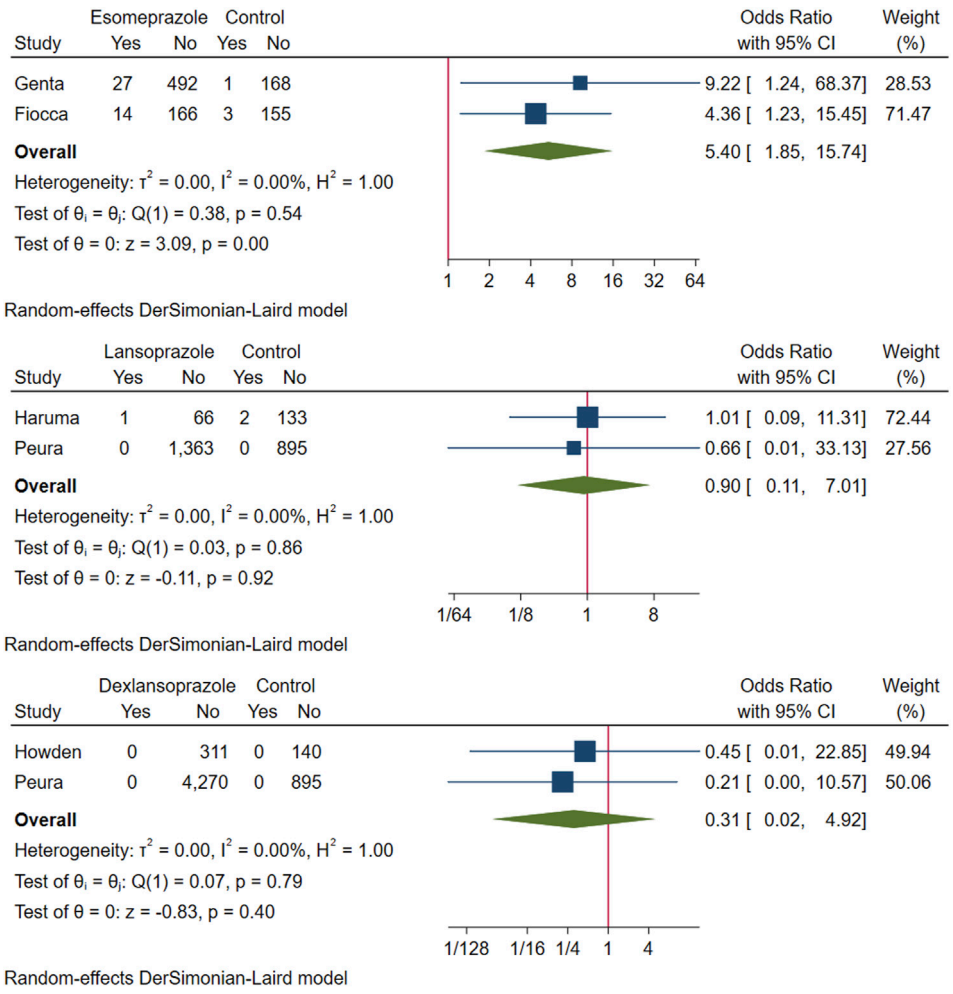


FIGURE 8
Forest plots of the odds of ECL cell proliferation in participants who received proton pump inhibitors compared to those who did not receive proton pump inhibitors by using different types of PPIs.

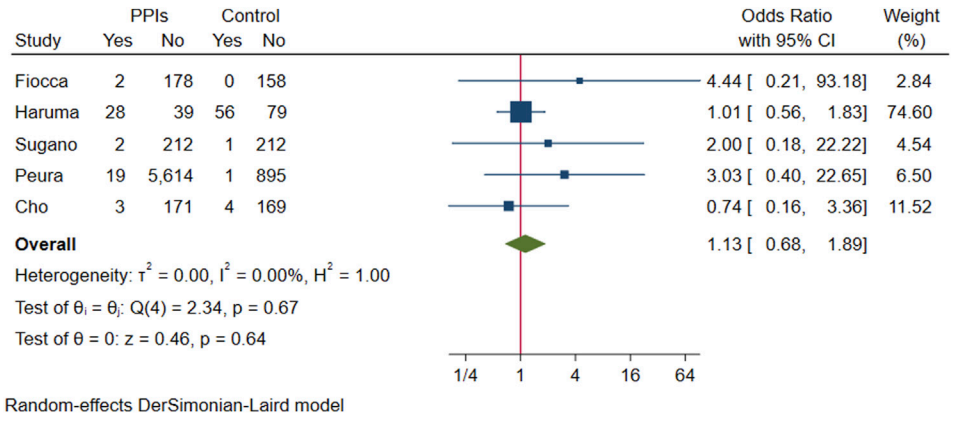


FIGURE 9
Forest plots of odds ratios for gastric polyps in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.

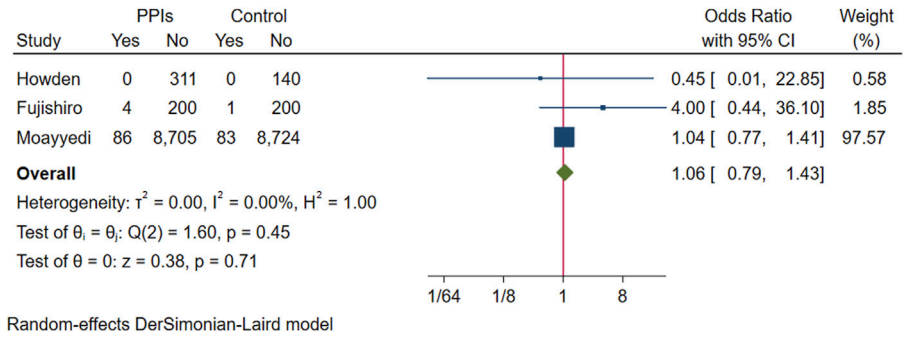


FIGURE 10
Forest plots of odds ratios for gastric cancer in participants receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors.

Ever since the observation of hypergastrinemia-induced ECL cell hyperplasia, a pre-cancerous condition, in the carcinogenicity study of omeprazole conducted on rats (Havu, 1986), the issue concerning the association between proton pump inhibitors (PPIs) and gastric cancer risk has never ceased. According to another study, when 75% of the acid-producing portion of a rat's stomach is removed, hypergastrinemia occurs, and over time, there is a proliferation of ECL cells (Mattsson et al., 1991). High-dose, potent, and long-acting acid secretion inhibitors can alter the pH of the gastrointestinal system, affecting acid feedback regulation, leading to an increase in gastrin levels, and subsequently resulting in hypergastrinemia (Håkanson and Sundler, 1990; Veysey-Smith et al., 2021), which has a direct trophic effect on ECL cells (Waldum and Mjønes, 2020). This may be the reason why ECL cell proliferation appears to be related to the long-term use of PPI maintenance therapy. There is no threshold concentration for the trophic effect of gastrin on ECL cells (Peghini et al., 2002), and long-term high gastrin levels will inevitably cause the proliferation of ECL cells (Rais et al., 2022), which may develop into tumour cells, thus increasing the risk of cancer development in the long run, which may be intestinal gastric adenocarcinoma or neuroendocrine cancer (Waldum and Mjønes, 2020; Rais et al., 2022). However, the process of inducing gastric tumours requires a considerable amount of time and may only manifest after several decades. We found that the studies using esomeprazole (Genta et al., 2003; Fiocca et al., 2012) had more ECL cell hyperplasia in participants treated with PPI maintenance therapy compared to those using dexlansoprazole (Howden et al., 2009; Peura et al., 2009) or lansoprazole (Peura et al., 2009; Haruma et al., 2021). In the classification of Proton Pump Inhibitors (PPIs), we categorize them based on their chemical structure and mechanism of action, primarily into benzimidazole and thiazole classes. The benzimidazole class includes omeprazole, lansoprazole, and esomeprazole, while the thiazole class includes pantoprazole and rabeprazole. The majority of PPIs are metabolized primarily through the hepatic cytochrome P450 enzyme system. For instance, omeprazole and lansoprazole are mainly metabolized through CYP2C19 and CYP3A4, while esomeprazole is primarily metabolized through CYP2C19 (Li et al., 2004). There are differences among various PPIs in terms of inhibiting gastric acid secretion, onset time, duration, and protective effects on the gastric mucosa. Generally, the acid-suppressing effect of esomeprazole is considered the strongest (Edwards et al., 2001; Edwards et al., 2006), followed by rabeprazole, then omeprazole, and finally lansoprazole (Miner et al., 2003). This is primarily due to their differing metabolic rates and pathways in the body, which influence their pharmacological effects. Esomeprazole, the S-isomer of omeprazole, has a more stable molecular structure, is more readily absorbed by the human body, and has a longer half-life in gastric acid, enabling it to continuously inhibit gastric acid secretion. Esomeprazole directly acts on the proton pumps of gastric wall cells, inhibiting their production of gastric acid, and its acid-suppressing effect is stronger than other proton pump inhibitors, this may trigger a reflection on the choice of clinical PPI type. The ECL cell density did not increase in many participants, suggesting that not all patients require strong inhibition of gastric acid secretion. Clinically, the appropriate type of PPI and the appropriate dosage should be chosen according to individual needs. The risk of elevated gastrin and consequent ECL cell hyperplasia due to long-term PPI use may lead to gastric neuroendocrine tumours or gastric adenocarcinoma is not negligible (Cavalcoli et al., 2015). However, this may be the result of a combination of causes. The presence of *H. pylori* and the patient's original gastric precancerous lesions are also considered to be the causes of elevated gastrin (Veysey-Smith et al., 2021). Therefore, in the long-term management of PPI maintenance therapy, it is important to consider the risk of ECL cell proliferation and manage any *H. pylori* infection or gastric precancerous lesions.

Regarding gastric polyps and gastric cancer, we did not restrict the location of polyps to include all RCT studies that reported gastric polyps because of the small number of studies addressing fundic gland polyps. Our results reflect some controversy compared to previous pooled analyses by Tran-Duy (Tran-Duy et al., 2016) and F.C. Martin (Martin et al., 2016) which were based on population cohort studies and mostly cross-sectional studies conducted during a specific period. We also found differing conclusions in this area of the literature (Hong et al., 2011; Krishnan et al., 2012; Brusselaers et al., 2020) when we reviewed RCT studies. In gastric cancer, there have also been several meta-analyses (Segna et al., 2021; Guo et al., 2023; Peng et al., 2023) based on case-control studies and retrospective cohort studies in recent years that support the idea that PPI use elevates the risk of gastric cancer, reaching different results than our analysis. The reasons for this may lie mainly in the

very limited number of relevant high-quality RCT studies, previous meta-analyses have relied on case-control studies and retrospective cohort studies, which leads to baseline imbalances triggered by inclusion and exclusion criteria, as well as potential difficulties in dosing control and prolonged follow-up, resulting in high heterogeneity. In contrast, our meta-analysis included only existing RCT studies, resulting in lower heterogeneity and different findings from those of recent meta-analyses. Our study offers a unique contribution to the literature by focusing exclusively on high-quality RCT studies, providing a clearer picture of the relationship between PPI use and gastric polyps and cancer. However, we still need more well-designed, high-quality studies to address the current controversy.

In the analyses of gastric atrophy and intestinal metaplasia, after including the data under extreme assumptions, $I^2 = 25.8\%$ for gastric atrophy and $I^2 = 35.21\%$ for intestinal metaplasia, and after excluding this data the I^2 decreased to 7.48% and 0, respectively, with the same direction of meta-analysis results before and after exclusion, suggesting that the scale of inclusion of data from this study does not affect the final conclusions of the analysis. In the analysis regarding ECL cells, $I^2 = 7.13\%$, and $I^2 = 0$ in the rest of the analyses. $p > 0.05$ was seen in all Q-tests, and the minimum value in several studies was $p = 0.19$. No significant heterogeneity was observed in our research. This is reassuring. However, there are some limitations in the following aspects. First, the number of pieces of literature included in this study is still relatively limited. We sought as much relevant literature as possible while ensuring the quality of the literature and included trials that had not yet been completed but for which data were published annually; second, since the publication of relevant data differed among the literature, and some literature only published the prevalence rate per year, and we could not identify the trend of change. We did not receive a reply after sending an email to the authors to ask about it. We accumulated this data and included it in the analysis, the lack of response to our email inquiries also resulted in some bias; third, the study had diverse control group intervention modalities, including placebo, surgery, and other therapeutic drugs, the association of the disease with the experimental group might not be stable due to the diverse intervention modalities in the control group; fourth, the primary outcomes of some of the literature did not match the present study. It mainly reported data of interest in the form of secondary results or adverse events found during the primary outcome, and we sought reports of relevant events in the eligible full texts, but there may still be incomplete or non-specific statistics for this part of the data; finally, some of the pieces of the literature may also have factors of bias such as open-label design and pharmaceutical industry funding, and other unidentified biases. This study exclusively incorporated Randomised Controlled Trials (RCTs), without considering real-world cohort studies. This was primarily due to the fact that RCTs are considered the gold standard for assessing intervention effects, given their design which minimizes bias to the greatest extent possible. However, we acknowledge that real-world cohort studies, offering a broader patient population and longer follow-up data, could potentially influence our results. In the literature where cohort studies were included, we found a significant association between long-term use of PPIs and premalignant gastric lesions. This could be attributed to the fact that cohort studies typically encompass a wider patient population, including those who might be excluded in RCTs, such as the elderly and patients with multiple chronic diseases. Furthermore, cohort studies usually have a longer follow-up period, which might allow us to observe the potential impacts of long-term PPI use, a feat quite challenging in RCTs. However, the occurrence of carcinogenesis requires a considerable length of time, possibly spanning decades, hence our results may be biased. Therefore, the conclusion should be that PPI treatment within the follow-up period of the included RCTs, ranging from 6 to 36 weeks, will not induce gastric cancer at the end of treatment, but long-term maintenance treatment with PPIs may increase susceptibility to gastric cancer, making individuals more prone to gastric cancer in their later years. Future research should consider incorporating real-world cohort studies to more comprehensively assess the association between long-term use of PPIs and premalignant gastric lesions.

PPIs are being used more frequently while their application is gradually expanding (Kinoshita et al., 2018), and their relationship with adverse effects such as pneumonia (Zirk-Sadowski et al., 2018) and osteoporosis (Park et al., 2022) has received attention. Despite the extensive use of Proton Pump Inhibitors (PPIs), the influence of long-term maintenance therapy on the risk of developing gastric cancer-related diseases remains uncertain. This necessitates further exploration in high-quality clinical studies, with this as the primary outcome. Nevertheless, our meta-analysis of the existing literature reveals no significant correlation between PPI maintenance therapy and an increased risk of gastric mucosal atrophy, intestinal metaplasia, or gastric polyps within a maximum follow-up period of 3 years. However, it does lead to ECL cell hyperplasia, a consequence of excessive gastrin triggered by strong acid suppression, which heightens the patient's susceptibility to gastric cancer. Therefore, our findings suggest that PPI therapy can be safely and effectively employed for the treatment of patients with gastrointestinal diseases requiring long-term maintenance therapy. However, caution should be exercised when considering the use of PPIs, and the potential risks and benefits of treatment should be meticulously evaluated for each patient. Not all patients necessitate treatment that strongly suppresses gastric acid secretion, such as the most potent acid-suppressing PPIs or PPIs at effective doses.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ZZ was responsible for overseeing the entire process from the beginning of the study until the publication of the article. ZZ was accountable for topic selection, literature screening, extraction of mergeable data, and overall study design and manuscript writing. ZL conducted literature screening, performed data extraction, and conducted statistical analysis. YS participated in manuscript writing and proofreading of the language. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1244400/full#supplementary-material

References

Allemani, C., Weir, H. K., Carreira, H., Harewood, R., Spika, D., Wang, X. S., et al. (2015). Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet (London, Engl.* 385 (9972), 977–1010. doi:10.1016/S0140-6736(14)62038-9

Brusselaers, N., Sadr-Azodi, O., and Engstrand, L. (2020). Long-term proton pump inhibitor usage and the association with pancreatic cancer in Sweden. *J. Gastroenterol.* 55 (4), 453–461. doi:10.1007/s00535-019-01652-z

Carmack, S. W., Genta, R. M., Graham, D. Y., and Lauwers, G. Y. (2009). Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat. Rev. Gastroenterology hepatology* 6 (6), 331–341. doi:10.1038/nrgastro.2009.70

Cavalcoli, F., Zilli, A., Conte, D., Ciafardini, C., and Massironi, S. (2015). Gastric neuroendocrine neoplasms and proton pump inhibitors: fact or coincidence? *Scand. J. Gastroenterol.* 50 (11), 1397–1403. doi:10.3109/00365521.2015.1054426

Cho, Y. K., Kim, J. H., Kim, H. S., Kim, T. O., Oh, J. H., Choi, S. C., et al. (2023). Randomised clinical trial: comparison of tegoprazan and lansoprazole as maintenance therapy for healed mild erosive oesophagitis. *Aliment. Pharmacol. Ther.* 57 (1), 72–80. doi:10.1111/apt.17255

Colquhoun, A., Arnold, M., Ferlay, J., Goodman, K. J., Forman, D., and Soerjomataram, I. (2015). Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 64 (12), 1881–1888. doi:10.1136/gutjnl-2014-308915

Correa, P., Haenszel, W., Cuello, C., Tannenbaum, S., and Archer, M. (1975). A model for gastric cancer epidemiology. *Lancet (London, Engl.* 2 (7924), 58–60. doi:10.1016/s0140-6736(75)90498-5

Correa, P. (1992). Human gastric carcinogenesis: a multistep and multifactorial process-first American cancer society award lecture on cancer epidemiology and prevention. *Cancer Res.* 52 (24), 6735–6740.

Dilaghi, E., Bellisario, M., Esposito, G., Carabotti, M., Annibale, B., and Lahner, E. (2022). The impact of proton pump inhibitors on the development of gastric neoplastic lesions in patients with autoimmune atrophic gastritis. *Front. Immunol.* 13, 910077. doi:10.3389/fimmu.2022.910077

Edwards, S., Lind, T., and Lundell, L. (2001). Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment. Pharmacol. Ther.* 15 (11), 1729–1736. doi:10.1046/j.1365-2036.2001.01128.x

Edwards, S., Lind, T., and Lundell, L. (2006). Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment. Pharmacol. Ther.* 24 (5), 743–750. doi:10.1111/j.1365-2036.2006.03074.x

Fiocca, R., Mastracci, L., Attwood, S. E., Galmiche, J. P., and Hatlebakk, J. (2012). Gastric exocrine and endocrine cell morphology under prolonged acid inhibition therapy: results of a 5-year follow-up in the LOTUS trial. *Alimentary Pharmacol. Ther.* 36 (10), 959–971. doi:10.1111/apt.12052

Fujishiro, M., Higuchi, K., Kato, M., Kinoshita, Y., Iwakiri, R., Watanabe, T., et al. (2015). Long-term efficacy and safety of rabeprazole in patients taking low-dose aspirin with a history of peptic ulcers: A phase 2/3, randomized, parallel-group, multicenter, extension clinical trial. *J. Clin. Biochem. Nutr.* 56 (3), 228–239. doi:10.3164/jcbn.15-1

Genta, R. M., Rindi, G., Fiocca, R., Magner, D. J., D'Amico, D., and Levine, D. S. (2003). Effects of 6-12 months of esomeprazole treatment on the gastric mucosa. *Am. J. gastroenterology* 98 (6), 1257–1265. doi:10.1111/j.1572-0241.2003.07489.x

Guo, H., Zhang, R., Zhang, P., Chen, Z., Hua, Y., Huang, X., et al. (2023). Association of proton pump inhibitors with gastric and colorectal cancer risk: A systematic review and meta-analysis. *Front. Pharmacol.* 14, 1129948. doi:10.3389/fphar.2023.1129948

Hagiwara, T., Mukaisho, K., Nakayama, T., Sugihara, H., and Hattori, T. (2011). Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with *Helicobacter pylori*. *Gut* 60 (5), 624–630. doi:10.1136/gut.2010.207662

Håkanson, R., and Sundler, F. (1990). Proposed mechanism of induction of gastric carcinoids: the gastrin hypothesis. *Eur. J. Clin. Invest.* 20, S65–S71. doi:10.1111/j.1365-2362.1990.tb01780.x

Haruma, K., Uemura, N., Kinoshita, Y., Yao, T., Kushima, R., Akiyama, J., et al. (2021). SA166 3-year interim analysis results of vision trial: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. *Gastroenterology* 160 (6), 447. doi:10.1016/s0016-5085(21)01779-0

Havu, N. J. D. (1986). Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion* 35, 42–55. doi:10.1159/000199381

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ Clin. Res. ed)* 343, d5928. doi:10.1136/bmj.d5928

Higgins, J. P., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ Clin. Res. ed).* 327 (7414), 557–560. doi:10.1136/bmj.327.7414.557

Higgins, J. P., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics Med.* 21 (11), 1539–1558. doi:10.1002/sim.1186

Hong, K., Kim, S., Kang, S., and Kim, J. (2011). Effect of long-term use of proton pump inhibitor on atrophic gastritis and gastric cancer: A 5-year longitudinal cohort study in South Korea. *Drug Saf.* 34 (10), 970.

Howden, C. W., Larsen, L. M., Perez, M. C., Palmer, R., and Atkinson, S. N. (2009). Clinical trial: efficacy and safety of dexlansoprazole MR 60 and 90 mg in healed erosive oesophagitis - maintenance of healing and symptom relief. *Alimentary Pharmacol. Ther.* 30 (9), 895–907. doi:10.1111/j.1365-2036.2009.04119.x

Johnson, D. A., Benjamin, S. B., Vakil, N. B., Goldstein, J. L., Lamet, M., Whipple, J., et al. (2001). Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am. J. gastroenterology* 96 (1), 27–34. doi:10.1111/j.1572-0241.2001.03443.x

Kim, G. H. (2021). Proton pump inhibitor-related gastric mucosal changes. *Gut liver* 15 (5), 646–652. doi:10.5009/gnl20036

Kinoshita, Y., Ishimura, N., and Ishihara, S. (2018). Advantages and disadvantages of long-term proton pump inhibitor use. *J. Neurogastroenterol. Motil.* 24 (2), 182–196. doi:10.5056/jnm18001

Krishnan, A., Rajesh Prabu, P., and Jayanthi, V. (2012). Long term acid suppression therapy: it's influence on gastric mucosa. *Dis. Esophagus* 25, 65A. doi:10.1111/j.1442-2050.2012.01405.x

Kushima, R., Uemura, N., and Kinoshita, Y. (2022). 4-Year interim analysis results of vision trial: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. *Gastroenterology* 162 (7)–1066. doi:10.1016/S0016-5085(22)62550-2

Lee, Y. C., Chen, T. H., Chiu, H. M., Shun, C. T., Chiang, H., Liu, T. Y., et al. (2013). The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. *Gut* 62 (5), 676–682. doi:10.1136/gutjnl-2012-302240

Li, X., Andersson, T., Ahlström, M., Weidolf, L., and Chemicals, D. (2004). Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab. Dispos.* 32 (8), 821–827. doi:10.1124/dmd.32.8.821

Lo, W. K., and Chan, W. W. (2013). Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin. gastroenterology hepatology* 11 (5), 483–490. doi:10.1016/j.cgh.2012.12.011

Lundell, L., Miettinen, P., Myrvold, H. E., Pedersen, S. A., Thor, K., Andersson, A., et al. (1999). Lack of effect of acid suppression therapy on gastric atrophy. Nordic Gerd Study Group. *Gastroenterology.* 117 (2), 319–326. doi:10.1053/gast.1999.0029900319

Lundell, L., Vieth, M., Gibson, F., Nagy, P., and Kahrilas, P. J. (2015). Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Alimentary Pharmacol. Ther.* 42 (6), 649–663. doi:10.1111/apt.13324

Malfertheiner, P., Kandulski, A., and Venerito, M. (2017). Proton-pump inhibitors: understanding the complications and risks. *Nat. Rev. Gastroenterology hepatology* 14 (12), 697–710. doi:10.1038/nrgastro.2017.117

Martin, F. C., Chenevix-Trench, G., and Yeomans, N. D. (2016). Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors. *Alimentary Pharmacol. Ther.* 44 (9), 915–925. doi:10.1111/apt.13800

Mattsson, H., Havu, N., Bräutigam, J., Carlsson, K., Lundell, L., and Carlsson, E. J. G. (1991). Partial gastric corpectomy results in hypergastrinemia and development of gastric enterochromaffinlike-cell carcinoids in the rat. *Gastroenterology* 100 (2), 311–319. doi:10.1016/0016-5085(91)90197-s

Mera, R. M., Bravo, L. E., Camargo, M. C., Bravo, J. C., Delgado, A. G., Romero-Gallo, J., et al. (2018). Dynamics of *Helicobacter pylori* infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. *Gut* 67 (7), 1239–1246. doi:10.1136/gutjnl-2016-311685

Miner, P., Katz, P., Chen, Y., and Sostek, M. (2003). Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am. J. Gastroenterol.* 98 (12), 2616–2620. doi:10.1111/j.1572-0241.2003.08783.x

Moayyedi, P., Eikelboom, J. W., Bosch, J., Connolly, S. J., Dyal, L., Shestakovska, O., et al. (2019). Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 157 (3), 682–691.e2. doi:10.1053/j.gastro.2019.05.056

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *Bmj* 372, n160. doi:10.1136/bmj.n160

Park, D. H., Seo, S. I., Lee, K. J., Kim, J., Kim, Y., Seo, W. W., et al. (2022). Long-term proton pump inhibitor use and risk of osteoporosis and hip fractures: A nationwide population-based and multicenter cohort study using a common data model. *J. Gastroenterol. Hepatol.* 37 (8), 1534–1543. doi:10.1111/jgh.15879

Park, D. Y., and Lauwers, G. Y. (2008). Gastric polyps: classification and management. *Archives pathology laboratory Med.* 132 (4), 633–640. doi:10.1043/1543-2165(2008)132[633:GPCAM]2.0.CO;2

Parsons, B. N., Ijaz, U. Z., D'Amore, R., Burkitt, M. D., Eccles, R., Lenzi, L., et al. (2017). Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of Helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use. *PLoS Pathog.* 13 (11), e1006653. doi:10.1371/journal.ppat.1006653

Peghini, P. L., Annibale, B., Azzoni, C., Milione, M., Corleto, V. D., Gibril, F., et al. (2002). Effect of chronic hypergastrinemia on human enterochromaffin-like cells: insights from patients with sporadic gastrinomas. *Gastroenterology* 123 (1), 68–85. doi:10.1053/gast.2002.34231

Peng, T. R., Wu, T. W., and Li, C. H. (2023). Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review and meta-analysis. *Int. J. Clin. Oncol.* 28 (1), 99–109. doi:10.1007/s10147-022-02253-2

Peura, D. A., Metz, D. C., Dabholkar, A. H., Paris, M. M., Yu, P., and Atkinson, S. N. (2009). Safety profile of dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed release formulation: global clinical trial experience. *Aliment. Pharmacol. Ther.* 30 (10), 1010–1021. doi:10.1111/j.1365-2036.2009.04137.x

Piazuelo, M. B., Bravo, L. E., Mera, R. M., Camargo, M. C., Bravo, J. C., Delgado, A. G., et al. (2021). The Colombian chemoprevention trial: 20-Year follow-up of a cohort of patients with gastric precancerous lesions. *Gastroenterology* 160 (4), 1106–1117.e3. doi:10.1053/j.gastro.2020.11.017

Rais, R., Trikalinos, N. A., Liu, J., and Chatterjee, D. (2022). Enterochromaffin-like cell hyperplasia-associated gastric neuroendocrine tumors may arise in the setting of proton pump inhibitor use. *Archives pathology laboratory Med.* 146 (3), 366–371. doi:10.5858/arpa.2020-0315-OA

Ren, R., Wang, Z., Sun, H., Gao, X., and Peng, L. (2018). The gastric mucosal-associated microbiome in patients with gastric polyposis. *Sci. Rep.* 8 (1), 13817. doi:10.1038/s41598-018-31738-2

Salvo, E. M., Ferko, N. C., Cash, S. B., Gonzalez, A., and Kahrilas, P. J. (2021). Umbrella review of 42 systematic reviews with meta-analyses: the safety of proton pump inhibitors. *Alimentary Pharmacol. Ther.* 54 (2), 129–143. doi:10.1111/apt.16407

Sanduleanu, S., Jonkers, D., De Bruïne, A., Hameeteman, W., and Stockbrügger, R. W. (2001). Double gastric infection with *Helicobacter pylori* and non-Helicobacter pylori bacteria during acid-suppressive therapy: increase of pro-inflammatory cytokines and development of atrophic gastritis. *Alimentary Pharmacol. Ther.* 15 (8), 1163–1175. doi:10.1046/j.1365-2036.2001.01029.x

Segna, D., Brusselaers, N., Glaus, D., Krupka, N., and Misselwitz, B. (2021). Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis. *Ther. Adv. Gastroenterol.* 14, 17562848211051463. doi:10.1177/17562848211051463

Song, H., Zhu, J., and Lu, D. (2014). Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. *Cochrane database Syst. Rev.* 2014 (12), Cd010623. doi:10.1002/14651858.CD010623.pub2

Sugano, K., Choi, M. G., Lin, J. T., Goto, S., Okada, Y., Kinoshita, Y., et al. (2014). Multinational, double-blind, randomised, placebocontrolled, prospective study of esomeprazole in the prevention of recurrent peptic ulcer in low-dose acetylsalicylic acid users: the lavender* study. *Gut* 63 (7), 1061–1068. doi:10.1136/gutjnl-2013-304722

Tran-Duy, A., Spaetgens, B., Hoes, A. W., de Wit, N. J., and Stehouwer, C. D. (2016). Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. *Clin. gastroenterology hepatology* 14 (12), 1706–1719. doi:10.1016/j.cgh.2016.05.018

Uemura, N., Kinoshita, Y., Haruma, K., Yao, T., Kushima, R., and Kanoo, T. (2018). Rationale and design of the VISION study: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis. *Clin. Exp. gastroenterology* 11, 51–56. doi:10.2147/CEG.S144149

Vakil, N. B., Shaker, R., Johnson, D. A., Kovacs, T., Baerg, R. D., Hwang, C., et al. (2001). The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. *Alimentary Pharmacol. Ther.* 15 (7), 927–935. doi:10.1046/j.1365-2036.2001.01024.x

Veysey-Smith, R., Moore, A. R., Murugesan, S. V., Tiszlavicz, L., Dockray, G. J., Varro, A., et al. (2021). Effects of proton pump inhibitor therapy, *H. pylori* infection and gastric preneoplastic pathology on fasting serum gastrin concentrations. *Front. Endocrinol.* 12, 741887. doi:10.3389/fendo.2021.741887

Waldum, H., and Mjønes, P. (2020). Towards understanding of gastric cancer based upon physiological role of gastrin and ECL cells. *Cancers* 12 (11), 3477. doi:10.3390/cancers12113477

Yadlapati, R., and Kahrilas, P. J. (2018). The "dangers" of chronic proton pump inhibitor use. *J. allergy Clin. Immunol.* 141 (1), 79–81. doi:10.1016/j.jaci.2017.06.017

Yan, L., Chen, Y., Chen, F., Tao, T., Hu, Z., Wang, J., et al. (2022). Effect of *Helicobacter pylori* eradication on gastric cancer prevention: updated report from a randomized controlled trial with 26.5 Years of follow-up. *Gastroenterology* 163 (1), 154–162.e3. doi:10.1053/j.gastro.2022.03.039

Yang, Y. X., and Metz, D. C. (2010). Safety of proton pump inhibitor exposure. *Gastroenterology* 139 (4), 1115–1127. doi:10.1053/j.gastro.2010.08.023

Zirk-Sadowski, J., Masoli, J. A., Delgado, J., Hamilton, W., Strain, W. D., Henley, W., et al. (2018). Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. *J. Am. Geriatr. Soc.* 66 (7), 1332–1338. doi:10.1111/jgs.15385

frontiers | Frontiers in Pharmacology

TYPE Case Report
PUBLISHED 31 August 2023
DOI 10.3389/fphar.2023.1242491

OPEN ACCESS

EDITED BY
Liren Qian,
Fifth Medical Center of the PLA General Hospital, China

REVIEWED BY
Yao Liu,
Daping Hospital, China
Mesut Gocer,
Antalya Training and Research Hospital, Türkiye
Poornima Ramadas,
Louisiana State University Health Shreveport, United States

*CORRESPONDENCE
Chenlu Yang,
672516342@qq.com
Yu Wu,
wu_yu@scu.edu.cn

†These authors have contributed equally to this work

RECEIVED 19 June 2023
ACCEPTED 21 August 2023
PUBLISHED 31 August 2023

CITATION
Yang J, Wang L, Zhong X, Yang C and Wu Y (2023), Zanubrutinib-induced aseptic meningitis: a case report and literature review.
Front. Pharmacol. 14:1242491.
doi: 10.3389/fphar.2023.1242491

Zanubrutinib-induced aseptic meningitis: a case report and literature review

Jinjun Yang[1†], Lian Wang[2†], Xiao Zhong[3], Chenlu Yang[1*] and Yu Wu[1*]

[1]Department of Hematology and Institute of Hematology, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Dermatology, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, China

Zanubrutinib is a Bruton tyrosine kinase (BTK) inhibitor used in B cell malignancy treatment and is generally well tolerated in most patients. Zanubrutinib-induced aseptic meningitis is currently not reported. Herein, we present the first case of zanubrutinib-induced aseptic meningitis. A 33-year-old woman was diagnosed with relapsed/refractory follicular lymphoma and subsequently developed aseptic meningitis after receiving zanubrutinib treatment. We reviewed the literature and uncovered the lack of current reports on zanubrutinib or other BTK inhibitor-induced aseptic meningitis. Moreover, we summarized cases on aseptic meningitis induced by common chemotherapy and targeted drugs used for hematological diseases. Drug-induced aseptic meningitis (DIAM) is a drug-induced meningeal inflammation. The possible pathogenesis is the direct stimulation of the meninges via intrathecal injection of chemotherapy drugs and immune hypersensitivity response caused by immunosuppressive drugs. It is more common in women with immune deficiency and mainly manifests as persistent headache and fever. Cerebrospinal fluid examinations mainly demonstrate a significant increase in cells and proteins. DIAM diagnosis needs to exclude bacterial, fungal, viral, and tuberculosis infections; neoplastic meningitis; and systemic diseases involving the meninges. The prognosis of DIAM is usually favorable, and physicians should detect and stop the causative drug. In conclusion, zanubrutinib-induced aseptic meningitis is a rare but serious complication, and physicians should be promptly aware of this adverse event to avoid serious consequences.

KEYWORDS

Zanubrutinib, bruton tyrosine kinase, follicular lymphoma, aseptic meningitis, hematological diseases

Introduction

Bruton tyrosine kinase (BTK) is a nonreceptor kinase that plays a crucial role in oncogenic signaling for leukemic cell proliferation and survival in multiple B cell malignancies (Pal Singh et al., 2018). BTK inhibitors form a covalent bond with a cysteine residue (Cys-481) in the kinase domain to inactivate BTK, which further restrains the B-cell antigen receptor pathway activation and blocks malignant B-cell proliferation and survival (Kim, 2019). Zanubrutinib is a next-generation BTK inhibitor that has presented promising antitumor activities in both preclinical models and clinical studies (Syed, 2020). Zanubrutinib monotherapy is generally well tolerated in patients with B cell malignancies. A pooled safety analysis of zanubrutinib reports that the common grade

of ≥ 3 nonhematologic treatment-emergent adverse events (AEs) (≥ 2%) are pneumonia, hypertension, upper respiratory tract infection, urinary tract infection, sepsis, diarrhea, and musculoskeletal pain (Tam et al., 2022). A grade of ≥ 3 headache is reported in 1% of patients and with no reports of severe AEs of the central nervous system (CNS). Herein, we report the first case of zanubrutinib-induced aseptic meningitis and performed a literature review of drug-induced aseptic meningitis (DIAM) in hematological diseases. We searched PubMed for articles containing the words "zanubrutinib," "ibrutinib," "acalabrutinib," "tirabrutinib," "orelabrutinib," "pirtobrutinib," "nemtabrutinib," "Bruton tyrosine kinase inhibitors," "rituximab," "cytarabine," "methotrexate," "apolizumab," "dasatinib," "RG7356," "daratumumab," "alemtuzumab," and "aseptic meningitis" from inception up to May 2023 with no language restrictions.

Case presentation

A 33-year-old Chinese woman presented to our department with the chief complaint of headache, fever, tremors, and unstable gait for 10 days in November 2020. She had a known history of relapsed/refractory follicular lymphoma (FL) for 2 years. Two years ago, she presented with multiple lymph node enlargement and splenomegaly a few months after giving birth. She had no symptoms of fever, night sweats, and weight loss. She visited a local hospital. The left armpit lymph node biopsy indicated FL (grade II). Positron emission tomography/computed tomography (PET/CT) revealed lymph node enlargement of ≥3 cm diameter and increased β-2-[18F]-Fluoro-2-deoxy-D-glucose (FDG) uptake in the neck, armpits, mediastinum, abdominopelvic cavity, and groin. Additionally, the FDG uptake was increased in both breasts, spleen, and multiple bones. Therefore, she was diagnosed with FL (stage IV, grade 2, group A, FLIPI 3 points). Considering the history of giving birth, she received four courses of R2 chemotherapy (rituximab and lenalidomide) for 4 months at the local hospital. However, remission was not achieved; thus, she was prescribed four courses of standard R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for 8 months, and she achieved partial remission. Afterward, she received maintenance therapy with rituximab every 2 months. However, 5 months ago, she experienced recurrent lymphadenopathy and hepatosplenomegaly, and she visited our hospital. The PET/CT confirmed lymphoma relapse. Considering that new targeted drugs, including obinutuzumab and phosphoinositide 3-kinase inhibitors, have not yet been marketed in China and this patient could not be a candidate in the clinical trial of FL at our hospital because of hepatitis B virus infection, she was scheduled to receive zanubrutinib treatment (560 mg per day) after obtaining informed consent. She re-achieved partial remission after taking zanubrutinib for 4 months, and oral zanubrutinib was continued. However, 10 days ago, the patient

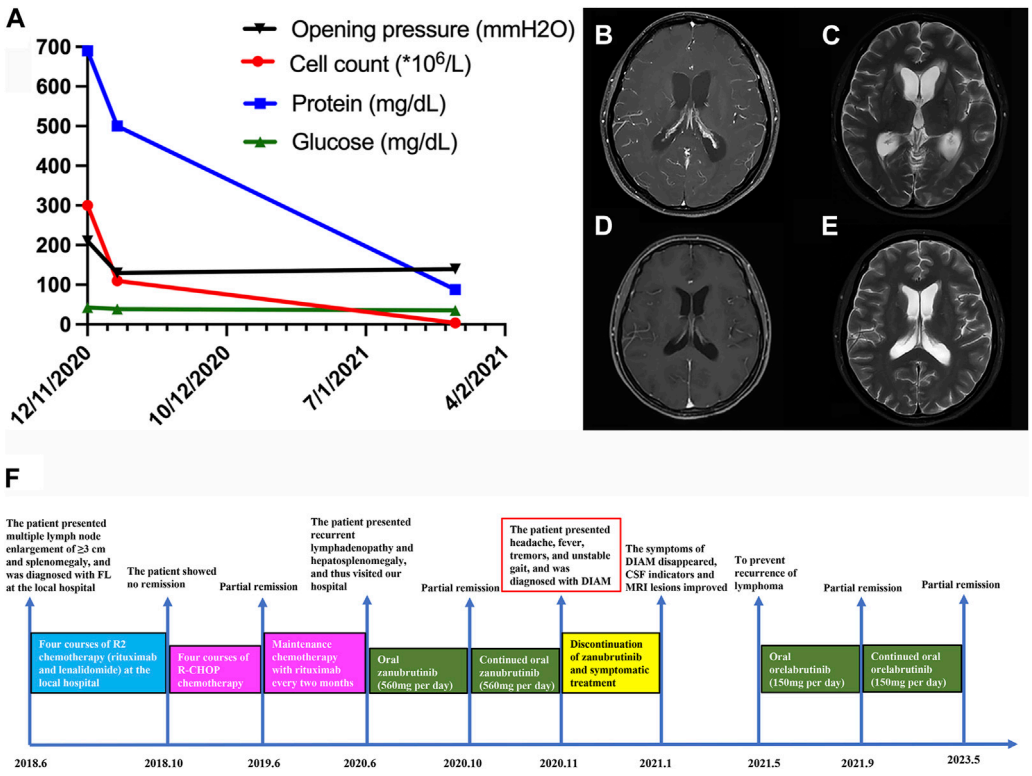


FIGURE 1
(A) Changes in various cerebrospinal fluid indicators before and after zanubrutinib discontinuation in the patient **(B–C)** Brain MRI of the patient before zanubrutinib discontinuation. **(B)** T1 enhancement; **(C)** T2. **(D–E)** Brain MRI after the patient stopped using zanubrutinib for 4 months. **(D)** T1 enhancement; **(E)** T2. **(F)** Detailed time course of the patient's clinical course and therapeutic regimen.

TABLE 1 Main criteria for DIAM differential diagnosis.

		DIAM (Yelehe-Okouma et al., 2018)	Bacterial meningitis (Hasbun, 2022)	Fungal meningitis (Bystritsky and Chow, 2022)	Viral meningitis (Gundamraj and Hasbun, 2023)	Tuberculous meningitis (Mount and Boyle, 2017)	Neoplastic meningitis (Tattevin et al., 2019)	Systemic diseases with meningeal involvement (Tattevin et al., 2019)
Etiology		NSAIDs, antibiotics, IVIG, monoclonal antibodies, and antiepileptic drugs	*Streptococcus* pneumoniae, group B *Streptococcus*, *Neisseria* meningitidis, *Haemophilus* influenzae, and *Listeria* monocytogenes	Cryptococcus neoformans, Cryptococcus gattii, Coccidioides, Histoplasma, Blastomyces, and Sporothrix schenckii	Enteroviruses, herpesviruses, mumps and measles viruses, arboviruses, and lymphocytic choriomeningitis virus	*Mycobacterium tuberculosis*	Leukemia, lymphoma, breast cancer, lung cancer, and melanoma	Sarcoidosis, Behcet's disease, Sjögren syndrome, systemic lupus erythematosus, and granulomatosis with polyangiitis
Clinical features		Headache, altered consciousness, fever, and myalgia	Fever, neck stiffness, altered mental status, and headache	Headache, fever, cranial nerve, and other focal neurologic deficits	Headache, fever, neck stiffness, and altered mental status	Headache, fever, cranial nerve, and other focal neurologic deficits	Multifocal neurological lesions, cranial nerve palsies, and cognitive impairment	Cranial nerves palsy, meningoencephalitis, cerebral vasculitis, polyneuropathy, convulsions, and pseudotumor cerebri
CSF	Pressure	Elevated	Elevated	Elevated	Normal	Normal or elevated	Elevated	-
	Cells ($\times 10^6$/L)	300	>1,000	Variable	<1,000	100–500	Elevated	>50 or <50
	Cell type	Neutrophils or lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes	Tumor cells	Neutrophils or lymphocytes
	Protein	Elevated	Elevated	Normal or elevated	Normal or elevated	Elevated	-	-
	Glucose	Normal	Reduced	Normal or reduced	Normal	Reduced	-	-
	Lactates	<3.5 mM	>3.5 mM	-	<3.5 mM	-	-	-
	Other criteria	Sterile	Bacterial culture	Fungal culture, (1,3)-β-D-glucan	PCR, and NGS	*Mycobacterium tuberculosis* culture, acid-fast bacilli staining, tuberculin skin testing, interferon-gamma release assay	-	Primary diseases
Management		Discontinuation of the causative drugs	Ampicillin, ceftriaxone, vancomycin, third-generation cephalosporin, oxacillin, corticosteroids	Amphotericin B, flucytosine, fluconazole, liposomal amphotericin B, itraconazole	Acyclovir	Isoniazid, rifampin, pyrazinamide, streptomycin, ethambutol, corticosteroids	Check-point inhibitors, monoclonal antibodies	Treatment of primary diseases
Time to regression		Within a few days	7–21 days	>4 weeks	7–15 days	>4 weeks	-	-
Outcome		Favorable	Poor	Poor	Favorable	Poor	Poor	-

Abbreviations: DIAM: drug-induced aseptic meningitis; NSAIDs: non-steroidal anti-inflammatory drugs; IVIG: intravenous immunoglobulin; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; NGS: next-generation sequencing.

developed neurological symptoms, including headache, fever, hand tremors, and unsteady gait. The laboratory examination revealed negative results for serum procalcitonin, C-reactive protein (1,3)-β-D-glucan and galactomannan test, tuberculosis antibody, and interferon-gamma release assay. Then, a lumbar puncture was performed, and the opening pressure of cerebrospinal fluid (CSF) was 210 mmH2O. The cell count, protein, and glucose were 300 × 10^6/L (normal range: 0–10 × 10^6/L), 690 mg/dL (normal range: 15–45 mg/dL), and 42.84 mg/dL (normal range: 45–79.2 mg/dL), respectively (Figure 1A). The ink stain, herpesvirus type II DNA, *mycobacterium tuberculosis* DNA, tuberculosis antibody, culture of bacteria, fungi, and

TABLE 2 Clinical characteristics of rare central nervous system complications induced by drugs in hematological malignancies.

Disease	Pathogenesis	Clinical manifestation	MRI of brain	CSF	Diagnostic criteria	Treatment strategy	Prognosis
PML Cortese, Reich, and Nath (2021)	JCV reactivation in the setting of impaired cellular immunity	Cognitive and behavioral abnormalities, sensory and motor deficits, ataxia, aphasia, cortical visual changes, and seizures	Multiple fusion leukoencephalopathies with asymmetric bilateral distribution	JCV DNA positive	Histopathological diagnosis (the triad of multifocal demyelination); JCV DNA of CSF positive, and clinical and imaging features	Antiviral therapies (cytarabine, cidofovir, topotecan, mirtazapine, mefloquine); Immune reconstitution (discontinuation of immunosuppressive therapy, plasma exchange or immunoadsorption, recombinant IL-2, filgrastim, IL-7, PD1 inhibitor, and adoptive immunotherapy with virus-specific T cells)	Unfavorable (high mortality rate, residual neurological disability, recurrent seizures, persistence of JCV, and recurrence)
PRES Geocadin (2023)	Dysregulated perfusion and reversible vasogenic edema	Headache, seizures, encephalopathy, visual disturbances, and focal neurologic deficits	Focal regions of symmetric hyperintensities	Unremarkable	Clinical and imaging features	Discontinuation of immunosuppressive therapies, anticonvulsants, management of hemorrhagic and increased intracranial pressure	Favorable (most patients can recover, with a mortality rate of 3%–6%)
DIAM Yelehe-Okouma et al. (2018)	Immunologic hypersensitivity reaction mediated by T-cell and direct inflammation of the meninges caused by intrathecal injection of antimetabolic drugs	Fever, headache, meningeal signs, altered consciousness, localization signs, seizures, and myalgia	Unremarkable	Frank meningitis with a predominance of neutrophils, normal glucose level, and moderately elevated protein level	The temporal association, clinical manifestations, and laboratory findings, excluding infectious meningitis	Suspected drug discontinuation and symptomatic treatment	Favorable (most patients can recover)

Abbreviations: PML: progressive multifocal encephalopathy; PRES: posterior reversible encephalopathy syndrome; DIAM: drug-induced aseptic meningitis; JCV: john cunningham polyoma virus; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; IL-2: interleukin 2; IL-7: interleukin 7; PD1: programmed cell death protein 1.

mycobacterium, exfoliated cells, metagenome, autoimmune encephalitis-related antibodies, paraneoplastic syndrome-related antibodies, and flow cytometry were negative. Brain magnetic resonance imaging (MRI) enhanced scan illustrated meninges thickening, cistern narrowing, third ventricle and bilateral lateral ventricle enlargement and hydrocephalus, and CSF exudation (Figures 1B, C). Zanubrutinib-induced aseptic meningitis diagnosis was highly suspected based on clinical manifestations and laboratory findings. Therefore, zanubrutinib was stopped and mannitol (125 mL, once every 12 h) was given for dehydration. The patient's neurological symptoms significantly improved, and headache, fever, hand tremors, and unsteady gait disappeared after stopping zanubrutinib for 2 months. The cell count and protein by the CSF analysis significantly decreased (Figure 1A). Enhanced brain MRI scanning revealed that the enhancement degree of intracranial pia mater and hydrocephalus was reduced (Figures 1D, E). We used another BTK inhibitor orelabrutinib to fight the lymphoma and the patient was well tolerated 4 months later. Up to now, the patient's lymphoma has been well controlled, and no CNS symptoms have reappeared after 3 years of follow-up. The therapeutic course is summarized in Figure 1F.

Discussion

Herein, we report a Chinese female patient with relapsed/refractory FL who developed aseptic meningitis after receiving zanubrutinib treatment for 4 months. The diagnosis of zanubrutinib-induced aseptic meningitis was established in our case according to the temporal association between zanubrutinib exposure and the development of CNS symptoms, clinical and laboratory findings, and typical MRI of meningitis. Currently, different BTK inhibitors, including ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib, orelabrutinib, pirtobrutinib, and nemtabrutinib, have been approved or used in the later stage of clinical development for B cell malignancy treatment, such as mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström's macroglobulinemia, and FL. Among these BTK inhibitors, except for acalabrutinib, which is prone to causing headaches, other BTK inhibitors rarely cause CNS symptoms (Lipsky and Lamanna, 2020). To the best of our knowledge, no cases of zanubrutinib- or other BTK inhibitor-induced aseptic meningitis have been reported, and this is the first case of zanubrutinib-induced aseptic meningitis. We reviewed the literature on the pathogenesis, clinical

TABLE 3 Summary of all published cases reporting DIAM in hematological diseases.

Reference	Sex/ Age	Disease	Drugs	Administration routs	Symptoms	CSF			Brain CT/MRI	Management	Outcome
						Cell count (cells/mm^3)	Protein (mg/dL)	Glucose (mg/dL)			
Thordarson and Talstad (1986)	F/24	ALL	Cytarabine	IV	Headache, fever, and neck stiffness	126	Normal	Normal	Normal	Discontinuation of cytarabine and empirical antibiotics treatment	Symptoms disappeared on the fifth day
Flasshove et al. (1992)	M/33	ALL	Cytarabine	IV	Symptoms of meningitis	6,600	Increased	-	Normal	Discontinuation of cytarabine and broad specific antibiotics	Symptoms disappeared within 4 days
van den Berg et al. (2001)	F/15	ALL	Cytarabine	IT, IV, and SC	Headache, fever, nausea, and mild nuchal rigidity	1,200	200	19.8	Normal	Discontinuation of cytarabine, empirical antibiotics treatment, and prevention of corticosteroids and clemastin	Symptoms disappeared
Pease et al. (2001)	F/8	ALL	Cytarabine	IV	Headache, fever, photophobia, and neck stiffness	113	55	50	-	Discontinuation of cytarabine and empirical antibiotics treatment	Symptoms disappeared
Lin et al. (2009)	M/65	CLL	Apolizumab	IV	Headache, fever, disoriented, and short-term memory deficits	840 (92% neutrophils)	113	47	Normal	Discontinuation of apolizumab and empirical antibiotics treatment	Symptoms disappeared over a week
Imataki et al. (2014)	F/53	Ph$^+$ ALL	Dasatinib	PO	Hypersensitivity on both palms	Increased (predominance of lymphocyte)	-	-	Normal	Discontinuation of dasatinib	Symptoms disappeared
Vey et al. (2016)	-	AML	RG7356	IV	-	-	-	-	-	Discontinuation of RG7356 and steroid administration	Symptoms disappeared over a week
	-	AML	RG7356	IV	-	-	-	-	-	Discontinuation of RG7356 and steroid administration	Symptoms disappeared over a week
Reddy et al. (2018)	F/46	MM	Daratumumab	IV	Headache, numbness in the chin, and tingling in the mouth and lips	46 (79% neutrophils)	24	89	Normal	Discontinuation of daratumumab and Empiric antibiotic therapy	Symptoms disappeared within 4 days
Kako et al. (2019)	M/19	AML	Alemtuzumab	IV	Headache and fever	Increased	-	-	-	Discontinuation of alemtuzumab and empiric antiviral therapy	Symptoms disappeared
	F/27	SAA	Alemtuzumab	IV	Headache and fever	Increased	-	-	-	Discontinuation of alemtuzumab and empiric antiviral therapy	Symptoms disappeared

(Continued on following page)

10.3389/fphar.2023.1242491

TABLE 3 (*Continued*) Summary of all published cases reporting DIAM in hematological diseases.

Reference	Sex/ Age	Disease	Drugs	Administration routs	Symptoms	CSF			Brain CT/MRI	Management	Outcome
						Cell count (cells/mm^3)	Protein (mg/dL)	Glucose (mg/dL)			
	M/58	FL	Alemtuzumab	IV	Headache and fever	Increased	-	-	-	Discontinuation of alemtuzumab and empiric antiviral therapy	Symptoms disappeared
Beaumont and Suner (2020)	F/70	Ph$^+$ ALL	Cytarabine and methotrexate	IT	Headache	710 (mostly neutrophils)	28	72	-	Discontinuation of IT	Symptoms disappeared within 2 weeks
Current report	F/33	FL	Zanubrutinib	PO	Headache, fever, hand tremors and unsteady gait	300	690	42.84	meninges thickening, cistern narrowing, third ventricle and bilateral lateral ventricle enlargement and hydrocephalus, and CSF exudation	Discontinuation of zanubrutinib	Symptoms disappeared

Abbreviations: DIAM: drug-induced aseptic meningitis; F: female; M: male; ALL: acute lymphoblastic leukemia; CLL: chronic lymphoblastic leukemia; Ph$^+$.
ALL: Philadelphia chromosome–positive acute lymphoblastic leukemia; AML: acute myeloid leukemia; MM: multiple myeloma; SAA: severe aplastic anemia; FL: follicular lymphoma; IV: intravenous infusion; IT: intrathecal injection; SC: subcutaneous injection; PO: peros; CSF: cerebrospinal fluid; CT: computed tomography; MRI: magnetic resonance imaging.

10.3389/fphar.2023.1242491

manifestations, laboratory test and imaging, diagnosis, differential diagnosis, and management of DIAM.

In DIAM, drug intake history is crucial because no specific characteristics are associated with a specific drug. Nonsteroidal anti-inflammatory drugs, intravenous immunoglobulins, antibiotics, monoclonal antibodies, anticonvulsants, vaccines, and intrathecal drugs are common causes of DIAM (Yelehe-Okouma et al., 2018). To date, no study on the mechanism of BTK inhibitor-induced aseptic meningitis has been published. The mechanisms of aseptic meningitis caused by other drugs may include direct meningeal irritation by intrathecal drug injection and immunologic hypersensitivity reaction caused by systemic administration (Yelehe-Okouma et al., 2018). We speculate that the mechanism of zanubrutinib-induced aseptic meningitis may be the immune hypersensitivity response caused by zanubrutinib that inhibits the activation of the B-cell antigen receptor pathway. Moreover, the patient did not develop DIAM with orelabrutinib; thus, we speculated whether it was related to the differences in CNS permeability between different BTK inhibitors. Currently, no study has compared head-to-head CSF concentrations under treatment with different BTK inhibitors. Three studies have reported that CSF concentrations of three BTK inhibitors (ibrutinib, zanubrutinib, and orelabrutinib) were 1.65, 2.94, and 20.10 ng/mL, respectively (Grommes et al., 2017; Song et al., 2021; Zhang et al., 2021). Therefore, high CSF concentrations of both zanubrutinib and orelabrutinib indicate that DIAM may not be related with the differences in CNS penetration between the different BTK inhibitors. In addition, BTK is the only kinase targeted by orelabrutinib (with >90% inhibition) (Dhillon, 2021), which may explain that aseptic meningitis developed with zanubrutinib rather with orelabrutinib. DIAM symptoms mainly include headache, fever, neck stiffness, nausea, photophobia, disoriented, and short-term memory deficits. The CSF analysis showed high cell and protein and normal glucose levels. MRI of the brain appeared to be normal or displayed signs of meningitis. DIAM is an exclusionary diagnosis, which requires exclusions of bacterial, fungal, viral, and tuberculosis infections, neoplastic meningitis, and systemic diseases involving the meninges (Tattevin et al., 2019). DIAM should be distinguished from these diseases, and we summarized the etiology, clinical features, CSF characteristics, treatment, and prognosis of these diseases in Table 1, which helps the doctors detect and identify DIAM promptly in clinical practice. Overall, no significant difference was found in the clinical symptoms between DIAM and other meningitis. The CSF analysis of DIAM showed high cell count, which may be confused with infectious meningitis and neoplastic meningitis. However, the CSF of DIAM does not present any pathogens or tumor cells, which can be distinguished from infectious meningitis and tumor meningitis. DIAM management mainly includes discontinuing the causative drugs and symptomatic treatments. Most patients can recover after stopping medication for approximately 1 week. Physicians must recognize and accurately discontinue relevant pathogenic drugs. Our patient with FL received immunosuppressive therapy, and CSF examination demonstrated a significant increase in cell and protein levels as previously reported. However, her glucose level was slightly lower than normal, and the brain MRI revealed typical signs of meningitis. In addition, her symptoms significantly improved after discontinuing zanubrutinib for approximately 2 months, which was longer than that previously reported.

Despite the lack of studies reporting aseptic meningitis induced by zanubrutinib and other BTK inhibitors except for our case, BTK inhibitors may cause some other serious and rare CNS AEs, including progressive multifocal encephalopathy (PML) and posterior reversible encephalopathy syndrome (PRES) (Zukas and Schiff, 2018). The mechanism may be associated with impaired cellular immunity caused by BTK inhibitors (Fugate and Rabinstein, 2015; Tattevin et al., 2019; Cortese et al., 2021; Zou et al., 2023). To distinguish aseptic meningitis from other rare complications induced by BTK inhibitors, Table 2 summarizes the pathogenesis, clinical manifestations, imaging features, CSF analysis, diagnostic criteria, treatment strategies, and prognosis of these three rare CNS complications to provide information regarding their management. PML is caused by the reactivation of John Cunningham polyoma virus in the presence of cellular immune impairment. PRES involves perfusion imbalance and reversible vascular edema. DIAM is caused by T cell-mediated immune hypersensitivity and meningeal direct inflammation caused by intrathecal injection of antimetabolic drugs. These three complications occur following immunosuppressive drug therapy, and physicians should promptly identify these rare complications and discontinue relevant suspected immunosuppressive drugs.

In addition, we reviewed the literature on common chemotherapy and targeted drugs that can induce aseptic meningitis in hematological diseases (Table 3). Currently, except for the case reported herein, 10 cases of DIAM have been reported, including a total of 13 patients (Thordarson and Talstad, 1986; Flasshove et al., 1992; van den Berg et al., 2001; Pease et al., 2001; Lin et al., 2009; Imataki et al., 2014; Vey et al., 2016; Reddy et al., 2018; Kako et al., 2019; Beaumont and Suner, 2020). The median patient age is 33 (interquartile range, 20.3–56.8) years, and the female patients are dominant (7/11, 63.6%, sexes of two patients were not reported). The primary diseases mainly include acute lymphoblastic leukemia (6/13, 46.2%), acute myeloid leukemia (3/13, 23.1%), chronic lymphoblastic leukemia (1/13, 7.7%), multiple myeloma (1/13, 7.7%), severe aplastic anemia (1/13, 7.7%), and FL (1/13, 7.7%). The associated drugs include cytarabine, apolizumab, dasatinib, daratumumab, alemtuzumab, methotrexate, and RG7356. The administration routes include intravenous infusion, intrathecal and subcutaneous injections, and oral administration. Hematologists should be vigilant for the occurrence of DIAM when these drugs are administered.

This study has some limitations. First, zanubrutinib was not rechallenged to deeply determine this adverse reaction in our patient. Additionally, this is the first case of zanubrutinib-induced aseptic meningitis, and further observation and the mechanism of zanubrutinib-induced aseptic meningitis should be explored in the future.

Conclusion

Zanubrutinib-induced aseptic meningitis should be considered a potentially serious adverse drug reaction, and whether other BTK inhibitors can cause aseptic meningitis remains unclear. Physicians, especially hematologists, should be aware of this potential AE. Relevant suspicious drugs should be promptly and effectively discontinued when suspected of DIAM because the symptoms of

DIAM are severe and most patients can quickly recover after discontinuing the causative drugs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JY and LW did the literature search and drafted the manuscript. XZ contributed to the imaging analysis. YW and CY conceived the case report and provided guidance for the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by 1•3•5 project for disciplines of excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University; Sichuan Provincial Academic and Technical Support Funding Project, Grant/Award Number: 2022YFS0191.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Beaumont, A. L., and Suner, L. (2020). Drug-induced aseptic meningitis in a Ph+ ALL patient with meningeal involvement. *Blood* 136 (4), 520. doi:10.1182/blood.2019004195

Bystritsky, R. J., and Chow, F. C. (2022). Infectious meningitis and encephalitis. *Neurol. Clin.* 40 (1), 77–91. doi:10.1016/j.ncl.2021.08.006

Cortese, I., Reich, D. S., and Nath, A. (2021). Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat. Rev. Neurol.* 17 (1), 37–51. doi:10.1038/s41582-020-00427-y

Dhillon, S. (2021). Orelabrutinib: first approval. *Drugs* 81 (4), 503–507. doi:10.1007/s40265-021-01482-5

Flasshove, M., Schütte, H. J., Kellner, R., Höffken, K., and Seeber, S. (1992). Meningeal fluid granulocytosis after cytarabine. *Eur. J. Cancer* 28 (1), 243. doi:10.1016/0959-8049(92)90418-2

Fugate, J. E., and Rabinstein, A. A. (2015). Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol.* 14 (9), 914–925. doi:10.1016/s1474-4422(15)00111-8

Geocadin, R. G. (2023). Posterior reversible encephalopathy syndrome. *N. Engl. J. Med.* 388 (23), 2171–2178. doi:10.1056/NEJMra2114482

Grommes, C., Pastore, A., Palaskas, N., Tang, S. S., Campos, C., Schartz, D., et al. (2017). Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. *Cancer Discov.* 7 (9), 1018–1029. doi:10.1158/2159-8290.Cd-17-0613

Gundamraj, V., and Hasbun, R. (2023). Viral meningitis and encephalitis: an update. *Curr. Opin. Infect. Dis.* 36 (3), 177–185. doi:10.1097/qco.0000000000000922

Hasbun, R. (2022). Progress and challenges in bacterial meningitis: A review. *Jama* 328 (21), 2147–2154. doi:10.1001/jama.2022.20521

Imataki, O., Arai, T., Yamaoka, G., Matsuoka, A., and Uemura, M. (2014). NKT cell-infiltrating aseptic meningitis on the central nervous system in Philadelphia chromosome-positive acute lymphoblastic leukemia treated with dasatinib. *Ann. Hematol.* 93 (11), 1935–1936. doi:10.1007/s00277-014-2074-4

Kako, S., Gomyo, A., Akahoshi, Y., Harada, N., Kameda, K., Ugai, T., et al. (2019). Haploidentical transplantation using low-dose alemtuzumab: comparison with haploidentical transplantation using low-dose thymoglobulin. *Eur. J. Haematol.* 102 (3), 256–264. doi:10.1111/ejh.13204

Kim, H. O. (2019). Development of BTK inhibitors for the treatment of B-cell malignancies. *Arch. Pharm. Res.* 42 (2), 171–181. doi:10.1007/s12272-019-01124-1

Lin, T. S., Stock, W., Xu, H., Phelps, M. A., Lucas, M. S., Guster, S. K., et al. (2009). A phase I/II dose escalation study of apolizumab (Hu1D10) using a stepped-up dosing schedule in patients with chronic lymphocytic leukemia and acute leukemia. *Leuk. Lymphoma* 50 (12), 1958–1963. doi:10.3109/10428190903186486

Lipsky, A., and Lamanna, N. (2020). Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematol. Am. Soc. Hematol. Educ. Program* 2020 (1), 336–345. doi:10.1182/hematology.2020000118

Mount, H. R., and Boyle, S. D. (2017). Aseptic and bacterial meningitis: evaluation, treatment, and prevention. *Am. Fam. Physician* 96 (5), 314–322.

Pal Singh, S., Dammeijer, F., and Hendriks, R. W. (2018). Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol. Cancer* 17 (1), 57. doi:10.1186/s12943-018-0779-z

Pease, C. L., Horton, T. M., McClain, K. L., and Kaplan, S. L. (2001). Aseptic meningitis in a child after systemic treatment with high dose cytarabine. *Pediatr. Infect. Dis. J.* 20 (1), 87–89. doi:10.1097/00006454-200101000-00022

Reddy, K., Htut, M., Krishnan, A., and Dadwal, S. S. (2018). Aseptic meningitis as a complication of daratumumab therapy. *Clin. Lymphoma Myeloma Leuk.* 18 (8), e333–e335. doi:10.1016/j.clml.2018.05.018

Song, Y., Deng, L., Zhang, B., Luo, H., and Zhao, R. (2021). "Preliminary results of orelabrutinib concentrations in peripheral blood and cerebrospinal fuid in patients with relapsed/refractory primary or secondary CNS lymphoma," in *The 24th national congress of clinical oncology*.

Syed, Y. Y. (2020). Zanubrutinib: first approval. *Drugs* 80 (1), 91–97. doi:10.1007/s40265-019-01252-4

Tam, C. S., Dimopoulos, M., Garcia-Sanz, R., Trotman, J., Opat, S., Roberts, A. W., et al. (2022). Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv.* 6 (4), 1296–1308. doi:10.1182/bloodadvances.2021005621

Tattevin, P., Tchamgoué, S., Belem, A., Bénézit, F., Pronier, C., and Revest, M. (2019). Aseptic meningitis. *Rev. Neurol. Paris.* 175 (7-8), 475–480. doi:10.1016/j.neurol.2019.07.005

Thordarson, H., and Talstad, I. (1986). Acute meningitis and cerebellar dysfunction complicating high-dose cytosine arabinoside therapy. *Acta Med. Scand.* 220 (5), 493–495. doi:10.1111/j.0954-6820.1986.tb02801.x

van den Berg, H., van der Flier, M., and van de Wetering, M. D. (2001). Cytarabine-induced aseptic meningitis. *Leukemia* 15 (4), 697–699. doi:10.1038/sj.leu.2402063

Vey, N., Delaunay, J., Martinelli, G., Fiedler, W., Raffoux, E., Prebet, T., et al. (2016). Phase I clinical study of RG7356, an anti-CD44 humanized antibody, in patients with acute myeloid leukemia. *Oncotarget* 7 (22), 32532–32542. doi:10.18632/oncotarget.8687

Yelehe-Okouma, M., Czmil-Garon, J., Pape, E., Petitpain, N., and Gillet, P. (2018). Drug-induced aseptic meningitis: A mini-review. *Fundam. Clin. Pharmacol.* 32 (3), 252–260. doi:10.1111/fcp.12349

Zhang, Y., Li, Y., Zhuang, Z., Wang, W., Wei, C., Zhao, D., et al. (2021). Preliminary evaluation of zanubrutinib-containing regimens in dlbcl and the cerebrospinal fluid distribution of zanubrutinib: A 13-case series. *Front. Oncol.* 11, 760405. doi:10.3389/fonc.2021.760405

Zou, X., Zhou, P., Lv, W., Liu, C., and Liu, J. (2023). Posterior reversible encephalopathy syndrome after anlotinib treatment for small cell lung cancer: A case report and literature review. *Front. Pharmacol.* 14, 1126235. doi:10.3389/fphar.2023.1126235

Zukas, A. M., and Schiff, D. (2018). Neurological complications of new chemotherapy agents. *Neuro Oncol.* 20 (1), 24–36. doi:10.1093/neuonc/nox115

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 September 2023
DOI 10.3389/fphar.2023.1226086

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Félix Javier Jiménez-Jiménez,
Hospital Universitario del Sureste, Spain
Zhigong Wei,
Sichuan University, China

*CORRESPONDENCE
Wei Wu,
cqcx@163.com
Yi Huang,
huangyi@tmmu.edu.cn
Xiaodan Lai,
laixiaodan0926@sina.com

†These authors have contributed equally to this work

RECEIVED 24 May 2023
ACCEPTED 04 September 2023
PUBLISHED 14 September 2023

CITATION
Xiong R, Lei J, Pan S, Zhang H, Tong Y, Wu W, Huang Y and Lai X (2023), Post-marketing safety surveillance of dalfampridine for multiple sclerosis using FDA adverse event reporting system. *Front. Pharmacol.* 14:1226086. doi: 10.3389/fphar.2023.1226086

Post-marketing safety surveillance of dalfampridine for multiple sclerosis using FDA adverse event reporting system

Rui Xiong[1†], Jing Lei[2†], Sicen Pan[1], Hong Zhang[3], Yongtao Tong[3], Wei Wu[2*], Yi Huang[4*] and Xiaodan Lai[1*]

[1]Department of Pharmacy, The 958th Hospital of Chinese People's Liberation Army, Chongqing, China, [2]Department of Pharmacy, Daping Hospital, Army Medical University, Chongqing, China, [3]Department of Pharmacy, The 956th Hospital of Chinese People's Liberation Army, Nyingchi, Tibet, China, [4]Biomedical Analysis Center, Army Medical University, Chongqing, China

Objective: To investigate and analyze the post-marketing adverse event (AE) data of multiple sclerosis (MS) therapeutic drug dalfampridine using the US Food and Drug Administration Adverse Event Reporting System (FAERS) for its clinical safety application.

Methods: Use OpenVigil2.1 platform to obtain AE data of dalfampridine from FAERS from February 2010 to September 2022. Match "adverse drug reaction" with preferred term (PT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), then merge the same PT and delete non-AE PT. Positive signals were identified by the reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN) methods. When AE signals met the criteria of those three methods, they were identified as positive signals.

Results: A total of 44,092 dalfampridine-related AE reports were obtained, and 335 AE signals were identified, including 11,889 AE reports. AEs were more common in females and in the 45–65 age group, which is consistent with the epidemiological characteristics of MS. The 335 AE signals involved 21 SOCs, including investigations, infections and infestations, eye disorders, etc. Among the top 20 PTs in signal strength, 10 were associated with abnormal lymphocyte percentage and count, and 5 were associated with abnormal urine tests, some of which were not described in the instruction, such as spinal cord injury cauda equina, haemoglobin urine present, urinary sediment abnormal and so on. The most frequently reported AE signals were urinary tract infection, dizziness, condition aggravated. In addition, 23 AE signals with death outcomes were identified, with an incidence of less than 0.1%.

Conclusion: Data mining of FAERS was conducted to analyze the AEs of dalfampridine, and new AE signals were found. This study provides a reference for the safe use of dalfampridine in the treatment of MS.

KEYWORDS

FAERS, dalfampridine, multiple sclerosis, adverse event, pharmacovigilance

1 Introduction

Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disorder characterized by inflammatory demyelination and axonal transection, defined as severed terminal axonal structures representing the pathological correlate of irreversible neurologic damage (McGinley et al., 2021). MS is a process that progresses from an at-risk state through asymptomatic, prodromic, and symptomatic stages, and axonal and neuronal loss begins at the early stages of the disease process, resulting in cognitive impairment and other early disability (Katz Sand, 2015). Typical clinical manifestations of MS include unilateral optic neuritis (blurred vision with associated pain), partial myelitis (extremity and torso impaired sensation, weakness, and/or ataxia), focal sensory disturbance (limb paresthesias, abdominal or chest banding dysesthesia), or brainstem syndromes (intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) (Dobson and Giovannoni, 2019; McGinley et al., 2021). The worldwide prevalence of MS ranges from 5 to 300 per 100,000 people, rising with increasing latitude, and is more common in young and middle-aged adults (mean age of diagnosis is 20–30 years) (Browne et al., 2014; Howard et al., 2016). The underlying cause of MS remains uncertain, but many genetic (e.g., major histocompatibility complex HLA-DRB1 locus) and environmental factors such as vitamin D levels, environmental UV radiation, Epstein-Barr virus infection, and smoking have been reported to be associated with MS (Dobson and Giovannoni, 2019).

Currently, there is no curative treatment available for MS, and its treatment mainly includes acute relapses therapies, which are mostly corticosteroids, disease-modifying therapies (DMTs), which mainly includes β-interferon, glatiramer acetate, teriflunomide, fingolimod, ozanimod, natalizumab, ofatumumab, etc., and symptomatic therapies, which aimed to manage the complications associated with MS (Zhang et al., 2021; Travers et al., 2022). Although DMTs are effective in reducing the risk of relapse and potentially disability, they cannot address the poor quality of life or stop disease progression.

Dalfampridine (4-aminopyridine) is a voltage-dependent potassium channel blocker that acts on potassium channels exposed in MS patients to restore conduction in local demyelinating axons (Ghebleh Zadeh et al., 2019). Dalfampridine also promotes calcium (Ca^{2+}) influx at presynaptic terminals, thereby enhancing the neuronal or neuromuscular transmission of normal myelin neurons (Zhang et al., 2021). These pharmacological properties suggest its therapeutic potential in neuromuscular transmission disorders and demyelinating diseases. In January 2010, dalfampridine was approved by the United States Food and Drug Administration (FDA) to improve walking speed and distance in MS patients. Dalfampridine, also known as fampridine in Europe, was conditionally approved for marketing by the European Medicines Agency (EMA) in July 2011 and fully approved for marketing in 2017, and is now available in Germany, the United Kingdom, France and other countries (Guo et al., 2016). Although dalfampridine has been approved for marketing in dozens of countries, treatment has been mainly limited to patients in western countries, and the drug is rarely included as a potential therapeutic option for the symptomatic treatment of MS in other countries or regions such as Latin America and Asia, which may be related to the limited financial resources allocated to healthcare in developing countries and the relatively high cost of treatment in dalfampridine (Zhang et al., 2021). Despite many clinical studies have demonstrated its positive efficacy, adverse reactions of dalfampridine, such as paresthesias, dizziness, anxiety, insomnia, and confusion, have troubled some patients (Goodman et al., 2009; Goodman et al., 2010; Hobart et al., 2019). In order to better apply dalfampridine, it is necessary to further explore and analyze the adverse events (AEs) caused by dalfampridine to reduce or avoid the occurrence of AEs.

Although many adverse reactions have been described in the instruction and in some clinical studies, the adverse reactions of dalfampridine may not be fully revealed due to sample size and ethical limitations. Real-world data contribute to a more comprehensive understanding of the safety of dalfampridine, and the FDA Adverse Event Reporting System (FAERS) is a representative AE database that provides a good paradigm for pharmacovigilance studies. In this study, AEs of dalfampridine were mined through the FAERS to provide an overall understanding of the safety of dalfampridine.

2 Materials and methods

2.1 Data sources

Data in this study were obtained from the FAERS through OpenVigil2.1, a software package for analyzing pharmacovigilance data (Bohm et al., 2021). Using drug name "Dalfampridine" as the keyword, the search time range was 1 February 2010 to 30 September 2022, and the minimum age of patients was limited to 18 years. By setting filter conditions such as gender, age, country, year and outcome, AE reports of dalfampridine were extracted respectively for subgroup analysis. The AE report outcomes included death, congenital anomaly, disability, life-threatening, hospitalization (initial or prolonged), required intervention to prevent permanent impairment, and others, with the first six being severe AE outcomes.

2.2 Data processing

The classification and standardization of AEs in FAERS data is referred to the Medical Dictionary for Regulatory Activities (MedDRA) (Tian et al., 2022). In the FAERS database, each report is coded using Preferred Terms (PTs) from MedDRA. In MedDRA, a given PT can be assigned to a specific High-level Term (HLT), High-level Group Term (HLGT), and System Organ Class (SOC) level, but each HLT, HLGT, and SOC often contains multiple PT. This study

TABLE 1 Two-by-two contingency table for disproportionality analyses.

Event groups	Drug used	Other drugs	Sums
Event	*a*	*c*	*a+c*
Other events	*b*	*d*	*b + d*
Sums	*a+b*	*c + d*	*a+b + c + d*

10.3389/fphar.2023.1226086

TABLE 2 Calculation formulas and thresholds of ROR, PRR, and BCPNN methods.

Methods	Calculation formula	Threshold
ROR	$ROR = (a/c)/(b/d)$	$a \geq 3$ and 95% CI lower limit of ROR >1
	$95\%\ CI = e^{lnROR \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	
MHRA	$PRR = [a(a+b)]/[c(c+d)]$	$a \geq 3$, PRR ≥2 and $\chi^2 \geq 4$
	$\chi^2 = \frac{(a+b+c+d)(ad-bc)^2}{(a+c)(a+b)(c+d)(b+d)}$	
BCPNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	$a \geq 3$ and IC-2SD > 0
	$IC\text{-}2SD = \log_2 \frac{(a+\gamma_{11})(N+\alpha)(N+\beta)}{(N+\gamma)(a+b+\alpha_1)(a+c+\beta_1)} - 2\sqrt{V(IC)}$	
	$V(IC) = (\frac{1}{log2})^2 [\frac{N-a+\gamma-\gamma_{11}}{(a+\gamma_{11})(1+N+\gamma)} + \frac{N-a-b+\alpha-\alpha_1}{(a+b+\alpha_1)(1+N+\alpha)} + \frac{N-a-c+\beta-\beta_1}{(a+c+\beta_1)(1+N+\beta)}]$	
	$\gamma = \gamma_{11}\frac{(N+\alpha)(N+\beta)}{(a+b+\alpha_1)(a+b+\beta_1)}$	
	$\gamma_{11} = 1,\ \alpha_1 = \beta_1 = 1,\ \alpha = \beta = 2,\ N = a+b+c+d$	

TABLE 3 Basic information about AE reports of dalfampridine from February 2010 to September 2022.

Entry	AE number	Percentage (%)
Gender of patient		
Male	11019	24.99
Female	32929	74.68
Unknown	144	0.33
Age		
18–45	8899	20.18
46–65	28177	63.91
>65	6968	15.80
Unknown	48	0.11
Reporter country		
United Sates	37170	84.30
Germany	1924	4.36
Canada	1646	3.73
France	426	0.97
United Kingdom	124	0.28
Australia	93	0.21
Others and unknown	2709	6.14

analyzed the data derived from OpenVigil2.1 platform under the definition of MedDRA. Standardize the PT of all AE terms through the MedDRA (version 26.0) and then merge the same PT entries. In addition, non-drug AE terms and AE terms associated with MS symptoms and indications for dalfampridine were removed. Then, a two-by-two contingency table was constructed (Table 1), and disproportional AEs and drug combinations were identified.

2.3 AE signal detection

Reporting odds ratio (ROR), United Kingdom medicines and healthcare products regulatory agency (MHRA), and Bayesian confidence propagation neural network (BCPNN) methods were used to detect AE signals. ROR, proportional reporting ratio (PRR) and information component (IC) values were calculated according to values a, b, c, and d in Table 1, and positive signals were identified according to the criteria in Table 2. Only AEs that meet the thresholds of all three methods are identified as positive AE signals. Microsoft Excel 2019 and Graphpad prism 8.0 software were used for data analysis.

3 Results

3.1 Descriptive analysis

From February 2010 to September 2022, a total of 4,541,880 AE reports were retrieved from the FAERS using the OpenVigil2.1 platform, of which 44,092 were AE reports with dalfampridine as the primary suspect drug, accounting for about 0.97%. By subgroup analysis of gender, age and country, we found that the patient gender in these AE reports was mainly female, accounting for 74.68%, the age of the patients was mainly 46–65, accounting for 63.91%, and the reporting country was mainly United States, accounting for 84.30% (Table 3). The annual distribution of AE reports showed a trend of increasing first and then decreasing, and the distribution of years reported by AEs with severe outcomes showed similar characteristics. (Figure 1A). In 2018, the number of AE reports reached 8780, among which 2940 were severe outcomes. There were 18,583 AE reports with severe outcomes, accounting for 42.15% of all reports, and hospitalization is the main severe outcome, accounting for 31.89%, while required intervention and congenital anomaly are sporadic, accounting for less than 0.1% (Figure 1B).

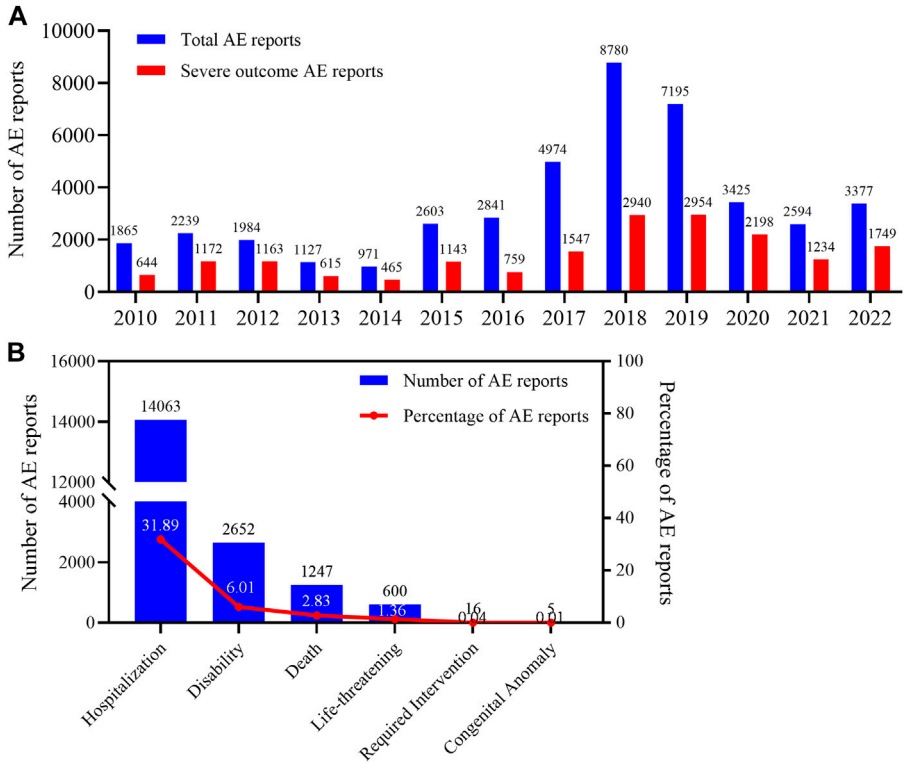


FIGURE 1
The annual distribution of AE reports and the composition of severe outcome AE reports for dalfampridine. **(A)** Annual distribution of AE reports, **(B)** The types, cases and proportion of severe outcome AE. Since the reporting years of some AE reports are not clear, the total AE in the Figure 1A shows only 43975.

3.2 Disproportionality analysis of AEs at the SOC level

By excluding and combining the PT entries, a total of 335 AE signals were identified, including 11,889 AE reports. These 335 AE signals were classified according to the corresponding SOC of MedDRA involving 21 SOCs. We evaluated the correlation between AEs and organs by ROR, MHRA, and BCPNN methods. The larger the ROR, PRR, and IC values, the stronger the correlation. The results showed that the SOCs with the strongest relevance were investigations, infections and infestations, eye disorders, and so on (Table 4). The SOCs containing the most positive signals are investigations (117), nervous system disorders (47), injury, poisoning and procedural complications (40), infections and infestations (27), and renal and urinary disorders (25) respectively, and eye disorders, skin and subcutaneous tissue disorders, cardiac disorders, and immune system disorders all contain only one positive signal. Among them, 6 SOCs, such as metabolism and nutrition disorders, reproductive system and breast disorders, injury, poisoning and procedural complications, neoplasms benign, malignant and unspecified (incl cysts and polyps), endocrine disorders, and ear and labyrinth disorders, were not reported in the instruction.

3.3 Disproportionality analysis of AEs at the PT level

The top 20 PTs of AE with the strongest relevance with dalfampridine are shown in Table 5, including spinal cord injury cauda equina, CD8 lymphocyte percentage decreased, haemoglobin urine present, etc. Among them, spinal cord injury cauda equina, haemoglobin urine present, urine leukocyte esterase positive, urinary sediment abnormal and specific gravity urine abnormal are AEs not mentioned in the instruction. In addition, as is shown in Supplementary Table S1, the highest number of AE reported included urinary tract infection (1061, 8.92%), dizziness (764, 6.43%), condition aggravated (606, 5.10%), etc., which were also the main adverse reactions reported in the instruction. In order to further understand the age, gender and countries/regions distribution of common AE, we conducted subgroup analysis of AE in the top 3 reported AE numbers. As shown in Table 6, the rates of urinary tract infection, dizziness, condition aggravated are all above 72% in females and above 60% in the 46–65 age group, and the rates reported by the United States are above 86%.

3.4 AE analysis of death outcome

In order to understand the severe AE with a death outcome, 23 AE signals were identified according to the criteria in Table 2, and

TABLE 4 The SOC of AEs associated with dalfampridine (Sort by IC value).

SOC name	PT number	N (%)	ROR (95% CI)	PRR (χ^2)	IC (IC-2SD)
Investigations	117	2181 (18.34)	13.49 (12.88, 14.14)	11.47 (20,447.67)	3.48 (3.26)
Infections and infestations	27	1511 (12.71)	9.61 (9.11, 10.15)	8.65 (10,096.25)	3.08 (2.85)
Eye disorders	1	3 (0.03)	7.84 (2.49, 24.62)	7.83 (17.48)	2.94 (2.29)
Metabolism and nutrition disorders	4	47 (0.40)	5.93 (4.44, 7.92)	5.92 (188.82)	2.54 (2.18)
Blood and lymphatic system disorders	3	61 (0.51)	5.57 (4.32, 7.17)	5.54 (223.73)	2.45 (2.10)
Vascular disorders	4	380 (3.20)	4.70 (4.24, 5.21)	4.60 (1062.07)	2.19 (1.92)
Renal and urinary disorders	25	795 (6.69)	4.77 (4.44, 5.13)	4.55 (2198.69)	2.17 (1.93)
Gastrointestinal disorders	4	33 (0.28)	4.15 (2.94, 5.85)	4.14 (77.64)	2.04 (1.65)
Skin and subcutaneous tissue disorders	1	18 (0.15)	3.75 (2.35, 5.96)	3.74 (35.80)	1.89 (1.46)
Reproductive system and breast disorders	2	10 (0.08)	3.70 (1.99, 6.91)	3.70 (19.51)	1.88 (1.40)
Injury, poisoning and procedural complications	40	1103 (9.28)	3.87 (3.64, 4.11)	3.63 (2129.85)	1.85 (1.61)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	58 (0.49)	3.56 (2.74, 4.61)	3.54 (104.98)	1.81 (1.46)
Respiratory, thoracic and mediastinal disorders	2	20 (0.17)	3.43 (2.21, 5.33)	3.42 (33.98)	1.77 (1.34)
Nervous system disorders	47	3411 (28.69)	4.13 (3.97, 4.29)	3.34 (5983.38)	1.73 (1.52)
General disorders and administration site conditions	14	976 (8.21)	3.42 (3.21, 3.66)	3.25 (1539.10)	1.69 (1.45)
Endocrine disorders	2	11 (0.09)	3.14 (1.73, 5.69)	3.14 (15.90)	1.64 (1.17)
Psychiatric disorders	14	694 (5.84)	2.95 (2.74, 3.19)	2.85 (844.00)	1.50 (1.26)
Cardiac disorders	1	11 (0.09)	2.85 (1.57, 5.16)	2.85 (13.09)	1.50 (1.03)
Musculoskeletal and connective tissue disorders	16	464 (3.90)	2.46 (2.24, 2.70)	2.41 (385.23)	1.26 (1.00)
Ear and labyrinth disorders	2	93 (0.78)	2.17 (1.77, 2.67)	2.17 (58.12)	1.11 (0.78)
Immune system disorders	1	9 (0.08)	2.15 (1.12, 4.14)	2.15 (5.48)	1.10 (0.61)

% indicates the proportion of corresponding AE, reports in the total reports of positive AE, signals (11,889 cases).

the results were shown in Table 7. Among them, pneumonia aspiration (12, 1.01‰), urinary tract infection (11, 0.93‰), progressive multifocal leukoencephalopathy (9, 0.76‰) and seizure (9, 0.76‰) have the largest number of reports. Erosive duodenitis, haemorrhagic erosive gastritis, duodenitis, osteoporosis, intracranial pressure increased, decubitus ulcer, lung cancer metastatic, transient ischaemic attack, aphasia, dysarthria, lung carcinoma cell type unspecified stage IV, and pneumonia aspiration are not mentioned in the instruction.

4 Discussion

Mobility impairment is one of the most widespread and serious consequences of MS, which has many adverse effects on emotional wellbeing, activities of daily living, quality of life of patients (Heesen et al., 2008; Larocca, 2011). Studies have shown that 45% of patients report mobility problems within the first month of diagnosis, and more than 90% report mobility problems within 10 years of diagnosis (Baird et al., 2018). Therefore, improving walking ability has positive significance for improving the quality of life of MS patients. Dalfampridine is the first symptomatic pharmacologic agent approved by the FDA to improve walking in patients with MS (Baird et al., 2018). In this study, AE signals of dalfampridine were mined on the basis of real-world data, aiming to provide a comprehensive understanding of the safety of dalfampridine. Since dalfampridine was first approved in January 2010, we collected AE reports submitted to FAERS from February 2010 to September 2022, and a total of 44,092 AE reports were obtained, 74.68% of which were women, which was close to the gender ratio of MS patients, as women are two to three times more frequently affected than men (Oh et al., 2018). However, different from the peak incidence of 20–40 years old, the age group with the most AE reported was 45–65 years old, accounting for more than 65%, suggesting that older patients or patients with longer course of disease were more likely to suffer drug-induced damage. Fewer AEs were reported in patients over 65 years of age, possibly due to the higher mortality rate and shorter life expectancy of MS (Thormann et al., 2017). Among reporting countries or regions, the United States reported the largest number of AE, accounting for 84.30%, followed by Germany (4.36%) and Canada (3.73%), which is related to the high prevalence among white person, especially those of northern European descent (Ascherio and Munger, 2016). Another important reason is that the FAERS was established by the FDA in the United States and may be less used in other countries or

TABLE 5 Top 20 PTs of signal strength of AEs associated with dalfampridine (Sort by IC value).

PT name	N (%)	ROR (95% CI)	PRR (χ^2)	IC (IC-2SD)
Spinal cord injury cauda equina	6 (0.05)	1011.04 (204.04, 5009.82)	1010.59 (1512.88)	7.99 (6.99)
CD8 lymphocyte percentage decreased	3 (0.03)	1010.81 (105.13, 9718.49)	1010.59 (756.44)	7.99 (6.31)
Haemoglobin urine present	17 (0.14)	337.29 (172.16, 660.78)	336.86 (2846.37)	7.40 (6.84)
CD8 lymphocytes increased	6 (0.05)	337.01 (108.68, 1045.08)	336.86 (1004.60)	7.40 (6.56)
Somatosensory evoked potentials abnormal	6 (0.05)	288.87 (97.07, 859.66)	288.74 (926.40)	7.28 (6.46)
CD4 lymphocyte percentage decreased	6 (0.05)	252.76 (87.69, 728.58)	252.65 (859.38)	7.18 (6.38)
Urine leukocyte esterase positive	51 (0.43)	233.04 (163.06, 333.06)	232.16 (6949.36)	7.11 (6.70)
B-lymphocyte count abnormal	11 (0.09)	231.78 (107.55, 499.53)	231.59 (1496.64)	7.10 (6.49)
B-lymphocyte count decreased	61 (0.51)	192.91 (140.80, 264.32)	192.04 (7383.87)	6.94 (6.55)
T-lymphocyte count increased	17 (0.14)	191.13 (105.39, 346.61)	190.89 (2049.72)	6.93 (6.41)
CD4 lymphocytes increased	15 (0.13)	174.43 (93.50, 325.42)	174.24 (1702.89)	6.85 (6.31)
Vitamin B12 abnormal	8 (0.07)	158.62 (68.44, 367.60)	158.52 (851.53)	6.76 (6.10)
CD8 lymphocytes decreased	14 (0.12)	152.29 (81.00, 286.33)	152.13 (1448.01)	6.72 (6.18)
Lymphocyte percentage abnormal	3 (0.03)	144.40 (37.34, 558.49)	144.37 (298.99)	6.66 (5.62)
Urinary sediment abnormal	5 (0.04)	129.61 (46.20, 363.61)	129.56 (460.67)	6.55 (5.79)
Urine analysis abnormal	179 (1.51)	124.45 (104.79, 147.80)	122.81 (15,850.60)	6.50 (6.19)
Cystitis *klebsiella*	8 (0.07)	112.35 (50.47, 250.13)	112.29 (661.78)	6.40 (5.78)
Specific gravity urine abnormal	3 (0.03)	112.31 (30.40, 414.91)	112.29 (248.17)	6.40 (5.42)
Culture urine positive	58 (0.49)	94.34 (70.48, 126.27)	93.93 (4170.19)	6.20 (5.83)
T-lymphocyte count decreased	27 (0.23)	92.99 (60.71, 142.43)	92.81 (1922.52)	6.19 (5.75)

% indicates the proportion of corresponding AE, reports in the total reports of positive AE, signals (11,889 cases).

TABLE 6 Age, gender and country/regional distribution of the top 3 PT.

Entry name	Urinary tract infection N (%)	Dizziness N (%)	Condition aggravated N (%)
Gender of patient			
Male	175 (16.49)	156 (20.42)	164 (27.06)
Female	882 (83.13)	605 (79.19)	440 (72.61)
Unknown	4 (0.38)	3 (0.39)	2 (0.33)
Age			
18–45	157 (14.80)	153 (20.03)	110 (18.15)
46–65	694 (65.41)	459 (60.08)	378 (62.38)
>65	207 (19.51)	150 (19.63)	118 (19.47)
Unknown	3 (0.28)	2 (0.26)	-
Reporter country/region			
United Sates	983 (92.65)	658 (86.13)	566 (93.40)
European	36 (3.39)	—	—
Canada	12 (1.13)	—	—
Others	30 (2.83)	106 (13.87)	40 (6.60)

% indicates the proportion of the entry to the corresponding total cases.

TABLE 7 The PT of AEs with a death outcome (Sort by IC value).

PT name	N (‰)	ROR (95% CI)	PRR (χ^2)	IC (IC-2SD)
Erosive duodenitis	3 (0.25)	253.72 (71.37, 901.98)	252.13 (600.34)	7.66 (5.14)
Haemorrhagic erosive gastritis	3 (0.25)	234.20 (66.52, 824.52)	232.74 (562.45)	7.56 (5.07)
Duodenitis	3 (0.25)	59.69 (18.57, 191.93)	59.33 (162.49)	5.81 (3.50)
Central nervous system lesion	5 (0.42)	30.50 (12.48, 74.59)	30.20 (137.09)	4.88 (2.70)
Immune reconstitution inflammatory syndrome	3 (0.25)	17.10 (5.44, 53.71)	17.00 (44.44)	4.06 (1.81)
Paraesthesia	5 (0.42)	14.14 (5.82, 34.35)	14.01 (59.61)	3.79 (1.63)
Progressive multifocal leukoencephalopathy	9 (0.76)	14.19 (7.31, 27.57)	13.94 (106.80)	3.78 (1.68)
Osteoporosis	3 (0.25)	13.90 (4.43, 43.58)	13.82 (35.20)	3.77 (1.52)
Intracranial pressure increased	3 (0.25)	12.27 (3.92, 38.44)	12.20 (30.49)	3.59 (1.35)
Decubitus ulcer	4 (0.34)	11.72 (4.35, 31.52)	11.63 (38.43)	3.52 (1.33)
Ill-defined disorder	4 (0.34)	10.06 (3.74, 27.05)	9.99 (32.05)	3.31 (1.12)
Hypoaesthesia	5 (0.42)	9.71 (4.01, 23.55)	9.62 (38.31)	3.25 (1.09)
Lung cancer metastatic	4 (0.34)	9.45 (3.52, 25.40)	9.38 (29.70)	3.22 (1.03)
Transient ischaemic attack	3 (0.25)	9.33 (2.98, 29.19)	9.28 (21.98)	3.20 (0.96)
Aphasia	4 (0.34)	8.00 (2.98, 21.49)	7.94 (24.10)	2.98 (0.79)
Urosepsis	3 (0.25)	5.94 (1.90, 18.55)	5.91 (12.18)	2.56 (0.32)
Dysarthria	3 (0.25)	5.77 (1.85, 18.02)	5.74 (11.69)	2.51 (0.28)
Lung carcinoma cell type unspecified stage IV	3 (0.25)	5.56 (1.78, 17.35)	5.53 (11.09)	2.46 (0.23)
Seizure	9 (0.76)	5.29 (2.73, 10.25)	5.21 (30.58)	2.38 (0.28)
Pneumonia aspiration	12 (1.01)	5.05 (2.84, 8.96)	4.95 (37.78)	2.30 (0.23)
Gastrointestinal disorder	3 (0.25)	4.95 (1.59, 15.45)	4.93 (9.36)	2.30 (0.06)
Urinary tract infection	11 (0.93)	4.88 (2.68, 8.89)	4.79 (33.03)	2.26 (0.18)
Metastases to central nervous system	4 (0.34)	4.61 (1.72, 12.37)	4.58 (11.18)	2.19 (0.01)

‰ indicates the proportion of corresponding AE, in the total AE, cases (11,889 cases).

regions. In addition, it may be related to the number of approved countries and the popularity of dalfampridine. From the perspective of the number of AE changes with the years, the number of AE reports showed a slight fluctuation from 2010 to 2016, reached a peak in 2017–2019, and then gradually fall back. It may be because fewer patients applied dalfampridine at the initial stage of its marketing. With the increase of clinical application of dalfampridine, the number of AE reports increased, and the decrease in the number of AE reports in recent years may be due to the fact that medical staff have a relatively full understanding of the safety of dalfampridine and have avoided some AE. The annual distribution of severe outcome AE reports was consistent with the change trend of total AE reports, accounting for about 42.15%. We also noted that the proportion of AE reports with serious outcomes fluctuated from year to year, which may be related to the continuous approval of dalfampridine in different countries, because the current safety studies on dalfampridine are mainly focused on Western countries and Caucasian populations, and there is less experience in other countries and ethnicities (Zhang et al., 2021). In addition, the outcome of AE report can only reflect the outcome of the patient with the corresponding AE, but whether these outcomes are caused by dalfampridine-induced adverse reaction or by disease progression remains to be distinguished.

In the current study, the AE signal of dalfampridine involved 21 SOC items, among which the strongest correlation was in investigations, suggesting that dalfampridine had a potential impact on investigations. The largest number of AE reports were for nervous system disorders, including dizziness, paresthesia, epilepsy, etc., which was consistent with the instruction of dalfampridine and may be related to its pharmacological mechanism of altering neuronal conduction or neuromuscular transmission (Pikoulas and Fuller, 2012). However, there are some nervous system disorders such as cognitive disorder, neuralgia and spinal cord disorder (Supplementary Table S2) that may also be associated with the progression of MS (Katz Sand, 2015; Dobson and Giovannoni, 2019). Therefore, clinicians should accurately identify the neurological symptoms of patients during dalfampridine treatment and take necessary measures. In our analysis, there are 6 SOCs that are not mentioned in the

instruction, namely, metabolism and nutrition disorders, reproductive system and breast disorders, injury, poisoning and procedural complications, neoplasms benign, malignant and unspecified (incl cysts and polyps), endocrine disorders, and ear and labyrinth disorders. It is suggested that dalfampridine may have potential adverse effects on these systems and should be paid attention to in clinical use.

In the PT item analysis, the most significant AE signal was spinal cord injury cauda equina, which may be related to disease progression, as spinal cord injury is common in MS patients. However, an early study showed that electrical conduction of the spinal cord from the sixth cervical spine (C6) to the first lumbar spine (L1) was slowed, while the cauda equina was unaffected (Snooks and Swash, 1985). Therefore, whether the spinal cord injury cauda equina is caused by dalfampridine or MS progression needs further study. For many years, MS has been considered to be an autoimmune disease of the central nervous system mediated by T lymphocytes, triggered by environmental factors on the basis of genetic susceptibility genes (Oh et al., 2018). $CD4^+$ T cells may play an important role in peripheral immune interactions leading to MS, while $CD8^+$ T cells are the predominant T-cell population in brain lesions in patients with MS, and the number of $CD8^+$ T cells is most correlated with the degree of axonal damage (Bar-Or and Li, 2021). Of the top 20 significant AE signals, 10 entries were associated with lymphocyte count or percentage abnormalities, including increased, decreased, or abnormal. Although abnormal lymphocyte counts or percentages are often associated with MS pathology, they are usually elevated rather than decreased, so excessive lymphocyte depletion may be an adverse outcome of dalfampridine. There were six signals associated with abnormal urine tests, which are likely related to kidney injury or urinary tract infection, consistent with the instructions and previous reports (Pikoulas and Fuller, 2012; Frejo et al., 2014; Zhong et al., 2017). Studies have shown that the plasma concentration (C_{max}) of dalfampridine and area under the plasma concentration-time curve (AUC) in mild and severe renal impairment are 166.5%–199.9% and 175.3%–398.7% of healthy individuals, respectively, and the mean terminal disposition half-life was 6.4 h in healthy individuals, compared with 7.4, 8.1, and 14.3 h in patients with mild, moderate, and severe renal impairment, respectively (Smith et al., 2010). This suggests that dalfampridine should be used with caution in patients with mild and moderate renal impairment and should be contraindicated in patients with severe renal impairment. Previous studies have shown decreased levels of vitamin B12 in MS patients, and appropriately elevated levels of vitamin B12 may be beneficial for anti-inflammatory and myelin regeneration (Miller et al., 2005; Nemazannikova et al., 2018). This suggests that vitamin B12 abnormal is not AE signals of dalfampridine. In terms of the number of reported AE, urinary tract infection, dizziness and condition aggravated were the most frequently reported AE. Subgroup analysis showed that the percentage of female patients reporting urinary tract infection and dizziness was higher than the proportion of female in the total number of AEs, suggesting that women were more prone to urinary tract infection and dizziness. The percentages of patients aged 18–45 years old reporting urinary tract infection and the percentages of patients aged 45–65 years old reporting dizziness and condition aggravated were lower than the proportion of corresponding age in total AE, while the percentages of patients over 65 years old reporting urinary tract infection, dizziness and condition aggravated were higher than the proportion of corresponding age in total AE, suggesting that older patients may be more prone to these AEs. The absence of reported dizziness and condition aggravated records from Europe and Canada does not mean that AEs did not occur in these regions, most likely due to incomplete or unreported regional records. In addition, we identified 23 AE signals with death outcome, which were relatively low in proportion (less than 0.1%) but still worthy of clinical attention.

In summary, this study investigated and analyzed the AE records of dalfampridine in the FAERS database, and found that the AEs of dalfampridine involved multiple system organ such as nervous system, blood system, urinary system, and some of AEs had gender and age differences. At the same time, we also pointed out some new potential AEs not reported in the instruction and literature. However, there are some shortcomings in this study: 1) This study relied on data recorded by FAERS, so we failed to analyze AE records that were not reported or had incomplete information; 2) the FAERS database was established by the United States FDA, and the recorded data were mainly from the United States, so the analysis in this study could not well distinguish the differences of these adverse events among ethnic groups; 3) this study is a descriptive study, only a description and analysis of existing data, which cannot reveal the causal relationship between AE and drug-used. Nevertheless, this study is of positive significance for the early warning of AEs in dalfampridine. Clinicians should take full consideration of health status of patients and possible AE, and take necessary measures to reduce or avoid the occurrence of AEs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

RX, WW, YH, and XL jointly planned this research, RX and JL collected the data and jointly excluded non-adverse event items, SP, HZ, and YT completed the adverse event signal detection, RX and JL wrote the draft of the manuscript, and WW, YH, and XL revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Natural Science Foundation of Chongqing, China [Grant Nos. CSTB2022NSCQ-MSX0163 and CSTB2023NSCQ-MSX0627].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar-2023-1226086/full#supplementary-material

References

Ascherio, A., and Munger, K. L. (2016). Epidemiology of multiple sclerosis: From risk factors to prevention-an update. *Semin. Neurol.* 36 (2), 103–114. doi:10.1055/s-0036-1579693

Baird, J. F., Sandroff, B. M., and Motl, R. W. (2018). Therapies for mobility disability in persons with multiple sclerosis. *Expert Rev. Neurother.* 18 (6), 493–502. doi:10.1080/14737175.2018.1478289

Bar-Or, A., and Li, R. (2021). Cellular immunology of relapsing multiple sclerosis: Interactions, checks, and balances. *Lancet Neurol.* 20 (6), 470–483. doi:10.1016/S1474-4422(21)00063-6

Bohm, R., Bulin, C., Waetzig, V., Cascorbi, I., Klein, H. J., and Herdegen, T. (2021). Pharmacovigilance-based drug repurposing: The search for inverse signals via OpenVigil identifies putative drugs against viral respiratory infections. *Br. J. Clin. Pharmacol.* 87 (11), 4421–4431. doi:10.1111/bcp.14868

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., et al. (2014). Atlas of multiple sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 83 (11), 1022–1024. doi:10.1212/WNL.0000000000000768

Dobson, R., and Giovannoni, G. (2019). Multiple sclerosis - a review. *Eur. J. Neurol.* 26 (1), 27–40. doi:10.1111/ene.13819

Frejo, M. T., Del Pino, J., Lobo, M., Garcia, J., Capo, M. A., and Diaz, M. J. (2014). Liver and kidney damage induced by 4-aminopyridine in a repeated dose (28 days) oral toxicity study in rats: Gene expression profile of hybrid cell death. *Toxicol. Lett.* 225 (2), 252–263. doi:10.1016/j.toxlet.2013.12.016

Ghebleh Zadeh, N., Vaezi, G., Bakhtiarian, A., Mousavi, Z., Shiravi, A., and Nikoui, V. (2019). The potassium channel blocker, dalfampridine diminishes ouabain-induced arrhythmia in isolated rat atria. *Arch. Physiol. Biochem.* 125 (1), 25–29. doi:10.1080/13813455.2018.1430158

Goodman, A. D., Brown, T. R., Edwards, K. R., Krupp, L. B., Schapiro, R. T., Cohen, R., et al. (2010). A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann. Neurol.* 68 (4), 494–502. doi:10.1002/ana.22240

Goodman, A. D., Brown, T. R., Krupp, L. B., Schapiro, R. T., Schwid, S. R., Cohen, R., et al. (2009). Sustained-release oral fampridine in multiple sclerosis: A randomised, double-blind, controlled trial. *Lancet* 373 (9665), 732–738. doi:10.1016/S0140-6736(09)60442-6

Guo, A., Grabner, M., Palli, S. R., Elder, J., Sidovar, M., Aupperle, P., et al. (2016). Treatment patterns and health care resource utilization associated with dalfampridine extended release in multiple sclerosis: A retrospective claims database analysis. *Clin. Outcomes Res.* 8, 177–186. doi:10.2147/CEOR.S99750

Heesen, C., Bohm, J., Reich, C., Kasper, J., Goebel, M., and Gold, S. M. (2008). Patient perception of bodily functions in multiple sclerosis: Gait and visual function are the most valuable. *Mult. Scler.* 14 (7), 988–991. doi:10.1177/1352458508088916

Hobart, J., Ziemssen, T., Feys, P., Linnebank, M., Goodman, A. D., Farrell, R., et al. (2019). Assessment of clinically meaningful improvements in self-reported walking ability in participants with multiple sclerosis: Results from the randomized, double-blind, phase III ENHANCE trial of prolonged-release fampridine. *CNS Drugs* 33 (1), 61–79. doi:10.1007/s40263-018-0586-5

Howard, J., Trevick, S., and Younger, D. S. (2016). Epidemiology of multiple sclerosis. *Neurol. Clin.* 34 (4), 919–939. doi:10.1016/j.ncl.2016.06.016

Katz Sand, I. (2015). Classification, diagnosis, and differential diagnosis of multiple sclerosis. *Curr. Opin. Neurol.* 28 (3), 193–205. doi:10.1097/WCO.0000000000000206

Larocca, N. G. (2011). Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient* 4 (3), 189–201. doi:10.2165/11591150-000000000-00000

McGinley, M. P., Goldschmidt, C. H., and Rae-Grant, A. D. (2021). Diagnosis and treatment of multiple sclerosis: A review. *JAMA* 325 (8), 765–779. doi:10.1001/jama.2020.26858

Miller, A., Korem, M., Almog, R., and Galboiz, Y. (2005). Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. *J. Neurol. Sci.* 233 (1-2), 93–97. doi:10.1016/j.jns.2005.03.009

Nemazannikova, N., Mikkelsen, K., Stojanovska, L., Blatch, G. L., and Apostolopoulos, V. (2018). Is there a link between vitamin B and multiple sclerosis? *Med. Chem.* 14 (2), 170–180. doi:10.2174/1573406413666170906123857

Oh, J., Vidal-Jordana, A., and Montalban, X. (2018). Multiple sclerosis: clinical aspects. *Curr. Opin. Neurol.* 31 (6), 752–759. doi:10.1097/WCO.0000000000000622

Pikoulas, T. E., and Fuller, M. A. (2012). Dalfampridine: A medication to improve walking in patients with multiple sclerosis. *Ann. Pharmacother.* 46 (7-8), 1010–1015. doi:10.1345/aph.1Q714

Smith, W., Swan, S., Marbury, T., and Henney, H., 3rd (2010). Single-Dose pharmacokinetics of sustained-release fampridine (Fampridine-SR) in healthy volunteers and adults with renal impairment. *J. Clin. Pharmacol.* 50 (2), 151–159. doi:10.1177/0091270009344857

Snooks, S. J., and Swash, M. (1985). Motor conduction velocity in the human spinal cord: slowed conduction in multiple sclerosis and radiation myelopathy. *J. Neurol. Neurosurg. Psychiatry* 48 (11), 1135–1139. doi:10.1136/jnnp.48.11.1135

Thormann, A., Sorensen, P. S., Koch-Henriksen, N., Laursen, B., and Magyari, M. (2017). Comorbidity in multiple sclerosis is associated with diagnostic delays and increased mortality. *Neurology* 89 (16), 1668–1675. doi:10.1212/WNL.0000000000004508

Tian, X., Chen, L., Gai, D., He, S., Jiang, X., and Zhang, N. (2022). Adverse event profiles of PARP inhibitors: Analysis of spontaneous reports submitted to FAERS. *Front. Pharmacol.* 13, 851246–859812. (Print)):851246. doi:10.3389/fphar.2022.851246

Travers, B. S., Tsang, B. K., and Barton, J. L. (2022). Multiple sclerosis: Diagnosis, disease-modifying therapy and prognosis. *Aust. J. Gen. Pract.* 51 (4), 199–206. doi:10.31128/AJGP-07-21-6103

Zhang, E., Tian, X., Li, R., Chen, C., Li, M., Ma, L., et al. (2021). Dalfampridine in the treatment of multiple sclerosis: A meta-analysis of randomised controlled trials. *Orphanet J. Rare Dis.* 16 (1), 87. doi:10.1186/s13023-021-01694-8

Zhong, J., Yang, H. C., and Fogo, A. B. (2017). A perspective on chronic kidney disease progression. *Am. J. Physiol. Ren. Physiol.* 312 (3), F375–F384. doi:10.1152/ajprenal.00266.2016

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 07 November 2023
DOI 10.3389/fphar.2023.1260535

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Islam M. Ghazi,
Long Island University-Brooklyn, United States
Gobena Ameni,
United Arab Emirates University, United Arab Emirates

*CORRESPONDENCE
Hong Lu,
1430368@qq.com

†These authors have contributed equally to this work

RECEIVED 19 July 2023
ACCEPTED 26 October 2023
PUBLISHED 07 November 2023

CITATION
Yan P, Shi Q-Z, Hu Y-X, Zeng Y and Lu H (2023), Evaluation of the impact of rifampicin on the plasma concentration of linezolid in tuberculosis co-infected patients.
Front. Pharmacol. 14:1260535.
doi: 10.3389/fphar.2023.1260535

Evaluation of the impact of rifampicin on the plasma concentration of linezolid in tuberculosis co-infected patients

Pan Yan†, Qun-Zhi Shi†, Yi-Xing Hu, Ying Zeng and Hong Lu*

Department of Pharmacy, The Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China, Changsha, China

Linezolid combined with rifampicin has shown excellent clinical outcomes against infection by multi-resistant Gram-positive bacteria. However, several studies have indicated that rifampicin reduces the plasma concentration of linezolid in patients with severe infection. Linezolid has been recommended for the treatment of patients with multidrug-resistant or extensively drug-resistant tuberculosis. However, studies on the interaction between linezolid and rifampicin in patients suffering from tuberculosis with infection are lacking. We evaluated the interaction between linezolid and rifampicin based on therapeutic drug monitoring (TDM). A retrospective analysis was undertaken for patients with tuberculosis and infection who were treated with linezolid and undergoing TDM. Patients were divided into the linezolid group and linezolid + rifampicin group. Data on demographic characteristics, disease, duration of linezolid therapy, and the plasma concentration of linezolid were used for statistical analyses. Eighty-eight patients with tuberculosis and infection were assessed. Values for the peak (C_{max}) and trough (C_{min}) concentrations of linezolid in plasma were available for 42 and 46 cases, respectively. Patients in the linezolid group had a significantly higher C_{max} [15.76 (8.07–26.06) vs. 13.18 (7.48–23.64) mg/L, p = 0.048] and C_{min} [8.38 (3.06–16.53) vs. 4.27 (0.45–10.47), p = 0.005] than those in the linezolid + rifampicin group. The plasma concentration of linezolid increased obviously in two patients after rifampicin discontinuation. However, the total efficiency and prevalence of hematologic adverse reactions were not significantly different in the linezolid group and linezolid + rifampin group. The plasma concentration of linezolid decreased upon combination with rifampicin, suggesting that TDM may aid avoidance of subtherapeutic levels of linezolid upon co-treatment with rifampicin.

KEYWORDS

linezolid, rifampicin, interaction, plasma concentration, tuberculosis

Introduction

Linezolid was the first antibacterial drug of the oxazolidinone class to be used clinically. It can inhibit the synthesis of bacterial proteins. Linezolid has a unique site and mode of action. Hence, cross-resistance with other inhibitors of protein synthesis and anti-tuberculosis drugs is unlikely, and it does not induce resistance readily *in vitro* (Singh et al., 2019). *In vitro* research suggests that linezolid has a strong effect against *M. tuberculosis*, and a minimum inhibitory concentration (MIC) of 0.125–1.0 mg/L has been documented. It has equal

activity against sensitive and resistant strains of *Mycobacterium tuberculosis*, and an effect against fast-growing bacteria and quiescent bacteria. Therefore, linezolid has become the main drug for long-term treatment for drug-resistant tuberculosis (TB) (Tuberculosis and Association, 2022). The oxidative metabolism of linezolid is non-enzymatic, and does not involve the cytochrome P450 (CYP) enzymes in hepatic microsomes. Clinical research has shown that ~65% of linezolid is cleared by non-renal mechanisms, and ~30% is excreted in urine (Slatter et al., 2001).

Rifampicin is the first-line drug used to counteract tuberculosis. It is a strong inducer of CYP and the P-glycoprotein transport system. Rifampicin has enzyme-inducing effects on CYP3A, CYP1A2, CYP2C, and CYP2D6, which leads to significant interactions with several drug types (Burman et al., 2001; Finch et al., 2002). A combination of vancomycin and rifampicin is usually recommended for the treatment of methicillin-resistant *Staphylococcus aureus* infections in endocarditis, osteomyelitis, and septic arthritis, whereas linezolid may be used if vancomycin is resistant (or ineffective) or if sequential therapy is required (Liu et al., 2011).

There have been several reports of interactions between linezolid with rifampicin, which have indicated that rifampicin reduces the plasma concentration of linezolid and poses a risk of therapeutic failure (Egle et al., 2005; Gebhart et al., 2007; Hoyo et al., 2012). Furthermore, the medication package insert for linezolid glucose injection (Zyvox™; Pfizer Pharmaceuticals, New York, NY, United Staes) states that patients receiving rifampicin with linezolid (p.o.) results in a 21% and 32% reduction in the peak serum concentration (C_{max}) and area under the drug concentration–time curve (AUC), respectively, for linezolid, but the clinical importance of this interaction is not known. The mechanism by which linezolid and rifampicin interact is not known. Moreover, reports on co-administration of linezolid and rifampicin in TB patients co-infected with other bacterial pathogens are lacking.

We undertook a retrospective analysis to reveal the effect of co-administration of rifampicin on the plasma concentration of linezolid in patients suffering from tuberculosis and infection. We wished to evaluate the efficacy and safety of linezolid and rifampicin if administered alone or in combination.

Materials and methods

Setting

This observational retrospective study was undertaken at Affiliated Changsha Central Hospital (ACCH) within the University of South China (Hengyang, China). ACCH, a grade-IIIA hospital, is a key medical research center for tuberculosis in Hunan province. The Clinical Pharmacology Department answers all requests for therapeutic drug monitoring (TDM) for ACCH and its healthcare area.

Inclusion and exclusion criteria

The inclusion criteria were patients: 1) aged ≥18 years; 2) receiving continuous linezolid injection with a standard administration [(600 mg every 12 h (Q12h)] for treatment >3 days; 3) for whom TDM results for linezolid at steady state were available.

The exclusion criteria were patients: 1) aged <18 years; 2) who were pregnant or lactating; 3) for whom the plasma concentration of linezolid did not reach a steady state or was below the limit of detection; 4) who were administered other drugs that strongly induced hepatic enzymes (e.g., carbamazepine, phenytoin sodium, phenobarbital) simultaneously; 5) undergoing blood purification or other forms of kidney-replacement therapy.

Patients

Cases from the Tuberculosis Diagnosis and Treatment Center of ACCH from January 2020 to June 2023 treated with linezolid injection (600 mg, Q12h) and for whom the plasma concentration of linezolid during hospitalization were monitored.

Patients were divided into two groups (linezolid and linezolid + rifampicin) according to whether the medication plan during hospitalization contained rifampicin.

Determination of drug concentration in plasma

When linezolid had reached a steady-state concentration (≥3 days), blood was collected 30 min before and 30 min after the next intravenous drip to monitor the trough concentration (C_{min}) and C_{max}, respectively. Plasma was obtained from blood by centrifugation (3,000 × *g* for 10 min at 4°C). Plasma was processed by protein precipitation. Then, high-performance liquid chromatography using a photodiode array (HPLC-PDA) was undertaken. Chromatographic separation was carried out on a Diamonsil C18 column (4.6 × 20 mm, 5 μm). The column oven was set at 30°C. The mobile phase consisted of methanol: water (40:60). The detection wavelength was 253 nm.

The analytical method met the requirements for determination of biological samples, with absolute recovery >85% and a linear range of 0.31–40.55 mg/L ($R^2 = 0.9997$). The intra-day precision and inter-day precision of low, medium, and high concentrations were <5%. Biological samples were stable within 24 h at room temperature, at two freeze–thaw cycles, and after freezing at −80°C for 3 months. The C_{min} range of linezolid is 2–8 mg/L, whereas the C_{max} range is 12–26 mg/L (Beijin Chest Hospital and Antituberculosis, 2021; Lin et al., 2022).

Data collection

The electronic medical record system (EMRS) of ACCH was used to retrieve and collect patient information. The data collected were organized as: 1) demographics (age, sex, bodyweight); 2) reason and time for administration of linezolid injection; 3) pathogen information; 4) detection time and results for the plasma concentration of linezolid; 5) laboratory data for liver function (albumin, total bilirubin), renal function (creatinine), and blood data before and after medication administration (white blood cell (WBC) count, percent neutrophils, hemoglobin, platelet count).

Clinical outcome

After anti-tuberculosis and anti-infection treatment with linezolid, if symptoms disappeared or improved significantly, pathogenic bacteria were cleared, or imaging suggested improvement, then this scenario was classified as "clinically effective"; if not, then the classification was "clinically ineffective."

Safety and tolerability of linezolid

Hematological adverse drug reactions (ADRs) and peripheral neuropathy were monitored. The physician presumed that the ADR was due to linezolid, then reduced the dose or stopped linezolid.

A hematological ADRs was defined as: 1) a reduction in the platelet count and/or hemoglobin level >30% in comparison with those at baseline; 2) a normal or high WBC count 3 days before or on the day of dosing but a WBC count below the lower limit of normal (3.5×10^9/L) after dosing (Takahashi et al., 2011).

Peripheral neuropathy was defined as follows: 1) patients were suspected to have developed neuropathy if the EMRS demonstrated nerve dysfunctions (pain, sensory loss, or numbness); 2) neurological symptoms reduced or disappeared upon withdrawal of linezolid.

Statistical analyses

Continuous variables are presented as the mean ± SD or median according to the normality (Kolmogorov–Smirnov) test. To estimate differences between variables, the chi-squared test and Student´s *t*-test were used for categorical variables and continuous parametric variables, respectively. Statistical analyses were undertaken using Prism 8 (GraphPad, San Diego, United States). $p < 0.05$ was considered significant.

Ethical statement

The study protocol was approved (2023-003) by the research ethics committee of the University of South China. The requirement for informed consent was waived because we collected data retrospectively.

Results

Patient characteristics

Eighty-eight tuberculosis patients with infection for whom the plasma concentration of linezolid were monitored. 42 patients were in the linezolid group and 46 cases in the linezolid + rifampicin group, in which the C_{max} and C_{min} of linezolid were obtained for 57 and 31 cases, respectively. The characteristics of patients are displayed in Tables 1, 2. Except for the platelet level at baseline before dosing, there were no significant differences in the basic characteristics of patients and reasons for using linezolid. The main reason for linezolid administration was to counteract tuberculous and to counteract tuberculosis and infection. Microbiological isolates were indentified in 30.95% and 15.22% of patients in the linezolid group and linezolid + rifampicin group, respectively, and *Enterococcus faecium* and *M. tuberculosis* were the most prevalent pathogens in both groups.

Distribution of the plasma concentration of linezolid

The times when the C_{max} and C_{min} were monitored in the linezolid and linezolid + rifampicin groups were different, and the results are shown in Table 3. The monitoring time (median) of C_{max} in linezolid and linezolid + rifampicin groups was 6 days and 10 days respectively, whereas the C_{min} was 5 days and 12.5 days, respectively. The median values for the monitoring time of C_{max} and C_{min} were significantly longer in the linezolid + rifampicin group than in the linezolid group, but the mean values of C_{max} and C_{min} in the linezolid group were significantly higher than those in the linezolid + rifampicin group [(15.76 ± 5.77) vs. (13.18 ± 3.88) mg/L and (8.38 ± 4.04) vs. (4.27 ± 3.00) mg/L]. Furthermore, there was a significant difference in the distribution of C_{min} values between the two groups. In the linezolid group, 47.37% (9/19) of patients had a higher C_{min}, whereas no patients had a lower C_{min}. However, 16.67% (2/12) of patients in the linezolid + rifampicin group had a higher C_{min}, whereas 25.00% (3/12) patients had a lower C_{min}. These results implied that the plasma concentration of linezolid in the linezolid + rifampicin group was lower than those in the linezolid group.

Efficacy and safety of linezolid

With respect to C_{max}, the proportion of hematological ADRs was 43.48% (10/23) and 44.12% (15/34) in the linezolid group and linezolid + rifampin group, respectively, and three patients in both groups experienced reductions in the platelet count and WBC count. With regard to C_{min}, the proportion of hematological ADRs was 47.37% (9/19) and 66.67% (8/12) in the linezolid group and linezolid + rifampin group, respectively, whereas two patients in the linezolid group and three patients in linezolid + rifampicin group experienced two reductions in three blood indicators. Meanwhile, we found the same clinical efficacy [73.81% (31/42)] in the linezolid group compared with that in the linezolid + rifampicin group [73.91% (34/46)]. In general, there was no significant difference in the prevalence of clinical efficacy or ADRs between the two groups (Table 4).

Typical cases

When linezolid and rifampicin were used concurrently, two patients exhibited a subtherapeutic plasma concentration of linezolid. Subsequently, a significant increase in the plasma concentration of linezolid was observed in two patients after rifampicin was discontinued. Both cases are detailed below.

Case 1

A 34-year-old man was found to have *M. tuberculosis* DNA in bronchoalveolar lavage fluid after testing in another hospital. Next-generation sequencing revealed 215 sequences of *M. tuberculosis*

TABLE 1 Characteristics of C_{max} of linezolid in the two groups.

	Linezolid group	Linezolid + rifampicin group	*p*-value
	(*n* = 23)	(*n* = 34)	
Age, years	57.70 ± 16.92	49.24 ± 20.55	0.108
Sex (Male/Female)	16/7	21/13	0.985
Albumin, g/L	29.65 ± 6.94	31.50 ± 5.33	0.261
TBIL, μmol/L	13.30 ± 12.58	10.41 ± 7.80	0.288
Creatinine, μmol/L	72.48 ± 51.21	60.91 ± 34.37	0.311
eGFR, mL/min/1.73m^2	103.35 ± 29.82	109.31 ± 27.96	0.445
White blood cell (10^9/L)[a]	9.20 ± 5.41	9.68 ± 5.11	0.736
Neutrophil percent (%)[a]	80.03 ± 13.67	80.46 ± 10.20	0.890
Hemoglobin (g/L)[a]	95.17 ± 22.59	102.74 ± 19.66	0.185
Blood platelet (10^9/L)[a]	250.48 ± 91.70	284.12 ± 130.63	0.290
Main Reasons for linezolid, n (%)			
Anti-infection + Antituberculous	14 (60.87)	11 (32.36)	0.104
Antituberculous	6 (26.09)	20 (58.82)	0.052
Anti-infection	3 (13.04)	3 (8.82)	0.878
Pathogenic bacteria, n (%)			
Mycobacterium tuberculosis	4 (17.39)	2 (5.88)	0.933
Enterococcus faecium	1 (4.35)	4 (11.76)	0.667
Enterococcus faecalis	1 (4.35)	0 (0)	NA
Undefined diagnosis	17 (73.91)	28 (82.36)	0.745

[a]On the day of medication (or 3 days before medication); TBIL, total bilirubin; eGFR, estimated glomerular filtration rate.

complex. He was admitted to the Tuberculosis Department of ACCH on 7 May 2022. He received anti-tuberculosis treatment consisting of isoniazid injection (0.3 g, once daily (Qd)), rifampicin injection (0.45 g, Qd), ethambutol tablets (0.75 g, Qd), pyrazinamide tablets (1.5 g, Qd), and moxifloxacin injection (0.4 g, Qd). However, due to limited improvement on 11 May, linezolid injection was added (0.6 g, i.v., Q12h). Nonetheless, the C_{max} of linezolid was 7.48 mg/L on 23 May, which fell below the recommended therapeutic concentration range of 12–26 mg/L. Consequently, the clinical pharmacist hypothesized that rifampicin may have contributed to the reduction in the plasma concentration of linezolid, and recommended discontinuation of rifampicin injection. On the morning of 26 May, the C_{max} of linezolid was 30.13 mg/L.

Case 2

A 53-year-old man was transferred to the Tuberculosis Department of ACCH on 22 September 2022 due to a diagnosis of active pulmonary tuberculosis confirmed by positive results for tuberculosis DNA and T-SPOT diagnosed at another hospital. He received isoniazid injection (0.3 g, Qd), rifampicin injection (0.45 g, Qd), and ethambutol tablets (0.75 g, Qd) as anti-tuberculosis treatment, as well as meropenem injection (1.0 g) every 6 h (Q6h), ornidazole injection (0.5 g, Q8h), and penicillin sodium injection (4 million U, Q4h) to fight infection. On 26 September, linezolid injection (0.6 g, i.v., Q12h) was added to cover Gram-positive bacteria and *M. tuberculosis*. The C_{min} for linezolid was only 0.40 mg/L on 29 September. The clinical pharmacist suggested that the significantly low C_{min} for linezolid was related to co-treatment with rifampicin, and recommended discontinuation of rifampicin. Therefore, rifampicin injection was ceased on 1 October. On 4 October, the C_{min} for linezolid was 0.85 mg/L. On 8 October, the C_{min} for linezolid was 1.59 mg/L.

Discussion

This clinical study is the first retrospective analysis of interactions between linezolid and rifampicin in Chinese patients. Patients in the linezolid + rifampicin group exhibited significantly lower plasma concentrations of linezolid (C_{max} and C_{min}) compared with those in the linezolid group. The plasma concentration of linezolid of two patients increased obviously after withdrawal of rifampicin, and the plasma concentration of linezolid decreased by ~75% when linezolid was combined with rifampicin. Hoyo *et al.* reported that in two patients, the C_{min} for linezolid during

TABLE 2 Characteristics of C_{min} of linezolid in the two groups.

	Linezolid group (n = 19)	Linezolid + rifampicin group (n = 12)	p-value
Age, years	62.21 ± 21.52	53.08 ± 24.49	0.284
Sex (Male/Female)	15/4	9/3	0.968
Albumin, g/L	26.26 ± 5.44	29.83 ± 6.53	0.111
TBIL, μmol/L	10.56 ± 7.20	12.54 ± 11.33	0.557
Creatinine, μmol/L	70.00 ± 46.33	59.83 ± 37.96	0.530
eGFR, mL/min/1.73m^2	99.62 ± 27.94	107.99 ± 34.87	0.466
White blood cell (10^9/L)$^{\#}$	12.24 ± 7.66	13.60 ± 7.26	0.627
Neutrophil percent (%)$^{\#}$	83.81 ± 10.10	83.86 ± 9.03	0.989
Hemoglobin (g/L)$^{\#}$	91.21 ± 16.64	102.00 ± 22.14	0.133
Blood platelet (10^9/L)$^{\#}$	226.47 ± 71.88	372.83 ± 199.61	0.007**
Main Reasons for linezolid, n (%)			
Anti-infection + antituberculous	10 (52.63)	7 (58.33)	0.953
Antituberculous	6 (31.58)	5 (41.67)	0.849
Anti-infection	3 (15.79)	0	NA
Pathogenic bacteria, n (%)			
Enterococcus faecium	4 (21.05)	1 (8.33)	0.713
Mycobacterium tuberculosis	1 (5.26)	0 (0)	NA
Mycobacterium abscess	1 (5.26)	0 (0)	NA
Staphylococcus haemolyticus	1 (5.26)	0 (0)	NA
Undefined diagnosis	12 (63.16)	11 (91.67)	0.210

*p < 0.05; **, p < 0.01 #, On the day of medication (or 3 days before medication); TB, total bilirubin; GFR, glomerular filtration rate.

co-administration with rifampicin was reduced by >50% compared to when rifampicin was discontinued (Hoyo et al., 2012). Ashizawa et al. reported that a 79-year-old woman for whom rifampicin was added had a significant decrease in the C_{min} of linezolid (48.20%–75.50%) compared with when linezolid was administered alone (Ashizawa et al., 2016).

The distribution of plasma concentrations of linezolid exhibited variations among patients in the linezolid and linezolid + rifampicin group. Specifically, the proportion of patients with a high plasma concentration of linezolid was greater in the linezolid group compared with that in the linezolid + rifampicin group [23.81% (10/42) vs. 4.35 (2/46)]. Conversely, the proportion of patients with a lower plasma concentration of linezolid in the linezolid + rifampicin group was greater than that in the linezolid group [30.43% (14/46) vs. 23.81% (10/42)]. A 10-year retrospective study involving 1,049 patients who received linezolid (0.6 g, Q12h) and including 2,484 C_{min} points was undertaken. Results showed that 50.8% of C_{min} values were within the reference concentration range, and the prevalence of linezolid overexposure (33%) was significantly higher than linezolid underexposure (16.2%) (Pea et al., 2017). Studies have reported that linezolid overexposure was significantly associated with advanced age and creatinine clearance rate (CrCl) < 40 mL/min, and linezolid underexposure to be significantly associated with CrCl >100 mL/min (Cattaneo et al., 2016; Pea et al., 2017). There were no significant differences in age or the glomerular filtration rate among patients in our study.

The mean value and distribution range of the plasma concentration of linezolid varied between the linezolid group and linezolid + rifampicin group, which were considered to be related to the combination with rifampicin. Recent reports have indicated a tendency toward a lower C_{min} for linezolid in patients co-administered linezolid and rifampicin (Pea et al., 2010; Morata et al., 2016). A study conducted in 2012 with 45 patients demonstrated that the C_{min} (3.71 vs. 1.37 mg/L) and $AUC_{24\ h}$ (212.77 vs. 123.33 mg/L h) of patients receiving linezolid monotherapy were significantly higher than those receiving linezolid in combination with rifampicin (Pea et al., 2010). Those reports considered rifampicin to be a P-glycoprotein inducer that can accelerate the clearance and excretion of linezolid to a certain extent. Rifampicin can induce drug-metabolism enzymes, including robust expression of CYP3A4 in the liver and small intestine, as well as expression of phase-2 drug-metabolism enzymes and drug-transport proteins such as UDP-glucuronyltransferase, sulfotransferase, P-glycoprotein, multi-drug resistance protein-2, and organic anion-transporting polypeptide. Rifampicin exerts a considerable impact on the pharmacokinetics of orally administered drugs metabolized by CYP3A4 and transported by P-glycoprotein, resulting in reduced drug concentrations after metabolism by

TABLE 3 Distribution of the plasma concentration of linezolid.

	C_{max} group		*p*-value	C_{min} group		*p*-value
	Linezolid group (n = 23)	Linezolid + rifampicin group (n = 34)		Linezolid group (n = 19)	Linezolid + rifampicin group (n = 12)	
Linezolid plasma concentrations (mg/L)	15.76 ± 5.77	13.18 ± 3.88	0.048*	8.38 ± 4.04	4.27 ± 3.00	0.005**
Number of TDM (days) median (IQR)	6 (3–28)	10 (3–48)	0.057	5 (3–10)	12.5 (4–47)	0.001**
Length of treatment (days), median (IQR)	11 (4–67)	17 (5–62)	0.307	9 (5–31)	29 (8–62)	0.001**
Plasma concentration distribution, n (%)			0.624			0.034*
High concentration	1 (4.35)	0 (0)		9 (47.37)	2 (16.67)	
Normal concentration	12 (52.17)	23 (67.65)		10 (52.63)	7 (58.33)	
Low concentration	10 (43.48)	11 (32.35)		0 (0)	3 (25.00)	
Co-treatment, n (%)						
Omeprazole	2 (8.70)	15 (44.12)	0.084	5 (26.32)	6 (50.00)	0.406
Amlodipine	2 (8.70)	6 (17.65)	0.453	3 (15.79)	3 (25.00)	0.818

*$p < 0.05$; **, $p < 0.01$.

TABLE 4 Evalution of efficacy and adverse drug reactions.

	C_{max} group		*p*-value	C_{min} group		*p*-value
	Linezolid group (n = 23)	Linezolid + rifampicin group (n = 34)		Linezolid group (n = 19)	Linezolid + rifampicin group (n = 12)	
Clinical improvement, n (%)	15 (65.22)	26 (76.47)	0.650	16 (84.21)	8 (66.67)	0.523
ADRs, n (%)	10 (43.48)	15 (44.12)	0.999	9 (47.37)	8 (66.67)	0.575
Thrombocytopenia, n (%)	9 (39.13)	15 (44.12)	0.932	7 (36.84)	7 (58.33)	0.504
Anaemia, n (%)	1 (4.35)	1 (2.94)	0.900	2 (10.53)	2 (16.67)	0.845
White blood cell decline, n (%)	3 (13.04)	3 (8.82)	0.878	2 (10.53)	2 (16.67)	0.884
Peripheral neuropathy, n (%)	2 (8.70)	1 (2.94)	0.672	0 (0)	0 (0)	NA
Dose reduction or discontinuation due to ADR, n (%)	7 (30.43)	8 (23.53)	0.845	9 (47.37)	4 (33.33)	0.743

*$p < 0.05$; **, $p < 0.01$.

CYP3A4 and CYP2C (Niemi et al., 2003; Semvua et al., 2015). However, the mechanisms of the interaction between linezolid and rifampicin require further exploration.

Linezolid is not metabolized directly by CYP enzymes. However, the optimal conditions for the formation of linezolid metabolites are alkaline pH (9.0), suggesting involvement by an uncharacterized P450 enzyme or an alternative microsomal-mediated oxidative pathway (Wynalda et al., 2000). A study on the pharmacokinetics of linezolid in healthy people showed that co-administration of linezolid and rifampicin resulted in an earlier time for linezolid to reach the maximum concentration (T_{max}): 0.24 h. In addition, prior administration of rifampicin can increase CYP3A activity in human hepatocytes, leading to a 1.3–1.6-times increase in the metabolism of linezolid (Gandelman et al., 2011). In 2018, a prospective study showed that multiple administrations of rifampicin reduced the concentration of linezolid (p.o.) at normal doses by an average of 65% (Hashimoto et al., 2018). Animal experiments revealed that multiple administrations of rifampicin resulted in reductions of 48%, 54%, and 48% in the AUC, C_{max}, and oral bioavailability, respectively. However, intestinal-permeability tests conducted on rifampicin-pretreated rats and control rats indicated no disparity in the absorption and secretion of linezolid across upper, middle, and lower intestinal tissues. Those results indicate that the primary cause for the interaction between linezolid and rifampicin may be the first-pass effect exerted by the liver (Hashimoto et al., 2018). One study showed that rifampicin pretreatment of mice resulted in a reduction in the blood concentration of linezolid and decrease in AUC of ~30%, implying that rifampicin may inhibit the absorption and accelerate the elimination of linezolid (Lampe et al., 2019).

Studies have shown that a combination of linezolid and rifampicin can reduce the prevalence of thrombocytopenia and the hemoglobin level in patients (Legout et al., 2010). Reported high-risk factors of linezolid-induced thrombocytopenia and reduction in the hemoglobin level include low platelet count, low body weight, low level of albumin, old age, longer duration of medication, renal insufficiency, and C_{min} >8 mg/L (Chen et al., 2012; Lin et al., 2022). Duration of linezolid therapy >14 days and renal insufficiency are independent high-risk factors of ADRs in the blood system (Hirano et al., 2014; Hanai et al., 2016). In the present study, there was no significant difference in the prevalence of hematological ADRs between the two groups, which may have been because of the significantly longer duration of linezolid use in the linezolid + rifampin group compared with that in the linezolid group. A report had demonstrated a significantly higher prevalence of C_{min} >10 mg/L for linezolid when linezolid was combined with P-glycoprotein inhibitors such as omeprazole, amiodarone, or amlodipine (Pea et al., 2010), but this phenomenon was not observed in our study.

The main limitation of our study was the small study cohort (especially C_{min}), which limited the robustness of statistical analyses between the two groups. In a follow-up study, we will utilize a larger study cohort to confirm our findings.

Conclusion

The plasma concentration of linezolid in the linezolid + rifampicin group was significantly lower than that in the linezolid group. In two patients, co-administration of rifampicin resulted in a 75% reduction in the plasma concentration of linezolid. However the total therapeutic efficiency and prevalence of hematologic ADRs were not significantly different in the linezolid group and linezolid + rifampin group. TDM was shown to be an important tool for evaluating the efficacy and safety of long-term treatment with linezolid combined with rifampicin in patients suffering from tuberculosis and infection. This study may improve understanding of the interactions between linezolid and rifampicin.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of Changsha Central Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PY: Writing–review and editing, Conceptualization. Q-ZS: Methodology, Writing–original draft. Y-XH: Writing–original draft, Investigation. YZ: Writing–original draft, Formal Analysis. HL: Formal Analysis, Writing–review and editing, Funding acquisition.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Affiliated Changsha Central Hospital University of South China Foundation of key Program (YNKY202305), National Natural Science Foundation of China (No. 82003870), Natural Science Foundation of Changsha (No. kq2014012), and Scientific Research Project of Health Commission of Hunan Province (D202303106224).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Ashizawa, N., Tsuji, Y., Kawago, K., Higashi, Y., Tashiro, M., Nogami, M., et al. (2016). Successful treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis with combination therapy using linezolid and rifampicin under therapeutic drug monitoring. *J. Infect. Chemother.* 22 (5), 331–334. doi:10.1016/j.jiac.2015.11.012

Beijin Chest Hospital, C. M. U., and Antituberculosis, E. B. O. C. J. O. (2021). Expert consensus on the therapeutic drug monitoring of anti-tuberculosis drugs. *Chin. J. Antituberc.* 43 (9), 867–873. doi:10.3969/j.issn.1000-6621.2021.09.003

Burman, W. J., Gallicano, K., and Peloquin, C. (2001). Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin. Pharmacokinet.* 40 (5), 327–341. doi:10.2165/00003088-200140050-00002

Cattaneo, D., Gervasoni, C., Cozzi, V., Castoldi, S., Baldelli, S., and Clementi, E. (2016). Therapeutic drug management of linezolid: a missed opportunity for clinicians? *Int. J. Antimicrob. Agents* 48 (6), 728–731. doi:10.1016/j.ijantimicag.2016.08.023

Chen, C., Guo, D.-H., Cao, X., Cai, Y., Xu, Y., Zhu, M., et al. (2012). Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. *Curr. Ther. Res. Clin. Exp.* 73 (6), 195–206. doi:10.1016/j.curtheres.2012.07.002

Egle, H., Trittler, R., Kümmerer, K., and Lemmen, S. W. (2005). Linezolid and rifampin: drug interaction contrary to expectations? *Clin. Pharmacol. Ther.* 77 (5), 451–453. doi:10.1016/j.clpt.2005.01.020

Finch, C. K., Chrisman, C. R., Baciewicz, A. M., and Self, T. H. (2002). Rifampin and rifabutin drug interactions: an update. *Arch. Intern Med.* 162 (9), 985–992. doi:10.1001/archinte.162.9.985

Gandelman, K., Zhu, T., Fahmi, O. A., Glue, P., Lian, K., Obach, R. S., et al. (2011). Unexpected effect of rifampin on the pharmacokinetics of linezolid: *in silico* and *in vitro* approaches to explain its mechanism. *J. Clin. Pharmacol.* 51 (2), 229–236. doi:10.1177/0091270010366445

Gebhart, B. C., Barker, B. C., and Markewitz, B. A. (2007). Decreased serum linezolid levels in a critically ill patient receiving concomitant linezolid and rifampin. *Pharmacotherapy* 27 (3), 476–479. doi:10.1592/phco.27.3.476

Hanai, Y., Matsuo, K., Ogawa, M., Higashi, A., Kimura, I., Hirayama, S., et al. (2016). A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. *J. Infect. Chemother.* 22 (8), 536–542. doi:10.1016/j.jiac.2016.05.003

Hashimoto, S., Honda, K., Fujita, K., Miyachi, Y., Isoda, K., Misaka, K., et al. (2018). Effect of coadministration of rifampicin on the pharmacokinetics of linezolid: clinical and animal studies. *J. Pharm. Health Care Sci.* 4 (27), 27–29. doi:10.1186/s40780-018-0123-1

Hirano, R., Sakamoto, Y., Tachibana, N., and Ohnishi, M. (2014). Retrospective analysis of the risk factors for linezolid-induced thrombocytopenia in adult Japanese patients. *Int. J. Clin. Pharm.* 36 (4), 795–799. doi:10.1007/s11096-014-9961-6

Hoyo, I., Martinez-Pastor, J., Garcia-Ramiro, S., Climent, C., Brunet, M., Cuesta, M., et al. (2012). Decreased serum linezolid concentrations in two patients receiving linezolid and rifampicin due to bone infections. *Scand. J. Infect. Dis.* 44 (7), 548–550. doi:10.3109/00365548.2012.663931

Lampe, J. N., Okazaki, F., Tsuji, Y., Seto, Y., Ogami, C., Yamamoto, Y., et al. (2019). Effects of a rifampicin pre-treatment on linezolid pharmacokinetics. *Plos One* 14 (9), e0214037. doi:10.1371/journal.pone.0214037

Legout, L., Valette, M., Dezeque, H., Nguyen, S., Lemaire, X., Loïez, C., et al. (2010). Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia? *J. Antimicrob. Chemother.* 65 (10), 2224–2230. doi:10.1093/jac/dkq281

Lin, B., Hu, Y., Xu, P., Xu, T., Chen, C., He, L., et al. (2022). Expert consensus statement on therapeutic drug monitoring and individualization of linezolid. *Front. Public Health* 10, 967311. doi:10.3389/fpubh.2022.967311

Liu, C., Bayer, A., Cosgrove, S. E., Daum, R. S., Fridkin, S. K., Gorwitz, R. J., et al. (2011). Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin. Infect. Dis.* 52 (3), e18–e55. doi:10.1093/cid/ciq146

Morata, L., De La Calle, C., Gómez-Cerquera, J., Manzanedo, L., Casals, G., Brunet, M., et al. (2016). Risk factors associated with high linezolid trough plasma concentrations. *Expert Opin. Pharmacother.* 17 (9), 1183–1187. doi:10.1080/14656566.2016.1182154

Niemi, M., Backman, J. T., Fromm, M. F., Neuvonen, P. J., and Kivistö, K. T. (2003). Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin. Pharmacokinet.* 42 (9), 819–850. doi:10.2165/00003088-200342090-00003

Pea, F., Cojutti, P. G., and Baraldo, M. (2017). A 10-year experience of therapeutic drug monitoring (TDM) of linezolid in a hospital-wide population of patients receiving conventional dosing: is there enough evidence for suggesting TDM in the majority of patients? *Basic Clin. Pharmacol. Toxicol.* 121 (4), 303–308. doi:10.1111/bcpt.12797

Pea, F., Furlanut, M., Cojutti, P., Cristini, F., Zamparini, E., Franceschi, L., et al. (2010). Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. *Antimicrob. Agents Chemother.* 54 (11), 4605–4610. doi:10.1128/AAC.00177-10

Semvua, H. H., Kibiki, G. S., Kisanga, E. R., Boeree, M. J., Burger, D. M., and Aarnoutse, R. (2015). Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. *Ther. Drug Monit.* 37 (1), 22–32. doi:10.1097/FTD.0000000000000108

Singh, B., Cocker, D., Ryan, H., and Sloan, D. J. (2019). Linezolid for drug-resistant pulmonary tuberculosis. *Cochrane Database Syst. Rev.* 3 (3), CD012836. doi:10.1002/14651858.CD012836.pub2

Slatter, J., Stalker, D., Feenstra, K., Welshman, I., Bruss, J., Sams, J., et al. (2001). Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [14C] linezolid to healthy human subjects. *Drug Metab. Dispos.* 29 (8), 1136–1145.

Takahashi, Y., Takesue, Y., Nakajima, K., Ichiki, K., Tsuchida, T., Tatsumi, S., et al. (2011). Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. *J. Infect. Chemother.* 17 (3), 382–387. doi:10.1007/s10156-010-0182-1

Tuberculosis, C. S. F., and Association, C. M. (2022). Consensus on linezolid in the treatment of tuberculosis (2022 update). *Chin. J. Tuberc. Respir. Dis.* 45 (10), 988–995. doi:10.3760/cma.j.cn112147-20220320-00220

Wynalda, M. A., Hauer, M. J., and Wienkers, L. C. (2000). Oxidation of the novel oxazolidinone antibiotic linezolid in human liver microsomes. *Drug Metab. Dispos.* 28 (9), 1014–1017.

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 16 January 2024
DOI 10.3389/fphar.2024.1312803

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Yoshihiro Noguchi,
Gifu Pharmaceutical University, Japan
Ning Zhang,
Fudan University, China

*CORRESPONDENCE
Masahiko Gosho,
mgosho@md.tsukuba.ac.jp

RECEIVED 10 October 2023
ACCEPTED 04 January 2024
PUBLISHED 16 January 2024

CITATION
Gosho M, Ishii R, Ohigashi T and Maruo K (2024), Multivariate generalized mixed-effects models for screening multiple adverse drug reactions in spontaneous reporting systems.
Front. Pharmacol. 15:1312803.
doi: 10.3389/fphar.2024.1312803

Multivariate generalized mixed-effects models for screening multiple adverse drug reactions in spontaneous reporting systems

Masahiko Gosho[1]*, Ryota Ishii[1], Tomohiro Ohigashi[2] and Kazushi Maruo[1]

[1]Department of Biostatistics, Institute of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Department of Biostatistics, Tsukuba Clinical Research and Development Organization, University of Tsukuba, Tsukuba, Japan

Introduction: For assessing drug safety using spontaneous reporting system databases, quantitative measurements, such as proportional reporting rate (PRR) and reporting odds ratio (ROR), are widely employed to assess the relationship between a drug and a suspected adverse drug reaction (ADR). The databases contain numerous ADRs, and the quantitative measurements need to be calculated by performing the analysis multiple times for each ADR. We proposed a novel, simple, and easy-to-implement method to estimate the PRR and ROR of multiple ADRs in a single analysis using a generalized mixed-effects model for signal detection.

Methods: The proposed method simultaneously analyzed the association between any drug and numerous ADRs, as well as estimated the PRR and ROR for a specific combination of drugs and suspected ADRs. Furthermore, the proposed method was applied to detect drug-drug interactions associated with the concurrent use of two or more drugs.

Results and discussion: In our simulation studies, the false-positive rate and sensitivity of the proposed method were similar to those of the traditional PRR and ROR. The proposed method detected known ADRs when applied to the Food and Drug Administration Adverse Event Reporting System database. As an important advantage, the proposed method allowed the simultaneous evaluation of several ADRs using multiple drugs.

KEYWORDS

database, drug-drug interaction, proportional reporting rate, reporting odds ratio, signal detection

Abbreviations: ADR, adverse drug reaction; BCPNN, Bayesian confidence propagation neural network; CI, confidence interval; DDI, drug-drug interaction; FAERS, FDA adverse event reporting system; FDA, food and drug administration; MedDRA, medical dictionary for regulatory activity; MGPS, multi-item gamma poisson shrinker; PRR, proportional reporting rate; ROR, reporting odds ratio; SGLT2, sodium glucose-linked transporter 2; SOC, system organ class.

1 Introduction

During the clinical development of new drugs, collecting sufficient information on drug safety poses a considerable challenge. Hence, spontaneous reporting systems are crucial sources for post-marketing drug safety surveillance. Importantly, these systems are commonly used to detect suspected adverse drug reactions (ADRs) and generate potential ADRs in real-world settings. Since the 1960s, regulatory authorities such as the US Food and Drug Administration (FDA) have established databases for spontaneous reporting.

When assessing drug safety using spontaneous reporting system databases, quantitative signal detection methods can be valuable for identifying the relationship between a drug and suspected ADR, given the considerable amount of data obtained. This data mining approach is crucial for the early detection of safety signals and for generating hypotheses regarding new ADRs. Several methods, including the proportional reporting rate (PRR) (Evans et al., 2001), reporting odds ratio (ROR) (Rothman et al., 2004), Bayesian confidence propagation neural network (BCPNN) (Bate et al., 1998), and multi-item gamma Poisson shrinker (MGPS) (DuMouchel, 1999), have been proposed and employed by regulatory authorities for signal detection. These methods typically assess disproportionality in the observed and expected numbers of counts for specific combinations of a drug and suspected ADRs. Thus, if the ratio of the observed count to the expected count (henceforth, the O/E ratio) estimated using these methods is far from 1, it is considered a signal. Although the performance of these methods has been extensively evaluated and compared (van Puijenbroek et al., 2002; Kubota et al., 2004; Almenoff et al., 2006; Matsushita et al., 2007; Hochberg et al., 2009; Ahmed et al., 2010; Bunchuailua et al., 2010; Chen et al., 2015), no gold standard method has been established worldwide.

Unlike the BCPNN and MGPS, the PRR and ROR are easy to calculate and interpret. The PRR is a simple risk ratio (or relative risk), while the ROR is a simple odds ratio derived from a 2 × 2 contingency table (Table 1), with both measurements closely related to statistical models occasionally used for signal detection. Considering Poisson regression models, the parameter estimates in the model yield the PRR, which is the reporting ratio of drug use to non-use. Likewise, the ROR can be estimated using a logistic regression model. In particular, these models help assess drug-drug interactions (DDIs) during the concurrent administration of two or more drugs (Thakrar et al., 2007). By including a statistical interaction term in the model, the presence of DDIs can be evaluated using a spontaneous reporting system (van Puijenbroek et al., 1999; van Puijenbroek et al., 2000). Importantly, these modeling approaches can detect only one ADR, and multiple models need to be constructed for each ADR to estimate the PRR and ROR of various ADRs. For example, to evaluate 100 types of ADRs, 100 regression models must be constructed with each ADR as a response variable.

As another approach for detecting DDIs, Norén et al. (2008) proposed a criterion using the O/E ratio of the number of reports for the ADR for a combination of two drugs. Gosho et al. (2017) also proposed a criterion based on chi-square test statistics to measure the discrepancy between the observed and expected number of reports. Although these methods have been effectively reviewed and compared (Noguchi et al., 2019; Noguchi et al., 2020), the detection of DDIs between three or more drugs is not possible. Moreover, similar to the analysis using regression models, the methods can detect only one ADR, and multiple analyses are required to assess each ADR.

In the present study, we propose a novel, simple, and easy-to-implement method using Poisson and logistic mixed-effect models for signal detection. The proposed method could simultaneously analyze the relationship between any drug and numerous ADRs and estimate the PRR and ROR for a specific combination of drugs and suspected ADRs. Furthermore, the proposed method could be applied to detect DDIs during the concurrent administration of two or more drugs. We also provide a sample SAS code for implementing the proposed method.

2 Methodology

2.1 Notation

Spontaneous reporting systems include multiple drugs and ADRs in each report. This information can be summarized in a 2 × 2 contingency table, as shown in Table 1. We used I drugs and J ADRs. Here, n_{ij} is the number of events reported for the i th drug ($i = 1, \ldots, I$) and j th ADR ($j = 1, \ldots, J$); $n_{i\cdot}$ is the total number of events reported with the target drug i; $n_{\cdot j}$ is the total number of events reported with specific ADR j; n indicates the total number of ADRs reported with any drug; p_{ij} is the incidence probability for the j th ADR with the i th drug. Let i^- denote all other drugs except the target drug i.

2.2 Standard strategy and signal detection methods

Typically, signal detection is used to assess disproportionality in the observed number of counts, n_{ij}, and the expected number of counts, E_{ij}, for a specific combination of drug i and ADR j. E_{ij} =

TABLE 1 Two-by-two contingency table for summarizing the specific ADR reported in the target drug.

Number of events (incidence probability for j th ADR)	Specific ADR j	All others	Total
Target drug, i	n_{ij} (p_{ij})	$n_{i\cdot} - n_{ij}$	$n_{i\cdot}$
All others, i^-	$n_{\cdot j} - n_{ij}$ $(p_{i^- j})$	$n - n_{i\cdot} - n_{\cdot j} + n_{ij}$	$n - n_{i\cdot}$
Total	$n_{\cdot j}$ $(p_{\cdot j})$	$n - n_{\cdot j}$	n

ADR, adverse drug reaction.

TABLE 2 ADRs detected with three or more kinds of SGLT2 inhibitors, and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 1 (single drug).

Detected ADR	SGLT2 inhibitors						
	Canagliflozin ($n_{i.}$ = 3933)	Empagliflozin ($n_{i.}$ = 36966)	Ipragliflozin ($n_{i.}$ = 553)	Dapagliflozin ($n_{i.}$ = 14054)	Tofogliflozin ($n_{i.}$ = 147)	Luseogliflozin ($n_{i.}$ = 133)	Ertugliflozin ($n_{i.}$ = 759)
Metabolism and nutrition disorders in system organ class							
Hypoglycemia	**7.35**	**4.18**	**8.55**	**10.23**	**1.61**	0.52	**2.50**
Diabetic ketoacidosis	**75.67**	-	**10.77**	**118.63**	**18.05**	**5.65**	**30.58**
Euglycemic diabetic ketoacidosis	**140.42**	**393.33**	**10.06**	**236.20**	**82.39**	**21.65**	**52.34**
Ketoacidosis	**76.20**	**131.99**	**32.16**	**171.53**	**2.88**	**3.19**	**17.90**
Diabetic ketosis	**14.97**	**39.91**	**16.05**	**189.73**	-	**226.11**	-
Ketosis	**127.62**	**74.74**	**22.47**	**217.34**	**24.72**	-	**49.15**
Dehydration	**3.17**	**3.71**	**4.04**	**3.95**	**5.23**	0.18	0.98
Polydipsia	**7.78**	**10.90**	-	**6.22**	-	-	-
Diabetes mellitus	**6.35**	**2.34**	**7.56**	**3.05**	**4.00**	**1.05**	0.06
Type 1 diabetes mellitus	0.15	**1.40**	1.00	**3.47**	**3.75**	-	-
Type 2 diabetes mellitus	**14.01**	**1.18**	**1.42**	**1.82**	0.53	-	0.35
Diabetes mellitus inadequate control	**13.05**	**6.90**	**20.31**	**18.71**	**28.29**	**13.81**	**5.37**
Hyperglycemia	**17.07**	**5.64**	**4.40**	**13.85**	**14.06**	**9.57**	**1.20**
Insulin resistance	-	**4.37**	-	**1.91**	**9.90**	-	-
Diabetic metabolic decompensation	-	**10.88**	-	**53.40**	-	-	**55.74**
Acetonemia	**38.53**	**75.23**	-	**51.36**	-	-	-
Acidosis	**8.46**	**9.47**	**2.84**	**6.99**	-	-	-
Decreased appetite	0.79	**1.42**	**1.46**	**1.33**	**1.15**	**2.95**	0.29
Dyslipidemia	**5.58**	**1.08**	-	**5.65**	-	-	-
Fluid intake reduced	**1.11**	**1.66**	-	**3.87**	**4.46**	-	-
Hyperglycemic hyperosmolar nonketotic syndrome	**5.43**	**13.97**	**19.85**	**38.27**	-	-	-
Hyperkalemia	**1.97**	**2.65**	**1.73**	**5.86**	0.64	-	0.43

(Continued on following page)

10.3389/fphar.2024.1312803

TABLE 2 (*Continued*) ADRs detected with three or more kinds of SGLT2 inhibitors, and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 1 (single drug).

Detected ADR	SGLT2 inhibitors						
	Canagliflozin ($n_{i.}$ = 3933)	Empagliflozin ($n_{i.}$ = 36966)	Ipragliflozin ($n_{i.}$ = 553)	Dapagliflozin ($n_{i.}$ = 14054)	Tofogliflozin ($n_{i.}$ = 147)	Luseogliflozin ($n_{i.}$ = 133)	Ertugliflozin ($n_{i.}$ = 759)
Hyperlipidemia	0.55	**1.93**	-	**2.05**	**2.23**	**8.36**	-
Hypernatremia	**5.17**	**3.27**	-	**11.06**	-	-	0.88
Hypertriglyceridemia	**3.87**	**1.41**	**3.45**	**1.27**	-	-	-
Hyperuricemia	**1.67**	**1.16**	**21.30**	**7.64**	-	-	-
Hypokalemia	**1.61**	**1.09**	0.80	**1.79**	-	-	0.31
Hypophagia	**2.30**	**2.36**	0.21	**1.24**	-	-	-
Hypovolemia	**7.67**	**11.50**	-	**6.91**	-	-	0.90
Obesity	**1.49**	0.88	**3.38**	**3.39**	**1.25**	-	0.84
Starvation	**1.23**	**2.88**	-	**6.14**	-	-	-
ADRs recognized in the package insert of SGLT2 inhibitors							
Coronary artery stenosis	**7.02**	**3.23**	**5.33**	**14.71**	**5.87**	-	-
Cerebral infarction	**19.66**	**2.74**	**24.66**	**8.60**	**8.84**	**6.27**	-
Thrombotic cerebral infarction	**1.75**	**5.82**	**78.94**	**38.16**	-	**49.76**	-
Embolic cerebral infarction	**1.07**	**1.57**	**7.39**	**1.01**	-	-	-
Cerebellar infarction	**5.43**	**1.54**	**3.79**	**4.06**	-	-	-
Lacunar infarction	**7.76**	**3.50**	**3.02**	**7.96**	-	**42.40**	**2.30**
Brain stem infarction	**5.68**	**1.68**	**6.12**	**13.76**	-	-	-
Carotid artery stenosis	**9.79**	**2.36**	-	**2.34**	-	**9.05**	-
Ketonuria	**72.99**	**86.02**	-	**211.69**	-	-	**17.74**
Nocturia	**3.06**	**2.83**	0.43	**1.38**	-	-	0.32
Polyuria	**13.18**	**8.70**	0.65	**19.31**	-	-	**3.13**
Balanoposthitis	**28.25**	**45.10**	-	**70.31**	-	-	**4.77**
Pruritus genital	**14.46**	**25.45**	**9.53**	**36.46**	**10.50**	-	**2.14**
Vulvovaginal pruritus	0.98	**14.40**	-	**7.15**	-	-	**2.65**
Genital discomfort	-	**19.05**	-	**17.82**	-	-	**46.07**

(Continued on following page)

10.3389/fphar.2024.1312803

TABLE 2 (*Continued*) ADRs detected with three or more kinds of SGLT2 inhibitors, and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 1 (single drug).

Detected ADR	SGLT2 inhibitors						
	Canagliflozin ($n_{i.}$ = 3933)	Empagliflozin ($n_{i.}$ = 36966)	Ipragliflozin ($n_{i.}$ = 553)	Dapagliflozin ($n_{i.}$ = 14054)	Tofogliflozin ($n_{i.}$ = 147)	Luseogliflozin ($n_{i.}$ = 133)	Ertugliflozin ($n_{i.}$ = 759)
Penile erythema	**2.05**	**20.82**	-	**3.70**	-	-	**10.71**
Penile pain	**5.33**	**2.73**	-	**2.60**	-	-	-
Scrotal swelling	**2.99**	**5.74**	-	**1.61**	-	-	-
Vulvovaginal erythema	-	**4.63**	-	**3.34**	-	-	**15.02**
Vulvovaginal swelling	0.39	**2.90**	-	**1.50**	-	-	**6.75**
Pyelonephritis	**6.73**	**3.50**	**5.88**	**8.55**	**7.39**	**8.16**	**1.46**
Pyelonephritis acute	**20.63**	**3.21**	-	**14.17**	**9.69**	-	-
Emphysematous pyelonephritis	**12.83**	**99.69**	**89.65**	**1.09**	-	**371.02**	-
Sepsis	**1.29**	**2.22**	0.68	**2.09**	**1.19**	0.20	0.80
Septic shock	**1.44**	**1.51**	-	**2.21**	0.50	-	0.33
Fournier's gangrene	**55.03**	**249.97**	-	**59.85**	-	-	**71.49**
Gangrene	**4.53**	**7.10**	-	**5.56**	-	-	**6.54**
Necrotizing fasciitis	**5.33**	**24.27**	-	**22.61**	-	-	**4.20**
Necrotizing soft tissue infection	**9.74**	**28.54**	-	**2.75**	-	-	**50.33**
Diabetic gangrene	**96.42**	**3.43**	-	**6.53**	-	-	-
Thirst	**4.00**	**8.64**	**1.99**	**6.26**	-	-	**6.04**
Amputation	**28.07**	**5.69**	-	**2.39**	-	-	-
Foot amputation	**6.43**	**7.02**	-	**5.93**	-	-	**8.13**
Leg amputation	**6.05**	**5.65**	-	**3.55**	-	-	-
Toe amputation	**10.72**	**9.57**	-	**8.26**	-	-	**2.18**

ADR, adverse drug reaction; CI, confidence interval; ROR, reporting odds ratio; SGLT2, sodium glucose-linked transporter 2.
- not reported; bold, detected ADR; $n_{i.}$, the number of the target drug *i* reported.

10.3389/fphar.2024.1312803

TABLE 3 ADRs detected with two or more kinds of SGLT2 inhibitors with glimepiride and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 2 (DDIs).

Detected ADR	Concomitant use of glimepiride and						
	Canagliflozin ($n_{ii'.}$ = 467)	Empagliflozin ($n_{ii'.}$ = 1346)	Ipragliflozin ($n_{ii'.}$ = 116)	Dapagliflozin ($n_{ii'.}$ = 780)	Tofogliflozin ($n_{ii'.}$ = 26)	Luseogliflozin ($n_{ii'.}$ = 20)	Ertugliflozin ($n_{ii'.}$ = 34)
Metabolism and nutrition disorders							
Hypoglycemia	**9.78**	**3.67**	**8.40**	-	-	**1.45**	-
Diabetic ketoacidosis	**31.63**	-	**5.62**	-	-	-	**1.40**
Euglycemic diabetic ketoacidosis	**70.15**	-	**3.69**	**86.16**	-	-	-
Ketoacidosis	**24.65**	**15.48**	-	**39.40**	-	-	**30.90**
Diabetic ketosis	-	**22.14**	-	**84.30**	-	-	-
Ketosis	**145.37**	**105.86**	-	**17.17**	**56.46**	-	-
Abnormal loss of weight	-	**10.64**	-	**10.87**	-	-	-
Dehydration	**5.07**	-	0.52	**4.58**	-	0.46	0.28
Diabetes mellitus	0.52	**2.89**	0.93	**2.44**	0.63	-	-
Type 2 diabetes mellitus	0.46	**2.06**	-	**2.62**	-	-	-
Diabetes mellitus inadequate control	**6.98**	**12.37**	0.79	**28.45**	-	**3.66**	**2.24**
Diabetic metabolic decompensation	-	0.85	-	**261.80**	-	-	**459.27**
Hyperglycemia	**1.82**	**4.89**	-	-	**1.37**	**1.78**	-
Hypercholesterolemia	-	**6.58**	-	**1.46**	-	-	-
Hyperuricemia	-	**6.49**	**14.61**	-	-	-	-
Increased appetite	**1.06**	0.09	-	**2.16**	-	-	-
Lactic acidosis	0.64	**1.76**	**2.40**	**21.13**	**1.61**	**2.10**	-
Metabolic acidosis	**4.91**	-	-	**1.28**	-	-	-
Obesity	-	**1.30**	-	**1.38**	-	-	-
Cardiac disorders							
Coronary artery disease	0.16	**1.25**	-	**2.13**	-	-	**1.50**
Coronary artery occlusion	-	**1.21**	-	**3.29**	-	-	-

(Continued on following page)

10.3389/fphar.2024.1312803

TABLE 3 (*Continued*) ADRs detected with two or more kinds of SGLT2 inhibitors with glimepiride and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 2 (DDIs).

Detected ADR	Concomitant use of glimepiride and						
	Canagliflozin ($n_{ii'.}$ = 467)	Empagliflozin ($n_{ii'.}$ = 1346)	Ipragliflozin ($n_{ii'.}$ = 116)	Dapagliflozin ($n_{ii'.}$ = 780)	Tofogliflozin ($n_{ii'.}$ = 26)	Luseogliflozin ($n_{ii'.}$ = 20)	Ertugliflozin ($n_{ii'.}$ = 34)
Coronary artery stenosis	**49.45**	**3.89**	**3.70**	**3.21**	-	-	-
Acute myocardial infarction	**5.26**	**7.37**	-	**8.11**	-	-	**1.35**
Angina pectoris	**5.22**	**7.76**	0.47	**3.12**	-	-	-
Angina unstable	0.67	**1.15**	-	**1.93**	-	-	-
Atrial fibrillation	**4.42**	0.82	0.69	**1.41**	-	-	-
Cardiac failure	**3.33**	**1.30**	0.16	**1.52**	**8.11**	-	-
Myocardial infarction	**1.64**	**1.85**	0.42	**1.22**	-	-	-
Myocardial ischemia	**3.83**	**3.08**	**1.31**	0.24	-	-	-
Ventricular extrasystoles	**4.73**	**3.81**	-	-	-	-	-
Ventricular fibrillation	-	**13.08**	-	**4.18**	-	-	-
Tricuspid valve incompetence	-	**2.30**	-	**3.92**	-	-	-
Nervous system disorders							
Cerebral infarction	**34.52**	**10.56**	**2.88**	-	-	**15.73**	-
Cerebellar infarction	**12.36**	**9.24**	**8.84**	-	-	-	-
Lacunar infarction	-	0.84	-	**12.79**	-	**207.12**	-
Brain stem infarction	-	**7.33**	**14.41**	**41.61**	-	-	-
Diabetic neuropathy	-	**1.52**	-	**8.46**	-	-	-
Altered state of consciousness	0.19	**2.45**	**17.03**	**5.06**	-	-	-
Cervicobrachial syndrome	**79.17**	**13.67**	-	-	-	-	-
Renal and urinary disorders							
Ketonuria	-	**35.49**	-	**37.32**	-	-	-
Nocturia	**1.38**	**1.04**	-	0.84	-	-	-
Pollakiuria	**2.58**	-	-	**1.94**	-	-	-
Polyuria	**4.49**	**6.01**	-	**16.92**	-	-	-

(Continued on following page)

10.3389/fphar.2024.1312803

TABLE 3 (*Continued*) ADRs detected with two or more kinds of SGLT2 inhibitors with glimepiride and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 2 (DDIs).

Detected ADR	Concomitant use of glimepiride and						
	Canagliflozin ($n_{ii'.}$ = 467)	Empagliflozin ($n_{ii'.}$ = 1346)	Ipragliflozin ($n_{ii'.}$ = 116)	Dapagliflozin ($n_{ii'.}$ = 780)	Tofogliflozin ($n_{ii'.}$ = 26)	Luseogliflozin ($n_{ii'.}$ = 20)	Ertugliflozin ($n_{ii'.}$ = 34)
Renal impairment	**6.84**	**2.19**	**2.66**	**1.75**	-	-	-
Acute kidney injury	**1.35**	-	**2.07**	**2.27**	0.21	-	0.99
Nephropathy	**1.32**	**1.58**	-	-	-	-	-
Renal failure	**1.07**	**1.01**	0.08	0.23	-	-	0.23
Dysuria	0.47	**2.12**	-	**2.67**	-	-	-
Hematuria	-	**1.30**	0.34	**1.78**	-	-	-
Urinary incontinence	**1.27**	0.73	-	**1.75**	-	-	-
Urinary retention	**5.24**	0.20	-	**6.05**	-	-	-
Reproductive system and breast disorders							
Balanoposthitis	**4.44**	**17.71**	-	**13.76**	-	-	-
Pruritus genital	-	**16.72**	-	**19.61**	**23.53**	-	-
Vulvovaginal pruritus	0.73	**7.91**	-	**2.12**	-	-	-
Testicular pain	**1.20**	**2.07**	-	**38.05**	-	-	-
Benign prostatic hyperplasia	**6.47**	**1.12**	-	0.41	-	-	-
Infections and infestations							
Pyelonephritis	**1.89**	0.69	**7.17**	**5.50**	**4.82**	-	-
Pyelonephritis acute	**8.58**	**6.41**	-	**49.32**	**21.72**	-	-
Sepsis	0.76	**1.64**	-	**1.57**	-	-	0.32
Septic shock	**3.42**	0.52	-	**2.48**	**1.10**	-	-
Escherichia sepsis	-	-	**85.55**	**3.88**	-	-	-
Fournier's gangrene	**1.52**	**93.96**	-	**21.73**	-	-	-
Gangrene	-	-	-	**8.33**	-	-	**35.25**
Necrotizing fasciitis	**1.17**	**2.14**	-	**11.50**	-	-	-
Scrotal abscess	-	**16.64**	-	**26.23**	-	-	-
Fungal infection	-	**8.85**	-	0.30	-	-	**13.78**

(Continued on following page)

10.3389/fphar.2024.1312803

10.3389/fphar.2024.1312803

TABLE 3 (*Continued*) ADRs detected with two or more kinds of SGLT2 inhibitors with glimepiride and the lower limit of 95% CI for ROR calculated using the proposed model in Scenario 2 (DDIs).

Detected ADR	Concomitant use of glimepiride and						
	Canagliflozin ($n_{ii'.} = 467$)	Empagliflozin ($n_{ii'.} = 1346$)	Ipragliflozin ($n_{ii'.} = 116$)	Dapagliflozin ($n_{ii'.} = 780$)	Tofogliflozin ($n_{ii'.} = 26$)	Luseogliflozin ($n_{ii'.} = 20$)	Ertugliflozin ($n_{ii'.} = 34$)
Gastroenteritis	**5.24**	0.09	0.78	**4.14**	-	-	-
Pneumonia aspiration	**2.44**	-	-	**6.38**	-	-	-
Surgical and medical procedures							
Leg amputation	**4.43**	**1.63**	-	**2.70**	-	-	-

ADR, adverse drug reaction; CI, confidence interval; DDI, drug-drug interaction; ROR, reporting odds ratio; SGLT2, sodium glucose-linked transporter 2.
- not reported; bold, detected ADR; $n_{ii'.}$, the number of the combined uses of drug i and drug i' reported.

$n_i n_j/n$ is defined as the expected number of counts under the null hypothesis, with no association between the i th drug and the j th ADR. O/E ratios were evaluated using several methods. The direct estimator of the O/E ratio is the relative reporting ratio, defined as:

$$\frac{n_{ij}/n_i}{n_j/n} = \frac{n_{ij}}{E_{ij}}$$

The PRR was calculated as the ratio of the proportion of the ADR j reported with drug i to the proportion of the same ADR reported with all other drugs combined:

$$\frac{n_{ij}/n_i}{\left(n_j - n_{ij}\right)/\left(n - n_i\right)} \tag{1}$$

The PRR can be interpreted as a measure of the reporting rate, with and without target drug i. In addition, PRR is considered an approximation of the relative reporting ratio, given that $n_{ij} \ll n_j$ and $n_i \ll n$ in almost cases. If PRR = 1, the absence of an association between the i th drug and the j th ADR can be assumed.

The ROR was calculated as the ratio of the odds for ADR j reported with drug i to the odds that the same ADR was reported with all other drugs combined, as follows:

$$\frac{n_{ij}/\left(n_i - n_{ij}\right)}{\left(n_j - n_{ij}\right)/\left(n - n_i - n_j + n_{ij}\right)} \tag{2}$$

If the lower limit of the 95% confidence interval (CI) for PRR is greater than 1, the relationship between the target drug and specific ADR was detected as a signal; the same was applied to ROR in Eq. 2.

2.3 Poisson mixed-effect model and PRR

We assumed that the random variable n_{ij} follows a Poisson distribution, expressed as $n_{ij} \sim \text{Poisson}(n_i p_{ij})$, where p_{ij} is the incidence probability of ADR j when drug i is used (Table 1). The probability function is expressed as

$$\Pr\left(n_{ij} \mid \lambda_{ij}\right) = \frac{\exp\left(-\lambda_{ij}\right)\lambda_{ij}^{n_{ij}}}{n_{ij}!}, n_{ij} = 0, 1, 2, \ldots$$

Here, λ_{ij} was defined as the mean (expected) value of n_{ij}. Accordingly, $\lambda_{ij} = n_i p_{ij}$. The relationship between mean value λ_{ij} and covariate x_i is generally modeled using a natural log link function, as follows:

$$\ln\left(\lambda_{ij}\right) = \beta_0 + \beta_i x_i \tag{3}$$

where β_i is the unknown regression parameter for drug i. We aimed to evaluate all ADRs ($j = 1, \ldots, J$) when drug i is used. Considering that x_i denotes the binary indicator for drug i, $x_i = 1$ if the use of drug i is reported, and $x_i = 0$ if the use of other drugs (excluding the i th drug) is reported. In this model, β_i can be interpreted as the marginal effect of all ADRs using drug i compared to the use of other drugs. Thus, β_i is a common effect that does not specify ADRs. Furthermore, $\exp(\beta_i)$ is the PRR for drug i that is not ADR specific. However, this interpretation of β_i must be oversimplified and cannot detect the signal of a specific ADR.

TABLE 4 Four-by-two contingency table summarizing the specific ADR reported with the target drugs for evaluating DDIs.

Number of events (incidence probability for j th ADR)	Specific ADR j	All others	Total
Neither drug 1 nor drug 2	n_{00} (p_{00})	$10,000,000 - n_{00}$	10,000,000
Only drug 1	n_{10} (p_{10})	$100,000 - n_{10}$	100,000
Only drug 2	n_{01} (p_{01})	$100,000 - n_{01}$	100,000
drug 1 and drug 2	n_{11} (p_{11})	$10,000 - n_{11}$	10,000

ADR, adverse drug reaction; DDIs, drug-drug interactions.

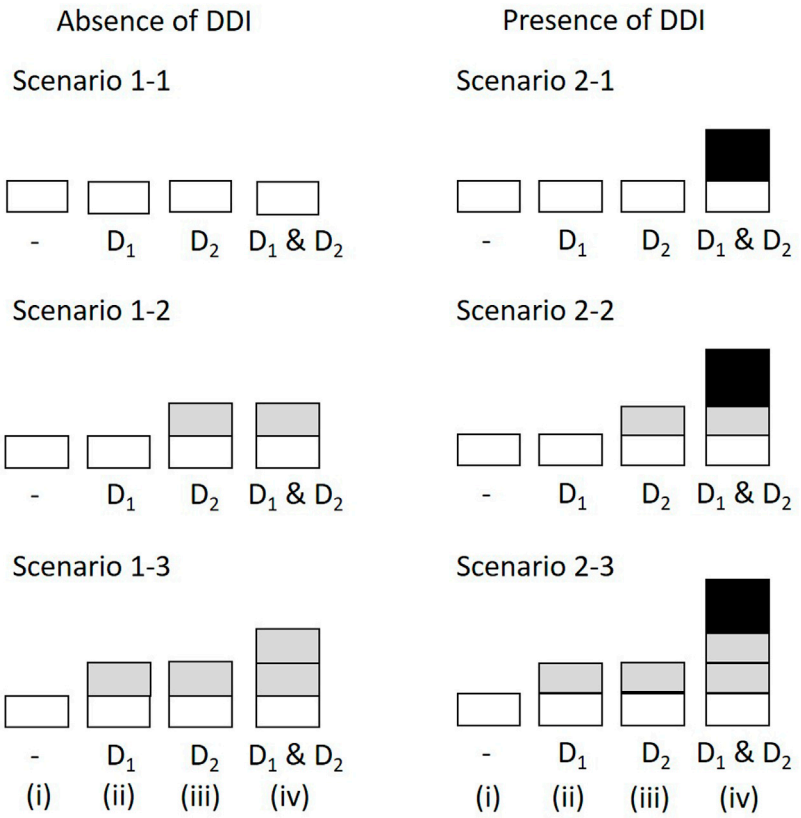


FIGURE 1
Simulation scenarios and settings. The height of *bars* correspond to the incidence probability of ADR A (i) in the absence of both D_1 and D_2; (ii) with D_1 but not D_2; (iii) with D_2 but not D_1; (iv) with D_1 and D_2. The *shades* correspond to the marginal relative probability of ADR A (*lightest*), the increased frequency attributable to D_1, the increased frequency attributable to D_2, and the increased incidence probability attributable to an interaction between D_1 and D_2 (*darkest*). The darkest bars indicate the DDI effect. ADR, adverse drug reaction; DDI, drug-drug interaction.

Next, to assess a specific ADR, we included a random effect in Eq. 3, with the linear predictor η_{ij} expressed as follows:

$$\eta_{ij} = \ln(\lambda_{ij}) = \beta_0 + b_0 + (\beta_i + b_j)x_i \quad (4)$$

where b_0 and b_j are random effects for the intercept and j th ADR, respectively, assumed to follow normal distributions, $b_0 \sim N(0, \gamma_0)$ and $b_j \sim N(0, \gamma_j)$. Here, γ_0 and γ_j are the variances of the random effects. Eq. 4, known as the Poisson mixed-effect model, was used to estimate the mean value λ_{ij} for each drug and each ADR.

Based on Eq. 4, the linear predictor for each x_i was

$$\ln(\lambda_{ij}) = \begin{cases} \beta_0 + b_0 + \beta_i + b_j, & x_i = 1 \\ \beta_0 + b_0, & x_i = 0 \end{cases}$$

Thus, the PRR of ADR j for drug i is

$$\mathrm{PRR}_{ij} = \exp(\beta_i + b_j).$$

Using Eq. 4, we simultaneously estimated the PRRs of all ADRs (i.e., any j) for drug i.

Extending Eq. 4 allowed the simultaneous evaluation effects mediated by multiple drugs; for example, consider a DDI in which two drugs (i and i') are administered simultaneously. In this case, the linear predictor in Eq. 4 is expressed as follows:

TABLE 5 Simulation results in Scenarios 1 and 2 with single-dose settings (the number of ADR types = 100).

$p_{1\text{-}j}$ (%)	p_{1j} (%)	Proposed method		Traditional method	
		PRR	ROR	PRR	ROR
False-positive rate					
0.05	0.05	3.27	3.27	3.27	3.27
0.1	0.1	2.04	2.04	2.05	2.05
0.2	0.2	2.78	2.79	2.80	2.80
0.05	0.05	2.56	2.56	2.59	2.59
0.1	0.1	2.56	2.56	2.57	2.57
0.2	0.2	2.58	2.59	2.60	2.60
Sensitivity					
0.05	0.075	23.6	23.6	23.6	23.6
	0.1	56.5	56.5	56.5	56.5
	0.125	80.2	80.2	80.2	80.2
0.1	0.15	35.1	35.1	35.2	35.1
	0.2	78.4	78.4	78.4	78.4
	0.25	95.6	95.6	95.6	95.6

ADR, adverse drug reaction; DDIs, drug-drug interactions; PRR, proportional reporting rate; ROR, reporting odds ratio.

$$\ln\left(\lambda_{ii'j}\right) = \beta_0 + b_0 + \beta_i x_i + \beta_{i'} x_{i'} + \beta_{ii'} x_i x_{i'} + b_{ij} x_i + b_{i'j} x_{i'} + b_{ii'j} x_i x_{i'}$$

where $x_i = 1$ if drug i was used, $x_i = 0$ otherwise, $x_{i'} = 1$ if drug i' was used, and $x_{i'} = 0$ otherwise. β_i, $\beta_{i'}$, and $\beta_{ii'}$ are unknown regression parameters for x_i, $x_{i'}$, and $x_i x_{i'}$, respectively; b_0, b_{ij}, $b_{i'j}$, and $b_{ii'j}$ are random effects for intercepts, x_i, $x_{i'}$, and $x_i x_{i'}$, respectively. Assuming that $b_0 \sim N(0, \gamma_0)$, $b_{ij} \sim N(0, \gamma_i)$, $b_{i'j} \sim N(0, \gamma_{i'})$, and $b_{ii'j} \sim N(0, \gamma_{ii'})$, each linear predictor can be calculated as follows:

$$\ln\left(\lambda_{ii'j}\right) = \begin{cases} \beta_0 + b_0, & x_i = 0 \text{ and } x_{i'} = 0 \\ \beta_0 + b_0 + \beta_i + b_{ij}, & x_i = 1 \text{ and } x_{i'} = 0 \\ \beta_0 + b_0 + \beta_{i'} + b_{i'j}, & x_i = 0 \text{ and } x_{i'} = 1 \\ \beta_0 + b_0 + \beta_i + \beta_{i'} + \beta_{ii'} + b_{ij} + b_{i'j} + b_{ii'j}, & x_i = 1 \text{ and } x_{i'} = 1 \end{cases}$$

Thus, the PRRs of ADR j for drugs i and i' and the combined use of drugs i and i' are as follows:

$$\mathrm{PRR}_{ij} = \exp\left(\beta_i + b_{ij}\right), \mathrm{PRR}_{i'j} = \exp\left(\beta_{i'} + b_{i'j}\right),$$
$$\text{and } \mathrm{PRR}_{ii'j} = \exp\left(\beta_{ii'} + b_{ii'j}\right),$$

Here, PRR_{ij} is the PRR of ADR j for drug i, $\mathrm{PRR}_{i'j}$ is the PRR of ADR j for drug i', and $\mathrm{PRR}_{ii'j}$ is the PRR of ADR j under the concomitant use of drugs i and i'. The proposed method could allow the detection of DDIs during the concurrent use of two or more drugs, as it allows for flexible modeling by including a statistical interaction term. The proposed method is based on a multiplicative model for DDI, whereas the criteria for detecting DDIs established by Norén et al. (2008) and Gosho et al. (2017) are based on an additive model for DDI (Thakrar et al., 2007).

The fixed and random effects in Eqs 3, 4 were estimated using the restricted pseudo-likelihood method (Wolfinger and O'Connell, 1993). The PRR and its 95% CI were estimated using the estimation of β_i and b_{ij}, $\hat{\beta}_i$ and $\hat{b}_{ij}$ and their variance estimates via pseudo-likelihood theory. Stroup (2013) provides a more detailed explanation regarding the theory of generalized mixed-effect models, such as Poisson and logistic mixed-effect models. If the lower limit of the 95% CI for the PRR was >1, the relationship between the target drug and the specific event was detected as a signal.

The simple PRR in Eq. 1 cannot be applied for signal detection when $n_{ij} = 0$, given that the 95% CI for PRR in Eq. 1 cannot be estimated when $n_{ij} = 0$. However, the proposed method could provide a 95% CI for the PRR estimated using Eq. 4 even when $n_{ij} = 0$.

2.4 Logistic mixed-effect model and ROR

The modeling strategies described in Section 2.3 can be easily applied to logistic regression analysis. We assumed that the random variable n_{ij} follows the binomial distribution $n_{ij} \sim \mathrm{Bin}(n_i, p_{ij})$. As described in Section 2.3., the logistic mixed-effects model can be expressed as follows:

$$\eta_{ij} = \ln\frac{p_{ij}}{1 - p_{ij}} = \beta_0 + b_0 + \left(\beta_i + b_j\right) x_i \quad (5)$$

Using Eq. 5, the linear predictor for each x_i can be calculated as follows:

$$\ln\frac{p_{ij}}{1 - p_{ij}} = \begin{cases} \beta_0 + b_0 + \beta_i + b_j, & x_i = 1 \\ \beta_0 + b_0, & x_i = 0 \end{cases}$$

Thus, the ROR of ADR j for drug i is

TABLE 6 Simulation results in Scenarios 1 and 2 with DDI settings (the number of ADR types = 100).

Scenario	p_{00} (%)	p_{10} (%)	p_{01} (%)	p_{11} (%)	Proposed method		Existing method	
					PRR	ROR	PRR	ROR
Scenario 1: false-positive rate (%)								
1–1	0.05	0.05	0.05	0.05	5.29	5.30	5.29	5.34
	0.1	0.1	0.1	0.1	3.86	3.87	3.96	4.03
	0.25	0.25	0.25	0.25	3.25	3.27	3.37	3.48
1–2	0.025	0.025	0.05	0.05	4.53	4.54	4.52	4.55
	0.05	0.05	0.1	0.1	3.48	3.48	3.59	3.64
	0.1	0.1	0.25	0.25	3.01	3.11	3.12	3.18
1–3	0.01	0.025	0.025	0.0625	3.35	3.35	3.30	3.33
	0.025	0.05	0.05	0.1	3.25	3.26	3.33	3.35
	0.05	0.1	0.1	0.2	3.04	3.06	3.13	3.17
Scenario 2: sensitivity (%)								
2–1	0.025	0.025	0.025	0.05	36.7	36.7	36.5	36.6
	0.05	0.05	0.05	0.1	53.9	53.9	54.1	54.3
	0.1	0.1	0.1	0.2	75.9	76.0	76.1	76.2
2–2	0.01	0.01	0.025	0.05	27.3	27.3	27.2	27.3
	0.025	0.025	0.05	0.1	48.0	48.1	47.7	47.9
	0.05	0.05	0.1	0.2	70.5	70.5	70.9	71.1
2–3	0.01	0.015	0.015	0.045	28.0	28.0	28.0	28.0
	0.02	0.03	0.03	0.09	45.1	45.2	44.9	45.0
	0.04	0.06	0.06	0.18	67.1	67.2	67.4	67.6

ADR, adverse drug reaction; DDIs, drug-drug interactions; PRR, proportional reporting rate; ROR, reporting odds ratio.
Simulation Scenario 1 (absence of DDI): 1–1, $p_{00} = p_{10} = p_{01} = p_{11}$; 1–2, $p_{00} = p_{10} < p_{01} = p_{11}$; 1–3 $p_{00} < p_{10} = p_{01} < p_{11}$.
Simulation Scenario 2 (presence of DDI): 2–1, $p_{00} = p_{10} = p_{01} < p_{11}$; 2–2, $p_{00} = p_{10} < p_{01} < p_{11}$; 2–3, $p_{00} < p_{10} = p_{01} < p_{11}$

$$\mathrm{ROR}_{ij} = \exp\left(\beta_i + b_j\right).$$

Based on Eq. 5, we could simultaneously estimate the RORs of all ADRs (i.e., any j) for drug i.

Using the method described in Section 2.3, Eq. 5 was used to simultaneously evaluate the effects of multiple drugs. For example, consider a DDI in which two drugs are administered simultaneously. The linear predictor in Eq. 5 is expressed as follows:

$$\ln\frac{p_{ii'j}}{1-p_{ii'j}} = \beta_0 + b_0 + \beta_i x_i + \beta_{i'} x_{i'} + \beta_{ii'} x_i x_{i'} + b_{ij} x_i + b_{i'j} x_{i'} + b_{ii'j} x_i x_{i'}$$

Thus, the RORs of ADR j for drugs i and i' and the combined use of drugs i and i' are as follows:

$$\mathrm{ROR}_{ij} = \exp\left(\beta_i + b_{ij}\right), \mathrm{ROR}_{i'j} = \exp\left(\beta_{i'} + b_{i'j}\right), \text{ and } \mathrm{ROR}_{ii'j} = \exp\left(\beta_{ii'} + b_{ii'j}\right).$$

ROR_{ij} is the ROR of ADR j for drug i, $\mathrm{ROR}_{i'j}$ is the ROR of ADR j for drug i', and $\mathrm{ROR}_{ii'j}$ is the ROR of ADR j during the concomitant use of drugs i and i'. If the lower limit of the 95% CI for the PRR was >1, the relationship between the target drug and the specific event was detected as a signal.

If p_{ij} is small, the ROR well-approximated the PRR. Given that p_{ij} is usually small in signal detection analyses, ROR and PRR did not differ significantly in almost all cases.

3 Application

We analyzed the FDA Adverse Event Reporting System (FAERS), a well-known database comprising adverse event reports designed to support the FDA's post-marketing drug safety surveillance program. FAERS includes seven data files: demographics (e.g., sex and age), drugs (e.g., drug name and route of drug administration), reaction (e.g., terms of an adverse event), outcome (patient outcome), report source (code for the source of the report), therapy date (e.g., the date on which the therapy was started and stopped), and indications for use. Adverse events are determined using the Medical Dictionary for Regulatory Activities (MedDRA) as the preferred term.

Recently, sodium glucose-linked transporter 2 (SGLT2) inhibitors, a class of oral antidiabetic drugs, have been widely used to treat type 2 diabetes. The FDA approved canagliflozin as the first SGLT2 inhibitor for treating type 2 diabetes in 2013 (Mosley et al., 2015). Since then, six SGLT2 inhibitors have been approved in the US and Japan. The proposed logistic mixed-effect and Poisson mixed-effect models were applied to the signal detection analysis of these SGLT2 inhibitors for potential ADRs in two scenarios: 1) signal detection for one drug and 2) DDIs following the concomitant use of two drugs, as well as a simulation study.

Data files were downloaded from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) and analyzed between 2014 Q1 and 2022 Q4 after the launch of SGLT2 inhibitors. The analyses included records describing 13,344,838 patient characteristics, 54,869,999 drug properties, and 43,029,283 reactions/events. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). The SAS code is provided in the Supplementary Material.

3.1 Scenario 1 (single drug)

We applied the two proposed models to the FAERS database to screen for ADRs when seven SGLT2 inhibitors (canagliflozin, empagliflozin, ipragliflozin, dapagliflozin, tofogliflozin, luseogliflozin, and ertugliflozin) were used. As a reference, we also applied the traditional ROR and PRR to the database.

A list of ADRs determined as signals using the proposed methods is presented in Supplementary Table S1. The total run time of the analysis was 30 min (2.2 GHz Intel Xeon processor with 64 GB memory). When the lower limit of the 95% CI for the proposed ROR and PRR was greater than 1, the ADR was considered detected. The results of the proposed ROR were similar to those of the proposed PRR owing to the low reporting rate. In addition, the ADRs detected using the proposed methods were similar to those detected using traditional methods. As numerous ADRs were detected (Supplementary Table S1), we summarized the ADRs detected with three or more SGLT2 inhibitors (Table 2). We only presented ROR results because there was no significant difference between PRR and ROR. In addition, owing to space limitation, only ADRs classified as "metabolism and nutrition disorders metabolism" in the system organ class (SOC) of MedDRA or recognized in the package insert of SGLT2 inhibitors are listed in Table 2.

In the current analysis, hypoglycemia, ketoacidosis, and several infarctions, all well-known ADRs of SGLT2 inhibitors, were detected with almost all SGLT2 inhibitors. Euglycemic diabetic ketoacidosis, ketoacidosis, and pyelonephritis were detected with all seven SGLT2 inhibitors. The detection results of the proposed methods were similar to those observed with the traditional ROR and PRR (Supplementary Table S1).

3.2 Scenario 2 (DDI)

Patients with diabetes frequently coadminister SGLT2 inhibitors with glimepiride, a sulfonylurea that stimulates pancreatic β cells to release insulin. Accordingly, the proposed models were applied to assess DDIs between seven SGLT2 inhibitors and glimepiride.

A list of ADRs determined as signals using the proposed methods is presented in Supplementary Table S2. The number of drugs reported is also shown in Supplementary Table S3. The total run time of the analysis was 232 min (2.2 GHz Intel Xeon processor with 64 GB memory). For the proposed PRR and ROR, an ADR was considered to be detected when the lower limits of 95% CI were >1. The results of the proposed ROR were similar to those of the proposed PRR. As observed in Scenario 1, Table 3 presents a list of ADRs detected with two or more types of SGLT2 inhibitors using the proposed methods. Only ROR results are presented, given the absence of any significant difference between the PRR and ROR. Owing to space limitations, only ADRs classified as "metabolism and nutrition disorders metabolism," "cardiac disorders," "nervous system disorders," "renal and urinary disorders," "reproductive system and breast disorders," "infections and infestations," and "surgical and medical procedures" in SOC of MedDRA are listed in Table 3. These SOC classes include ADRs that are likely to occur with the use of SGLT2 inhibitors.

In addition, ketosis-related ADRs were frequently detected following the concomitant use of glimepiride and several SGLT2 inhibitors. Coronary artery stenosis, acute myocardial infarction, cardiac failure, cerebral infarction, renal impairment, and acute pyelonephritis were detected in patients treated with four SGLT2 inhibitors (Table 3).

4 Simulation study

We examined the performance of the proposed method using a simulation study. We calculated the ROR and PRR using the logistic mixed-effect and Poisson mixed-effect models, respectively, as defined in Section 2.

The performance was evaluated in terms of sensitivity and false-positive rates. Sensitivity is the proportion of correctly identified signals, whereas the false-positive rate is the proportion of falsely detected signals. In this section, we considered two simulations: 1) signal detection for one drug and 2) DDI for the concomitant use of two drugs.

4.1 Data generation

Data generation was repeated 1,000 times for each setting. The number of ADR types was set as $J = 100, 500$.

4.1.1 Simulation 1 (single drug)

Signal detection was considered when only one drug was administered. The number of ADRs reported for each drug was set to $n = 10,000,000$. For drug 1 ($i = 1$), the number of prescriptions with drug 1 was set to $n_{1\cdot} = 10,000, 50,000$. In Scenario 1, we investigated the false-positive rate of the proposed method, setting the incidence probabilities of ADR j to $p_{1j} = p_{1^-j} = 0.05, 0.1, 0.2$ (%). Here, p_{1^-j} is the incidence probability of ADR j when drug 1 is not used (see Table 1). In Scenario 2, we examined the sensitivity by setting $(p_{1^-j}, p_{1j}) = (0.05, 0.075), (0.05, 0.1), (0.05, 0.125), (0.1, 0.15), (0.1, 0.2), (0.1, 0.25)$ (%). In both

scenarios, the values of n_{1j} and $n_j - n_{1j}$ were independently generated by the binomial distributions Bin($n_{1\cdot}$, p_{1j}) and Bin($n - n_{1\cdot}$, p_{1^-j}), respectively.

4.1.2 Simulation 2 (DDI)

We evaluated DDIs with the concomitant use of drugs 1 (D_1) and 2 (D_2) by assuming the number of prescriptions in the absence of both drugs, the presence of either D_1 or D_2, and the presence of both drugs to be 10,000,000, 100,000, and 10,000, respectively (Table 4). The incidence probabilities in Table 4 vary depending on the simulation scenario. In Scenario 1, we determined the false-positive rate of the proposed method. In this case, no DDIs were observed. We then set (1–1) $p_{00} = p_{10} = p_{01} = p_{11}$; (1–2) $p_{00} = p_{10} < p_{01} = p_{11}$; and (1–3) $p_{00} < p_{10} = p_{01} < p_{11}$ (Figure 1). An additional effect was observed between drugs 1 and 2 in (1–2) and (1–3), although no interaction was observed under the multiplicative assumption because $p_{00}p_{11}/(p_{10}p_{01}) = 1$. In Scenario 2, we investigated the sensitivity and detected a positive DDI because $p_{00}p_{11}/(p_{10}p_{01}) > 1$. Under this assumption, we set (2–1) $p_{00} = p_{10} = p_{01} < p_{11}$, (2–2) $p_{00} = p_{10} < p_{01} < p_{11}$, and (2–3) $p_{00} < p_{10} = p_{01} < p_{11}$ (Figure 1). The details of these settings are shown in Figure 1 and described in the Results section. In both scenarios, the values of n_{00}, n_{10}, n_{01}, and n_{11} were independently generated using binomial distributions. As a competitor (henceforth, the existing method), we calculated the PRR and ROR using simple Poisson and logistic models, including two factors D_1 and D_2, and the interaction term for each ADR, respectively (van Puijenbroek et al., 1999).

4.2 Results

4.2.1 Simulation 1 (single drug)

Table 5 presents the false-positive rate in Scenario 1 and the sensitivity in Scenario 2 when the traditional and proposed PRR and ROR are applied under $J = 100$. The simulation results under $J = 500$ are presented in Supplementary Table S4. At the top of Table 5, the false-positive rates of the proposed PRR and ROR were similar to those of the traditional PRR and ROR across all simulation settings. Additionally, false-positive rates of the PRR and ROR differed minimally. The false-positive rate for the proposed method was not dependent on the incidence probability or the number of ADR types. As shown in Table 5 (bottom), the sensitivities of the proposed PRR and ROR were similar to those of the traditional PRR and ROR for all simulation settings. Furthermore, the false-positive rate of PRR and ROR differed minimally.

4.2.2 Simulation 2 (DDI)

Table 6 presents the false-positive rate in Scenario 1 and the sensitivity in Scenario 2 when the proposed PRR and ROR were applied under $J = 100$. The simulation results under $J = 500$ are presented in Supplementary Table S5. At the top of Table 6, the false-positive rate for DDIs using the proposed PRR and ROR was generally controlled at a nominal significance level of 5%. The false-positive rates of the proposed PRR and ROR were similar to those of the PRR and ROR derived using existing methods across all simulation settings. In addition, the false-positive rates of the PRR and ROR differed minimally. The false-positive rate for the proposed method was not dependent on the incidence probability or the number of ADR types. As shown in Table 6 (bottom), there was minimal difference in the sensitivity between PRR and ROR as a false-positive rate. The sensitivities of the proposed PRR and ROR were also similar to those of the PRR and ROR from the existing method across all simulation settings. Although the sensitivity of PRR and ROR increased as the incidence probability increased, the sensitivity was not dependent on the number of ADR types.

5 Discussion

Herein, we proposed a new signal detection method within the framework of a generalized mixed-effect model. The proposed models can directly estimate the PRR and ROR, which are used worldwide to detect signals in spontaneous reporting systems. In terms of the advantages, the proposed method can allow the simultaneous evaluation of several ADRs using multiple drugs. The proposed method is suitable for signal detection because ADRs should be comprehensively and efficiently screened in post-marketing drug safety surveillance. Our study also found that the PRR and ROR calculated using the proposed model were almost identical to the traditional PRR and ROR. While the traditional PRR and ROR can only be calculated in the presence of one drug, the proposed method can be applied to multiple drugs and is a more generalized and convenient method.

For screening ADRs in spontaneous reporting systems, the Medicines and Healthcare Products Regulatory Agency adopts the traditional PRR, and the Netherlands Pharmacovigilance Center and the Pharmaceutical and Medical Devices Agency in Japan employ the traditional ROR (Noguchi et al., 2021). The proposed method also provides the PRR and ORR, and it can be interpreted similarly to the results of traditional methods routinely used by the regulatory authorities. Although the criterion established by Norén et al. (Norén et al., 2008) would be the most widely used for detecting DDIs, the method proposed in the current study is more convenient for practical applications, given that ADRs from "single use of a drug" and "concomitant use of drugs" can be uniformly evaluated using one methodology. Thus, we anticipate that the proposed method will become one of the most useful applications in drug safety surveillance in the future.

However, some ingenuity is required to construct a generalized mixed-effects model. For example, the model may lead to convergence problems in numerical optimization when many drugs are included in the model as factors. Specifically, we cannot obtain PRR and ROR estimates when the constructed model is markedly complicated. In this case, the model is simplified. In addition, the calculation to obtain parameter estimates may be prolonged in the presence of numerous ADRs and drug types.

Several limitations need to be cautiously considered when undertaking signal detection analyses. For example, only observed ADRs are registered in spontaneous reporting systems databases, resulting in underreporting bias (Noguchi et al., 2021). Furthermore, the incidence rate for ADRs cannot

be calculated because databases collect only patient information with the ADR (Tada and Gosho, 2022). Moreover, even if the patients are actually taking multiple drugs, some drug information might be missing. Therefore, the measures for detecting DDI tend to be underestimated (Norén et al., 2008). These limitations are inherent to databases and cannot be overcome even when using the proposed method. Although signal detection analysis fails to establish definite conclusions regarding the association between ADRs and target drugs due to the limitations, the analysis results generate hypotheses about the association.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Publicly available datasets were analyzed in this study. This data can be found here: The following publicly available datasets were used in this study: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

MG: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Project administration, Software, Supervision, Visualization, Writing–original draft, Writing–review and editing. RI: Writing–review and editing, Methodology. TO: Writing–review and editing. KM: Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by JSPS KAKENHI (Grant number: 22K19682).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1312803/full#supplementary-material

References

Ahmed, I., Thiessard, F., Miremont-Salamé, G., Bégaud, B., and Tubert-Bitter, P. (2010). Pharmacovigilance data mining with methods based on false discovery rates: a comparative simulation study. *Clin. Pharmacol. Ther.* 88, 492–498. doi:10.1038/clpt.2010.111

Almenoff, J. S., LaCroix, K. K., Yuen, N. A., Fram, D., and DuMouchel, W. (2006). Comparative performance of two quantitative safety signalling methods: implications for use in a pharmacovigilance department. *Drug Saf.* 29, 875–887. doi:10.2165/00002018-200629100-00005

Bate, A., Lindquist, M., Edwards, I. R., Olsson, S., Orre, R., Lansner, A., et al. (1998). A Bayesian neural network method for adverse drug reaction signal generation. *Eur. J. Clin. Pharmacol.* 54, 315–321. doi:10.1007/s002280050466

Bunchuailua, W., Zuckerman, I. H., Kulsomboon, V., Suwankesawong, W., Singhasivanon, P., and Kaewkungwal, J. (2010). Detection of adverse drug reaction signals in the Thai FDA database: comparison between reporting odds ratio and Bayesian confidence propagation neural network methods. *Drug Inf. J.* 44, 393–403. doi:10.1177/009286151004400404

Chen, M., Zhu, L., Chiruvolu, P., and Jiang, Q. (2015). Evaluation of statistical methods for safety signal detection: a simulation study. *Pharm. Stat.* 14, 11–19. doi:10.1002/pst.1652

DuMouchel, W. (1999). Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am. Stat.* 53, 177–190. doi:10.1080/00031305.1999.10474456

Evans, S. J. W., Waller, P. C., and Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol. Drug Saf.* 10, 483–486. doi:10.1002/pds.677

Gosho, M., Maruo, K., Tada, K., and Hirakawa, A. (2017). Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems. *Eur. J. Clin. Pharmacol.* 73, 779–786. doi:10.1007/s00228-017-2233-3

Hochberg, A. M., Hauben, M., Pearson, R. K., O'Hara, D. J., Reisinger, S. J., Goldsmith, D. I., et al. (2009). An evaluation of three signal-detection algorithms using a highly inclusive reference event database. *Drug Saf.* 32, 509–525. doi:10.2165/00002018-200932060-00007

Kubota, K., Koide, D., and Hirai, T. (2004). Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiol. Drug Saf.* 13, 387–394. doi:10.1002/pds.964

Matsushita, Y., Kuroda, Y., Niwa, S., Sonehara, S., Hamada, C., and Yoshimura, I. (2007). Criteria revision and performance comparison of three methods of signal detection applied to the spontaneous reporting database of a pharmaceutical manufacturer. *Drug Saf.* 30, 715–726. doi:10.2165/00002018-200730080-00008

Mosley, J. F., Smith, L. S., Everton, E., and Fellner, C. (2015). Sodium-glucose linked transporter 2 (SGLT2) inhibitors in the management of type-2 diabetes: a drug class overview. *P T* 40, 451–462.

Noguchi, Y., Tachi, T., and Teramachi, H. (2019). Review of statistical methodologies for detecting drug–drug interactions using spontaneous reporting systems. *Front. Pharmacol.* 10, 1319. doi:10.3389/fphar.2019.01319

Noguchi, Y., Tachi, T., and Teramachi, H. (2020). Comparison of signal detection algorithms based on frequency statistical model for drug-drug interaction using spontaneous reporting systems. *Pharm. Res.* 37, 86. doi:10.1007/s11095-020-02801-3

Noguchi, Y., Tachi, T., and Teramachi, H. (2021). Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief. Bioinform.* 22, bbab347. doi:10.1093/bib/bbab347

Norén, G. N., Sundberg, R., Bate, A., and Edwards, I. R. (2008). A statistical methodology for drug–drug interaction surveillance. *Stat. Med.* 27, 3057–3070. doi:10.1002/sim.3247

Rothman, K. J., Lanes, S., and Sacks, S. T. (2004). The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol. Drug Saf.* 13, 519–523. doi:10.1002/pds.1001

Stroup, W. W. (2013). *Generalized linear mixed models*. Boca Raton, FL: CRC Press.

Tada, K., and Gosho, M. (2022). Increased risk of urinary tract infection and pyelonephritis under concomitant use of sodium-dependent glucose cotransporter 2 inhibitors with antidiabetic, antidyslipidemic, and antihypertensive drugs: an observational study. *Fundam. Clin. Pharmacol.* 36, 1106–1114. doi:10.1111/fcp.12792

Thakrar, B. T., Grundschober, S. B., and Doessegger, L. (2007). Detecting signals of drug-drug interactions in a spontaneous reports database. *Br. J. Clin. Pharmacol.* 64, 489–495. doi:10.1111/j.1365-2125.2007.02900.x

van Puijenbroek, E. P., Bate, A., Leufkens, H. G., Lindquist, M., Orre, R., and Egberts, A. C. (2002). A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol. Drug Saf.* 11, 3–10. doi:10.1002/pds.668

van Puijenbroek, E. P., Egberts, A. C., Heerdink, E. R., and Leufkens, H. G. (2000). Detecting drug-drug interactions using a database for spontaneous adverse drug reactions: an example with diuretics and non-steroidal anti-inflammatory drugs. *Eur. J. Clin. Pharmacol.* 56, 733–738. doi:10.1007/s002280000215

van Puijenbroek, E. P., Egberts, A. C., Meyboom, R. H., and Leufkens, H. G. (1999). Signalling possible drug-drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. *Br. J. Clin. Pharmacol.* 47, 689–693. doi:10.1046/j.1365-2125.1999.00957.x

Wolfinger, R., and O'Connell, M. (1993). Generalized linear mixed models a pseudo-likelihood approach. *J. Stat. Comput. Simul.* 48, 233–243. doi:10.1080/00949659308811554

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 January 2024
DOI 10.3389/fphar.2024.1288362

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Pedro Dorado,
University of Extremadura, Spain
Linan Zeng,
Sichuan University, China

*CORRESPONDENCE
Zeming Mo,
smollstar@126.com
Weiliang Zhu,
duarion@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 04 September 2023
ACCEPTED 08 January 2024
PUBLISHED 24 January 2024

CITATION
Bao Y, Chen J, Duan L, Wang F, Lai H, Mo Z and Zhu W (2024), Comparing the difference of adverse events with HER2 inhibitors: a study of the FDA adverse event reporting system (FAERS).
Front. Pharmacol. 15:1288362.
doi: 10.3389/fphar.2024.1288362

Comparing the difference of adverse events with HER2 inhibitors: a study of the FDA adverse event reporting system (FAERS)

Yiwen Bao[1,2†], Jiaju Chen[3†], Luting Duan[4†], Fujue Wang[5], Han Lai[1], Zeming Mo[1,6*] and Weiliang Zhu[2*]

[1]Department of Oncology, The People's Hospital of Qiannan, Duyun, Guizhou, China, [2]Department of Oncology, Zhujiang Hospital, Southern Medical University, Guangzhou, China, [3]Gastrointestinal Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China, [4]Department of Cardiovascular Medicine, The People's Hospital of Qiannan, Duyun, Guizhou, China, [5]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, China, [6]Division of Head and Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Aim and background: This study attempted to identify similarities and differences in adverse events (AEs) between human epidermal growth factor receptor 2 (HER2) inhibitors, especially those related to hemorrhagic events and nervous system disorders.

Methods: This study summarized the types, frequencies, and system organ classes (SOCs) of AEs of HER2 inhibitors. The US Food and Drug Administration Adverse Event Reporting System (FAERS) data from January 2004 through March 2022 was collected and analyzed. Disproportionality analyses were conducted to detect AEs signals for every HER2 inhibitor. The chi-square test, Wilcoxon test, and descriptive analysis were used to compare the differences of AEs for specific SOCs or drugs.

Results: A total of 47,899 AE reports were obtained for eight HER2 inhibitors. Trastuzumab-related AEs were reported in the highest number and combination of regimens. In monotherapy, trastuzumab had the highest reported rate of cardiac disorders-related AEs (24.0%). However, small-molecule drugs exceeded other drugs in the reported rates of AEs related to gastrointestinal disorders, metabolism and nutrition disorders. The highest reported rates of respiratory disorders (47.3%) and hematologic disorders (22.4%) were associated with treatment with trastuzumab deruxtecan (T-DXd). Patients treated with trastuzumab emtansine (TDM-1) had the highest reported rate (7.28%) of hemorrhagic events, especially intracranial haemorrhage events. In addition, patients treated with TDM-1 with concomitant thrombocytopenia were likely to experience hemorrhagic events compared to other HER2 inhibitors ($p < 0.001$). The median time to onset of intracranial haemorrhage associated with trastuzumab (0.5 months) and TDM-1 (0.75 months) was short. However, there

Abbreviations: BC, Breast Cancer; HER2, Human Epidermal Growth Factor Receptor 2; ADC, Anti-body Drug Conjugates; AEs, Adverse Events; FAERS, The US Food and Drug Administration Adverse Event Reporting System; PRR, Proportional Reporting Ratio; PTs, Preferred terms; SOCs, System Organ Classes; TDM-1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan.

was no significant difference in median time to onset intracranial haemorrhage between patients in different age groups or with different outcomes. *Disproportionality analysis* results reveal that cerebral haemorrhage is a positive signal associated with T-DXd and TDM-1. In addition, tucatinib was the drug with the highest rate of reported nervous system disorders (31.38%). Memory impairment (83 cases) is a positive signal for tucatinib.

Conclusion: The types and reporting rates of AEs associated with different HER2 inhibitors vary across multiple systems. In addition, hemorrhagic events concomitant with TDM-1 treatment and nervous system disorders concomitant with tucatinib treatment may be worthy of attention.

KEYWORDS

HER2 inhibitors, FAERS database, adverse drug events, hemorrhagic events, nervous system disorders, TDM-1, Tucatinib

1 Introduction

HER2 is a vital driving gene for many malignant tumors, such as breast cancer (BC), gastric cancer, and ovarian cancer. Overexpression and amplification of HER2 are closely related to the rapid progress of tumors (Cianfrocc et al., 2004; Rakhshani et al., 2014; Berchuck et al., 1990). Considering the incidence and prevalence of these tumors worldwide, how to effectively control the invasion and metastasis of HER2-positive (HER2+) tumors has become an important issue. Due to the reliability of HER2 as a target antigen, the types of HER2 inhibitors are diversifying. Currently, there are three main types of HER2 inhibitors used in clinical practice: small-molecule drugs (lapatinib, neratinib, tucatinib, and pyrotinib), monoclonal antibodies (trastuzumab, pertuzumab), and antibody-conjugated drugs (ADCs): TDM-1, T-DXd, et al. (Schlam and Swain, 2021; Singh et al., 2022; Banys-Paluchowski et al., 2023). For example, many guidelines recommend the combination of trastuzumab, pertuzumab, and taxane as the standard first-line treatment for patients with advanced HER2+ BC (Swain et al., 2020). In addition, T-DXd has been successively approved for second-line treatment of BC and gastric carcinoma and also approved for treatment of metastatic BC with low HER2 expression (Grieb and Agarwal, 2021; Singh et al., 2022). In addition, the number of cancer types for which HER2 inhibitors are used is still increasing (Oh and Bang, 2020). Moreover, as the reliability of HER2 inhibitor efficacy has been validated, many oncology patients have received different HER2 inhibitors in concomitant combinations or phases (Giordano et al., 2022).

Many studies have suggested that HER2 inhibitors related to adverse events (AEs) significantly reduce patients' quality of life, lead to treatment interruption, and ultimately impair the efficacy of inhibitors and the survival period of patients (Hedhli and Russell, 2011; Zambelli et al., 2011). However, there are still relatively few reports on the lateral comparison of AEs in all SOCs. Therefore, we were curious if the AEs in patients treated with only one HER2 inhibitor differed from those who received multiple HER2 inhibitors. Furthermore, are there significant differences in AEs associated with different types of HER2 inhibitors? For example, some studies have found severe hemorrhagic events with treatment with TDM-1 (Thuss-Patience et al., 2017; Delgado et al., 2021; Wuerstlein et al., 2022). The issue of potential hemorrhagic events with the use of other HER2 inhibitors is then equally worth evaluating. Meanwhile, because the permeability of the blood-brain barrier between small-molecule drugs and ADCs is significantly different, the differences in these drug-induced nervous system disorders remain unknown (Stemmler et al., 2007; Guntner et al., 2020). FAERS database can provide a full range of reported events related to AEs of different drugs in real-world evidence from worldwide (Mo et al., 2023). Therefore, this study is based on the FAERS database to assess the differences in multiple SOC-related AEs suspected to be associated with one HER2 inhibitor or multiple HER2 inhibitors, especially those related to hemorrhagic events and nervous system disorders. Subsequently, the reported rates of AEs for preferred terms (PTs) and affiliated SOCs associated with monotherapy and combination therapy were itemized.

2 Materials and methods

2.1 Data collection and extraction

Data for the retrospective pharmacovigilance study were obtained from the FAERS database. FAERS database is a recognized source for timely, real-world safety assessments of drugs and therapeutic biological products (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). FAERS database was searched (1 January 2004–31 March 2022) for AEs data of FDA-approved HER2 inhibitors (lapatinib, neratinib, tucatinib, pyrotinib, trastuzumab, pertuzumab, TDM-1, T-DXd across all indications). Trade names and generic names of drugs in the National Center for Biotechnology Information (NCBI) were used as the search terms for HER2 inhibitors. Since Product Active ingredients (PROD_AI) were added to drug/biologic information (DRUG) of FAERS data files after 2014, PROD_AI of drugs was also added as search terms. Then, the relatively comprehensive results were obtained.

2.2 Data cleaning procedures

We only selected reported events for HER2 inhibitors judged to be primary suspect (PS) and second suspect (SS) in "ROLE_COD". As recommended by the FDA, we removed duplicate

records prior to statistical analysis by selecting the most recent FDA_DT when the CASEID was the same and the higher PRIMARYID when the CASEID and FDA_DT were the same. Specific reports indicated as erroneous on the FDA website were removed as recommended. The preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) was used to standardize the AEs data, and SOC was utilized to classify AEs into various systems. The data cleaning process relied on SAS statistical soft-ware (version 9.4; SAS Institute, Cary, NC, United States). Cases with only a single HER2 inhibitor in the DRUGNAME list were categorized as monotherapy. Cases with two or more HER2 inhibitors in the DRUGNAME list were categorized as combination therapy. Finally, all cases that contained the same PRIMARYID for the combination therapy were finally de-weighted again.

2.3 Statistical analysis

2.3.1 Disproportionality analysis.

Disproportionality analysis is a data mining method now widely used in monitoring adverse drug reactions (Chuma et al., 2022; Raschi et al., 2022). The Proportional Reporting Ratio (PRR) method, and Bayesian Confidence Propagation Neural Network method were utilized to detect safety signals for the drugs under study. We calculated PRR, information components (IC) and the corresponding 95% confidence intervals lower limit by using a 2 × 2 contingency table to detect potential associations between HER2 inhibitors and AEs. The AEs was considered significantly associated with the targeted drug relative to other drugs when the number of cases of AEs was greater than 3, PRR ≥ 2, and the lower limit of the 95% CI of PRR values exceeded 1.0.

2.3.2 Descriptive analysis

The adverse event reporting rate was set as the total number of specific AEs as a percentage of the total number of cases for the targeted HER2 inhibitor. Hemorrhagic events include AEs related to haemorrhage and hemorrhagic in the pt_name list. The time of onset of an intracranial hemorrhagic event was recognized to be the time of the event minus the time of initial treatment with the drug.

The chi-square test was performed based on the R package ggstatsplot (version 0.12.1; Indrajeet Patil) (Patil, 2021); The Wilcoxon test and the Kruskal Wallis test were performed based on the R package ggpubr (version 0.6.0; Alboukadel Kassambara [aut, cre]) (Kassambara, 2023).

2.3.3 Data visualization

ggplot2 (version 3.4.1; Hadley Wickham) (Wickham, 2016), ggVennDiagram (version 1.4.9; Chun-Hui Gao) (ggVennDiagram, 2023), ggalluvial (version 0.12.5; Hadley Wickham) (Brunson, 2020), ComplexHeatmap (version 2.16.0; Zuguang Gu) (Gu et al., 2016), and UpSetR (version 1.4.0, Jake Conway, Nils Gehlenborg) (Conway et al., 2017) were employed for visualization. Data visualizations were processed by the software Rstudio (version 2023.03.0; Build 353 © 2009–2022 Posit Software PBC) in the R environment (version 4.3.2). $p < 0.05$ was statistically significant, and the *p*-value was bilateral.

3 Results

3.1 Basic clinical characteristics of patients treated with HER2 inhibitors

What are the clinical characteristics of patients treated with HER2 inhibitors in reports derived from the FAERS database? After extracting and cleaning the FAERS raw data, all subtypes of the final eight HER2 inhibitors were identified for monotherapy and combination therapy (Figure 1A). Among monotherapy, trastuzumab (19,894 cases), lapatinib (7,135 cases), TDM-1 (2,283 cases), and pertuzumab (1,006 cases) had the top 4 highest number of reported cases. Trastuzumab plus pertuzumab (10,214 cases), trastuzumab plus lapatinib (1,748 cases), trastuzumab plus pertuzumab plus TDM-1 (1,131 cases), and trastuzumab plus TDM-1 (819 cases) are the first four common HER2 inhibitor combination strategies. In addition, we found that some patients received a combination strategy of three, four, or even five HER2 inhibitors. Figure 1A also shows the total number of reported HER2 inhibitor-related AEs in different countries worldwide. The United States (9,281 cases), United Kingdom (3,190 cases), Japan (2,687 cases), and China (2,629 cases) were the top 4 countries in terms of the number of AEs. In addition, the number of reported cases of pertuzumab in combination therapy was significantly higher (12,115 cases) than in monotherapy (1,006 cases) (Figure 1B).

In monotherapy, trastuzumab had the highest reported rate of cardiac disorders-related AEs (24.0%) (Figure 1C). However, small molecule agents exceeded monoclonal antibodies and ADCs in the reported rates related to gastrointestinal disorders, metabolism and nutrition disorders, and skin and subcutaneous tissue disorders. The reported rate of gastrointestinal disorders was more pronounced in patients who had received neratinib. The highest reported rates of respiratory disorders (47.3%) and hematologic disorders (22.4%) were associated with treatment with T-DXd. Patients treated with TDM-1 had the highest reported rate (7.28%) of hepatobiliary disorders. These results suggest differences in the presence of potential AEs for each HER2 inhibitor. In addition, combination therapy had a higher reported rate of AEs involving blood and lymphatic system disorders, infections and infestations, investigations, neoplasms benign, malignant and unspecified, and nervous system disorders than monotherapy.

3.2 Distribution statistics of adverse events based on PTs and SOCs classification in monotherapy

The frequency and type of PTs that were primarily suspected and secondarily suspected of being associated with monotherapy were counted (Figure 2A). Diarrhea was the most frequently reported PTs for tucatinib, neratinib, lapatinib, and pertuzumab. Besides, fatigue, nausea, and vomiting were also common AEs in all HER2 inhibitor users. In addition, dehydration is a common PTs for small-molecule drugs. However, ejection fraction decreased (8.78%) and cardiac failure (7.68%) were the top 10 reported PTs for trastuzumab application, which was not found for other drugs.

10.3389/fphar.2024.1288362

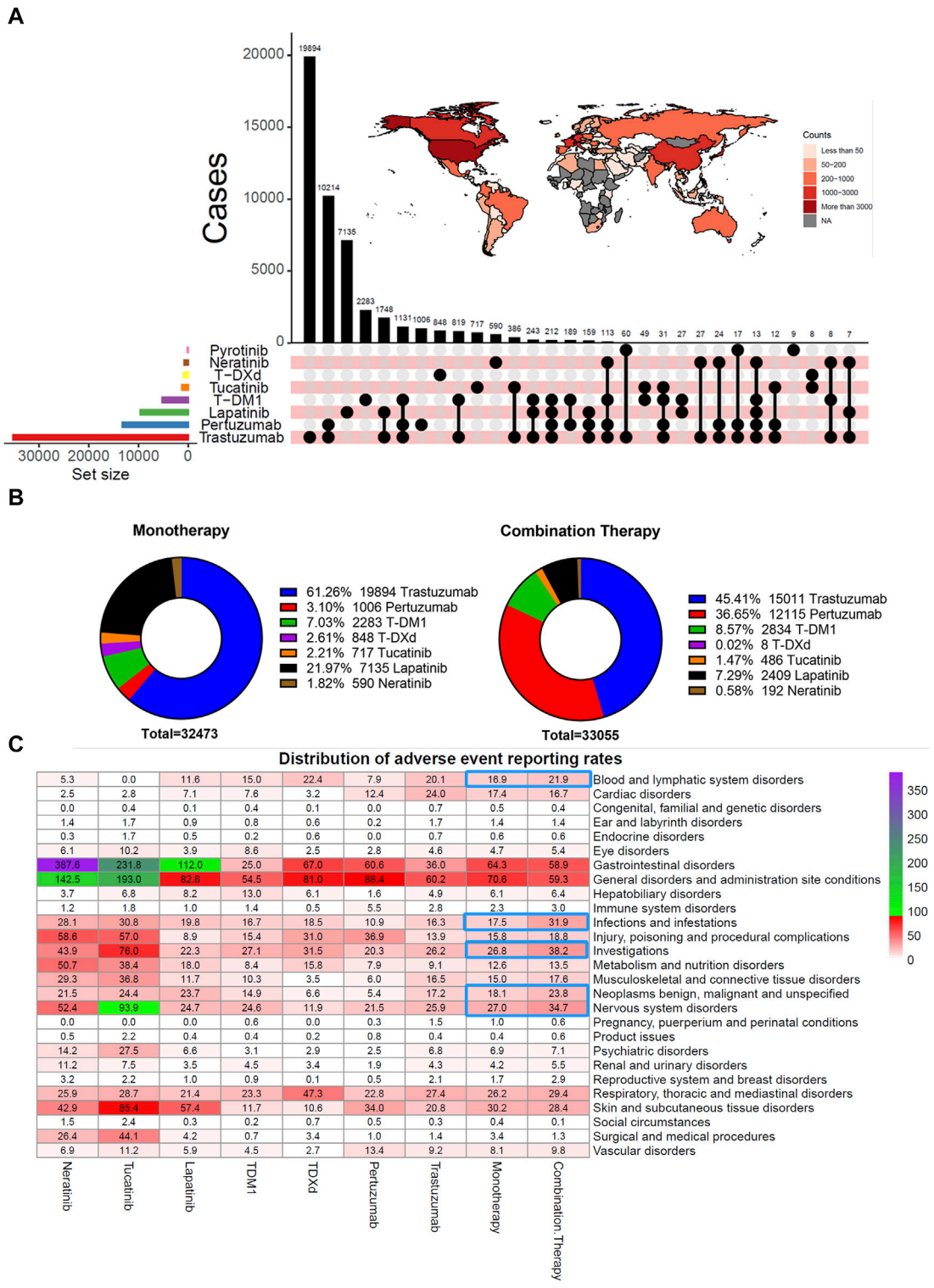


FIGURE 1
Clinical characteristics of patients treated with HER2 inhibitors and distribution of adverse event reporting rates. **(A)** Visualization of overlapping relationships between users of different HER2 inhibitors and the total number of all HER2 inhibitors reported in different countries was based on the R packages UpSetR and ggplot2. **(B)** Number and percentage of cases of each HER2 inhibitor in monotherapy and combination therapy. Considering that the total number of pyrotinib was too small, they were excluded from monotherapy and combination therapy statistics. **(C)** Heat map displays the distribution of adverse event reporting rates for seven HER2 inhibitors.

10.3389/fphar.2024.1288362

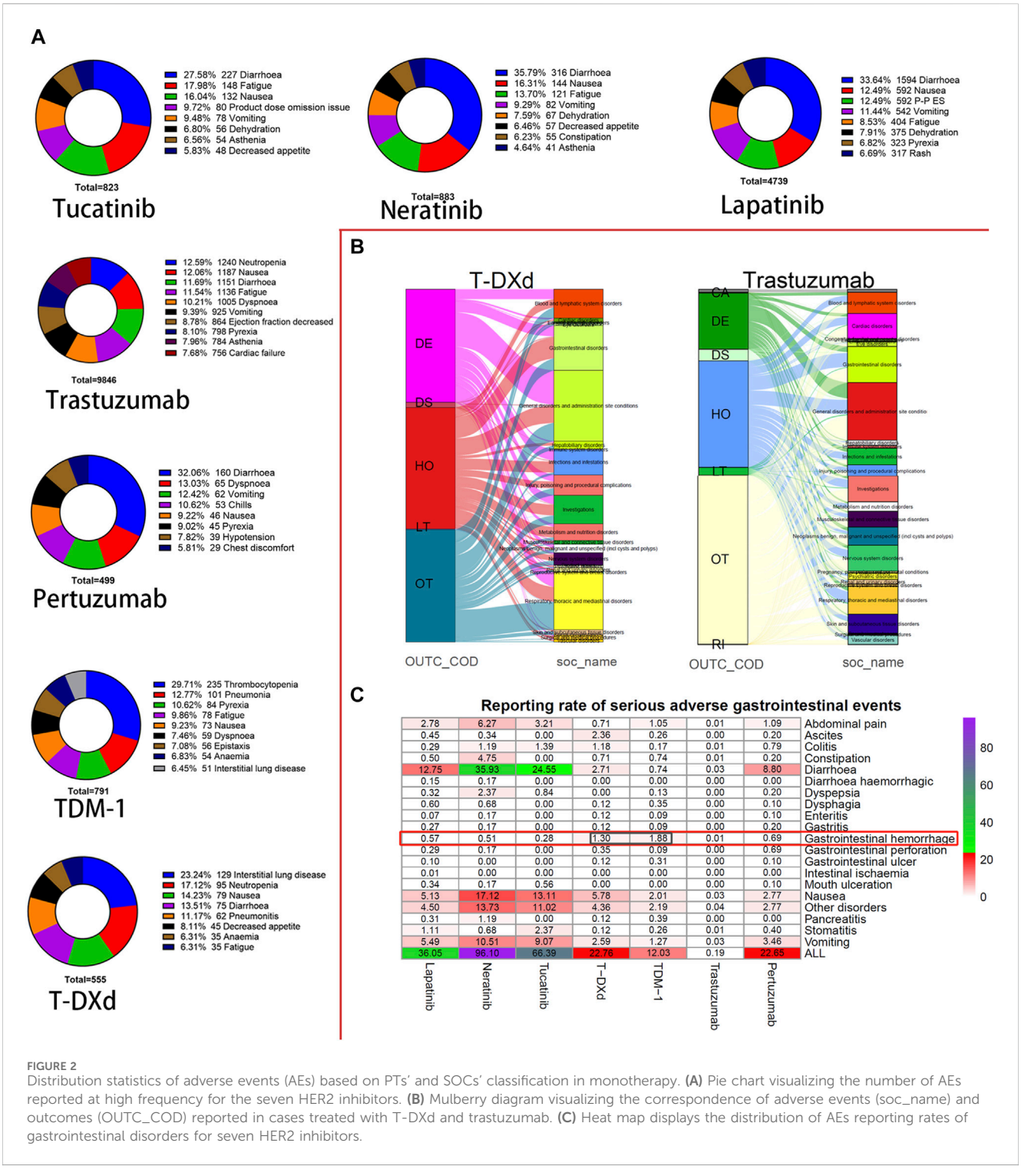


FIGURE 2
Distribution statistics of adverse events (AEs) based on PTs' and SOCs' classification in monotherapy. **(A)** Pie chart visualizing the number of AEs reported at high frequency for the seven HER2 inhibitors. **(B)** Mulberry diagram visualizing the correspondence of adverse events (soc_name) and outcomes (OUTC_COD) reported in cases treated with T-DXd and trastuzumab. **(C)** Heat map displays the distribution of AEs reporting rates of gastrointestinal disorders for seven HER2 inhibitors.

Another concern is thrombocytopenia (235 cases), the most frequently reported AEs in TDM-1 applicants. Pneumonia (101 cases) occurrence is a close second. Pulmonary and hematologic toxicity remains a significant concern for TDM-1 applications.

Subsequently, the inter-correlation between the outcomes of AEs and SOCs of HER2 inhibitor monotherapy was visualized (Figure 2B, Supplementary Figure S1). We found that gastrointestinal disorders accounted for a relatively high proportion of specific adverse severe outcomes (death, life-threatening, and hospitalization—initial or prolonged) for all HER2 inhibitors. The distribution of gastrointestinal disorders among patients with specific serious adverse outcomes was further analyzed, and the reporting rate of AEs was counted. Diarrhea, nausea, vomiting, and abdominal pain were the higher reported PTs, with neratinib- and tucatinib-related ones being more

10.3389/fphar.2024.1288362

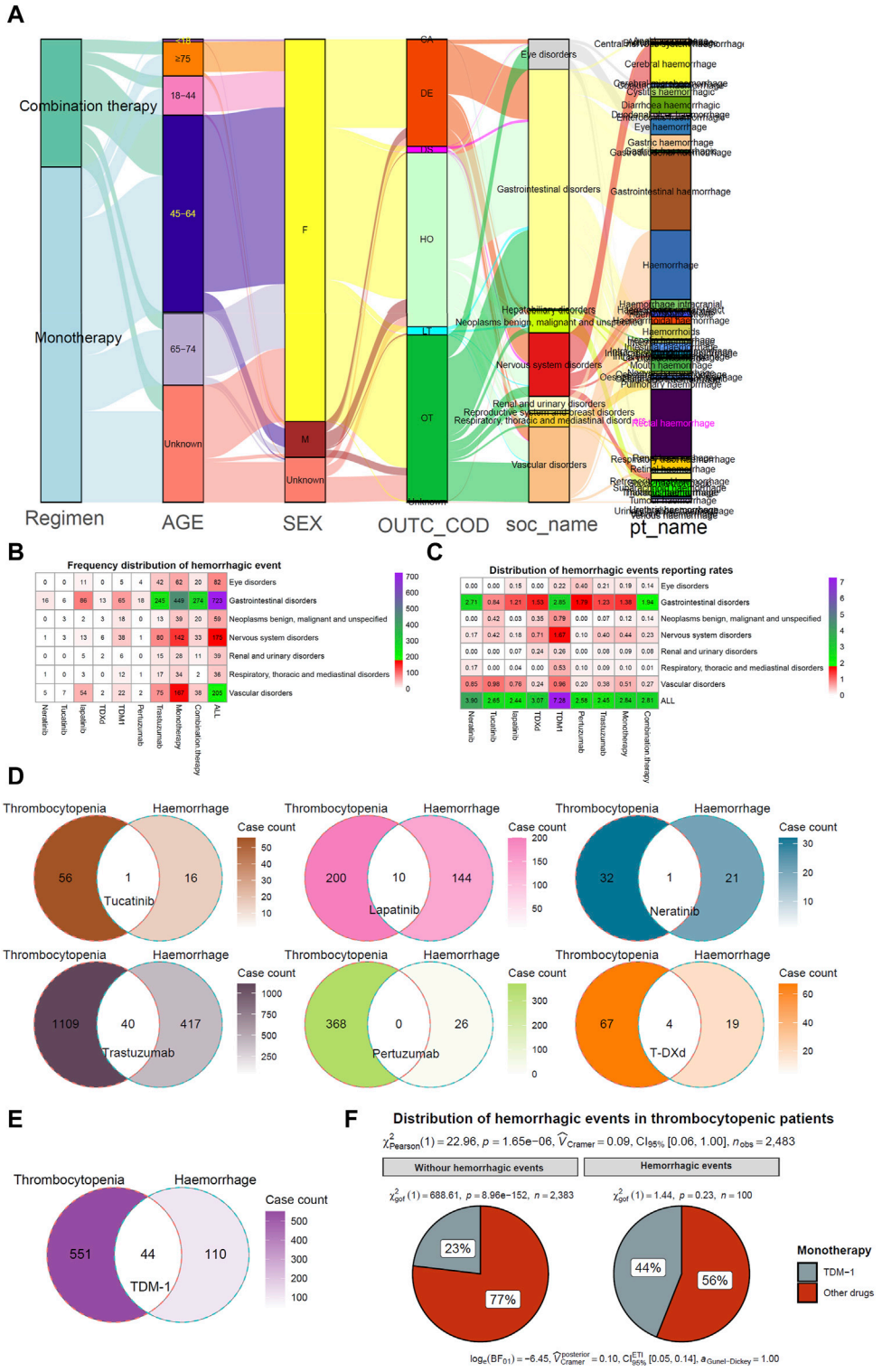


FIGURE 3
Hemorrhagic events and thrombocytopenia with HER2 inhibitors. **(A)** Mulberry map of clinical characteristics of patients with hemorrhagic events. Data were collected from regimen, age, sex, outcome (OUTC_COD), SOC types (soc_name), and preferred terms types (pt_name). Unknown indicates those not explicitly stated in the factor. **(B, C)** Heat map visualization of frequency distribution and reporting rates distribution of hemorrhagic events. **(D, E)** Wayne Map visualizes the overlapping relationship between haemorrhage and thrombocytopenia in patients receiving HER2 inhibitor therapy. **(F)** Chi-Square Test compares differences in Hemorrhagic events between TDM-1 and other HER2 inhibitors in patients reporting the presence of thrombocytopenia.

pronounced (Figure 2C). At the same time, trastuzumab had a very low reporting rate for almost all PTs. However, the reported rates of T-DXd (1.30%) or TDM-1 (1.88%) associated gastrointestinal haemorrhage were greater than 1%, significantly exceeding that of other HER2 inhibitors. Therefore, we pondered whether there was a pharmacologic predisposition to the occurrence of hemorrhagic events.

3.3 Hemorrhagic events with HER2 inhibitors

They were considering that hemorrhagic events, especially haemorrhage of vital organs, are severe or even lethal AEs. Hemorrhagic events associated with different HER2 inhibitors were further explored. The statistics on the percentage of the number of reported cases found the highest percentage of patients in the 45–64 age range (544 cases, 43%), followed by the 65–74 age range (198 cases, 16%) and the 18–44 age range (108 cases, 8.5%) (Figure 3A; Table 1). The overall percentage of patients who experienced a hemorrhagic event that resulted in death was 23% (294 cases). The top three frequencies of hemorrhagic events originating from gastrointestinal disorders (661 cases, 52%), vascular disorders (208 cases, 16%), and nervous system disorders (175 cases, 14%) (Figure 3B). Specifically, gastrointestinal haemorrhage (214 cases, 17%), rectal haemorrhage (186 cases, 15%), and cerebral haemorrhage (107 cases, 8.4%) occurred with relatively high frequency. In addition, TDM-1 (7.28%) had the highest total adverse event reporting rate of any drug (Figure 3C). However, the reported rate of hemorrhagic events in the combination therapy group (2.81%) was close to that of monotherapy (2.84%).

Previous studies have suggested that thrombocytopenia induced by antineoplastic therapy may be a risk factor for hemorrhagic events (Elting et al., 2001; Chari et al., 2019). Thus, the overlapping relationship between patients with thrombocytopenia and those with bleeding events was counted. Figure 3D demonstrates that none of the six HER2 inhibitor monotherapy users had more than 10% of concurrent thrombocytopenia and bleeding events. However, 40% (44/110) of TDM-1 applicants who experienced hemorrhagic events had coexisting thrombocytopenia (Figure 3E). Thus, TDM-1 had a significantly higher rate of thrombocytopenia with coexisting bleeding events compared to other drugs ($p < 0.001$) (Figure 3F).

3.4 Evaluation of intracranial haemorrhage events

Intracranial haemorrhage is a severe and lethal adverse event. Evaluation of the interval between the initiation of HER2 inhibitors and the occurrence of intracranial haemorrhage is warranted. Among them, the median time to onset of intracranial haemorrhage was significantly higher for lapatinib than for trastuzumab, TDM-1, or T-DXd ($p < 0.05$) (Figure 4A). In addition, the median time to onset intracranial haemorrhage was significantly higher for combination therapy than for monotherapy (20.0 months VS. 1.5 months, $p < 0.001$) (Figure 4C). However, there was no significant difference in median time to onset intracranial haemorrhage between patients in different age groups or with different outcomes (Figures 4B, D). In addition, the distribution of thrombocytopenia in patients who developed intracranial haemorrhage was counted. The results again suggested that TDM-1 applicants who suffered intracranial haemorrhage were more likely to have thrombocytopenia complications (Figure 4E). It may be necessary to analyze further whether patients treated with TDM-1 are more likely to report nervous system disorders than other HER2 inhibitors.

3.5 AEs involving nervous system disorders

Evaluating AEs involving nervous system disorders originating from HER2 inhibitors is becoming increasingly important as more and more drugs that enhance the control of intracranial lesions are developed. Of these, the highest percentage of patients treated with tucatinib (31.38%) developed nervous system disorders, and the lowest was with T-DXd (7.31%), and the percentage of TDM-1 was only 15.84% (Figure 5A). Figure 5B demonstrates the difference in the number of cases of AEs involving nervous system disorders reported by users of monotherapy with seven different HER2 inhibitors. The percentage of patients whose outcome was death fluctuated from 3.36% to 17.4% of the total. Neuropathy, headache, dizziness, paraesthesia, and memory impairment are common PTs (Figure 5C). The results of the disproportionality analysis suggested that cerebral haemorrhage is a positive signal for TDM-1 and T-DXd (Figure 5D). In addition, among the seven HER2 inhibitors, demyelination and leukoencephalopathy were the only positive signals in TDM-1 applicants. Therefore, myelin damage in TDM-1 applicants might be worth emphasizing.

On the other hand, applicants of tucatinib had the highest reported rates of nervous system disorders, so the positive signals unique to this drug were also spotlighted. PPR signals were positive for encephalopathy, epilepsy, balance disorder, hypersomnia, memory impairment, and sleep deficit. In addition, neuropathy peripheral was also a factor in the high prevalence of tucatinib applicants. The number of reports of neuropathy peripheral (95 cases), memory impairment (83 cases), and balance disorder (37 cases) were among the top three PTs with PRR-positive signals for tucatinib. Since that memory impairment is a relatively insidious symptom, it may be worth further attention.

4 Discussion

Reducing the risk of various AEs associated with HER2 inhibitors and improving patients' quality of life is one of the keys to the success of antitumor therapy. The FAERS database provides us with follow-up data on drug safety, allowing us to better monitor the distribution of AEs for various drugs, especially those that occur outside the hospital. By comparing eight HER2 inhibitors horizontally and vertically, our study partially demonstrates the changes and status of anti-HER2 therapy over the past decade or so.

10.3389/fphar.2024.1288362

TABLE 1 Clinical characteristics of patients with hemorrhagic events.

Characteristic	N = 1,274[1]
Regimen	
Combination therapy	352 (28%)
Monotherapy	922 (72%)
Age	
<18	7 (0.5%)
≥75	94 (7.4%)
18–44	108 (8.5%)
45–64	544 (43%)
65–74	198 (16%)
Unknown	323 (25%)
Sex	
F	1,051 (82%)
M	99 (7.8%)
Unknown	124 (9.7%)
OUTC_COD	
CA	1 (<0.1%)
DE	294 (23%)
DS	18 (1.4%)
HO	477 (37%)
LT	23 (1.8%)
OT	457 (36%)
Unknown	4 (0.3%)
soc_name	
Eye disorders	83 (6.5%)
Gastrointestinal disorders	661 (52%)
Hepatobiliary disorders	4 (0.3%)
Neoplasms benign, malignant and unspecified	59 (4.6%)
Nervous system disorders	175 (14%)
Renal and urinary disorders	39 (3.1%)
Reproductive system and breast disorders	8 (0.6%)
Respiratory, thoracic and mediastinal disorders	37 (2.9%)
Vascular disorders	208 (16%)
pt_name	
Anal haemorrhage	7 (0.5%)
Arterial haemorrhage	1 (<0.1%)
Bronchial haemorrhage	3 (0.2%)
Central nervous system haemorrhage	3 (0.2%)
Cerebral haemorrhage	107 (8.4%)

(Continued on following page)

TABLE 1 (*Continued*) Clinical characteristics of patients with hemorrhagic events.

Characteristic	N = 1,274[1]
Cerebral microhaemorrhage	1 (<0.1%)
Conjunctival haemorrhage	9 (0.7%)
Cystitis haemorrhagic	27 (2.1%)
Diarrhoea haemorrhagic	46 (3.6%)
Duodenal ulcer haemorrhage	8 (0.6%)
Enterocolitis haemorrhagic	7 (0.5%)
Eye haemorrhage	44 (3.5%)
Gastric haemorrhage	43 (3.4%)
Gastritis haemorrhagic	5 (0.4%)
Gastroduodenal haemorrhage	2 (0.2%)
Gastrointestinal haemorrhage	214 (17%)
Haemorrhage	191 (15%)
Haemorrhage intracranial	26 (2.0%)
Haemorrhage urinary tract	4 (0.3%)
Haemorrhagic ascites	2 (0.2%)
Haemorrhagic stroke	12 (0.9%)
Haemorrhoidal haemorrhage	21 (1.6%)
Haemorrhoids	41 (3.2%)
Hepatic haemorrhage	4 (0.3%)
Internal haemorrhage	7 (0.5%)
Intestinal haemorrhage	22 (1.7%)
Intra-abdominal haemorrhage	1 (<0.1%)
Intracranial tumour haemorrhage	10 (0.8%)
Intraventricular haemorrhage	6 (0.5%)
Laryngeal haemorrhage	1 (<0.1%)
Lip haemorrhage	3 (0.2%)
Mouth haemorrhage	35 (2.7%)
Naevus haemorrhage	6 (0.5%)
Oesophageal haemorrhage	5 (0.4%)
Oesophageal varices haemorrhage	9 (0.7%)
Oesophagitis haemorrhagic	1 (<0.1%)
Optic disc haemorrhage	1 (<0.1%)
Pulmonary haemorrhage	27 (2.1%)
Rectal haemorrhage	186 (15%)
Renal haemorrhage	1 (<0.1%)
Respiratory tract haemorrhage	5 (0.4%)
Retinal haemorrhage	29 (2.3%)
Retroperitoneal haemorrhage	3 (0.2%)

(Continued on following page)

TABLE 1 (*Continued*) Clinical characteristics of patients with hemorrhagic events.

Characteristic	N = 1,274[1]
Shock haemorrhagic	7 (0.5%)
Subarachnoid haemorrhage	19 (1.5%)
Thalamus haemorrhage	1 (<0.1%)
Thoracic haemorrhage	1 (<0.1%)
Tumour haemorrhage	43 (3.4%)
Ureteric haemorrhage	1 (<0.1%)
Urethral haemorrhage	1 (<0.1%)
Urinary bladder haemorrhage	5 (0.4%)
Uterine haemorrhage	8 (0.6%)
Venous haemorrhage	2 (0.2%)

We visualized the number of various HER2 inhibitors applied alone, sequentially, or combined based on overlap relationships (Figure 1A). Our statistics suggest that trastuzumab remains the most reported drug for AEs, both in number and in combination. However, more than 300 tumor patients had been treated with four or even five HER2 inhibitors, which predicts fair compatibility between these drugs. These drug combinations will continue to evolve as more emerging HER2 inhibitors advance in therapeutic lines and efficacy is confirmed (Giordano et al., 2023; Najminejad et al., 2023).

The distribution of adverse event reporting rates suggests that those patients treated with two or more HER2 inhibitors were more likely to report AEs for SOCs such as blood and lymphatic system disorders, infections and infestations, investigations, and neoplasms benign, malignant, and unspecified compared to monotherapy. This phenomenon may contribute to may be the accumulation of HER2 inhibitor-related toxicity, disease progression, and the superimposition of toxicity from other antitumor agents, among other factors. In addition, the reported rates of AEs demonstrated that TDM-1 and T-DXd appeared significantly different in multiple SOCs (Figure 1C). For example, patients treated with T-DXd reported a higher proportion of respiratory, thoracic, and mediastinal disorders, whereas patients treated with TDM-1 reported a higher proportion of hepatobiliary disorders. These results are consistent with previous studies (Yan et al., 2016; Battisti et al., 2020; Swain et al., 2022). In addition, we visualized the distribution of all reported AEs in patients treated with only one HER2 inhibitor by mulberry plots, incorporating seven inhibitors in addition to pyrotinib (Figure 2B, Supplementary Figure S1). These data may help clinicians or patients choose appropriate anti-HER2 therapy. Indeed, our study once again demonstrates the tendency of small-molecule drugs to be highly prevalent in gastrointestinal disorders, especially such common disorders as diarrhea, nausea, and vomiting. Therefore, good management of gastrointestinal AEs is necessary when applying this class of drugs.

The correlation between the occurrence of hemorrhagic events during antitumor therapy and thrombocytopenia has remained inconclusive (Wuerstlein et al., 2022; Wang et al., 2023). Considering the dangers of hemorrhage, especially the fatal consequences of intracranial and gastrointestinal hemorrhage, our study focused on hemorrhagic events potentially associated with anti-HER2 therapy. Few previous studies have conducted side-by-side comparisons of these drugs. We found that TDM-1 had a significantly higher proportion of reported hemorrhagic events than other HER2 inhibitors. Furthermore, patients treated with TDM-1 who experienced hemorrhagic events had a significantly higher rate of thrombocytopenia. Based on the inherent flaws in the evidence from the spontaneous reporting system, we cannot directly assume that thrombocytopenia-induced hemorrhagic events in patients treated with TDM-1, especially since 60% (66/110) of such patients did not report the occurrence of thrombocytopenia (Figure 3E). However, thrombocytopenia may have partially influenced the occurrence of haemorrhage. Of course, we also noted that the percentage of bleeding events intersecting with thrombocytopenia was less than 10% for each of the other six HER2 inhibitors, which may prove that thrombocytopenia is not strongly correlated with bleeding events in users of these drugs. In addition, our study also attempted to investigate the effect of different factors on the time of initiation of intracranial hemorrhagic events. Age and outcome of AEs are not important intervening factors. We note that the median time to onset of intracranial haemorrhage associated with trastuzumab (0.5 months) and TDM-1 (0.75 months) was short. This result warns us that we need to be concerned about the possibility of hemorrhagic events when applying these HER2 inhibitors initially.

As the control of extracranial diseases improves, the probability of malignant tumors metastasizing within the central nervous system gradually increases (Ferrario et al., 2022). The blood-brain barrier is a major obstacle to the effective penetration and diffusion of antitumor drugs to intracranial lesions (Giordano et al., 2023). Therefore, some HER2 inhibitors, such as tucatinib and neratinib, emphasize high blood-brain barrier permeability (Giordano et al., 2023). However, could increase intracranial drug concentrations exacerbate or induce some neurologic toxicity that was previously easily overlooked in the clinic? Our study found

10.3389/fphar.2024.1288362

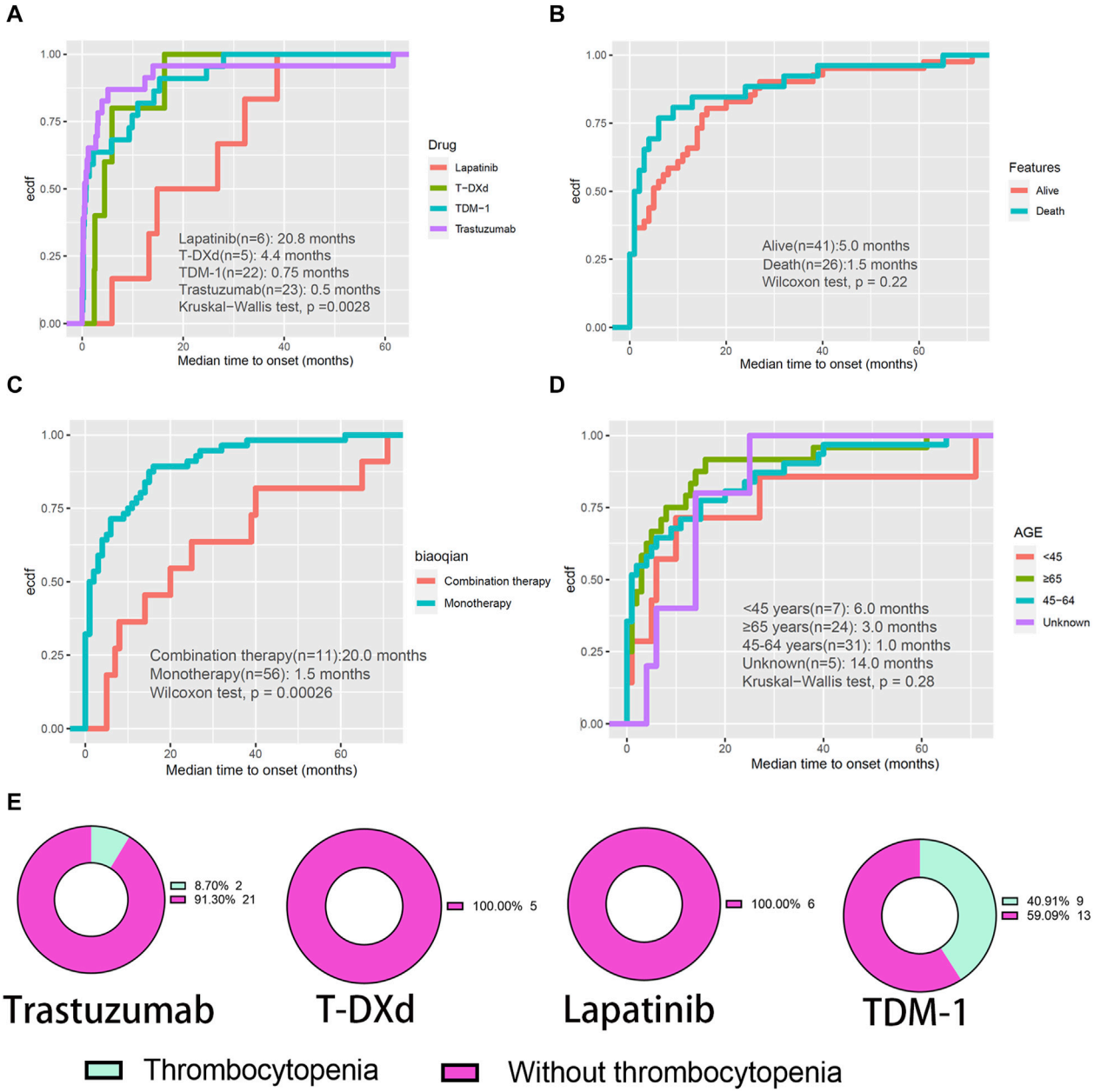


FIGURE 4
Evaluation of intracranial haemorrhage events. **(A–D)** The cumulative curve visualizes the interval between the initiation of HER2 inhibitors and the occurrence of intracranial haemorrhage. **(E)** Percentage of patients treated with four HER2 monotherapies who developed intracranial haemorrhage who had concomitant thrombocytopenia.

that the reported rates of nervous system disorders associated with either tucatinib or neratinib were more than twice that of other HER2 inhibitors (Figure 1C). The FAERS database has reported 83 cases of memory impairment in patients treated with tucatinib. This is rarely mentioned in previous studies.

4.1 Limitation

The present study is mainly based on the exploration of public databases, but further validation of our analytical conclusions requires more real-world prospective studies and large-scale clinical trials. Due to the limitations of spontaneous reporting systems and the differences in the importance placed on AEs in different countries and regions, there are situations such as under-reporting, missing patient basic information, and inability to estimate the incidence of ADR. The AEs mining method used in this paper is the disproportionality analysis, which highlights the differences in the number of reports between a specific drug-event combination in the database and other drug-event combinations in the database, and is only used to generate drug safety signals (i.e., provide clues to

10.3389/fphar.2024.1288362

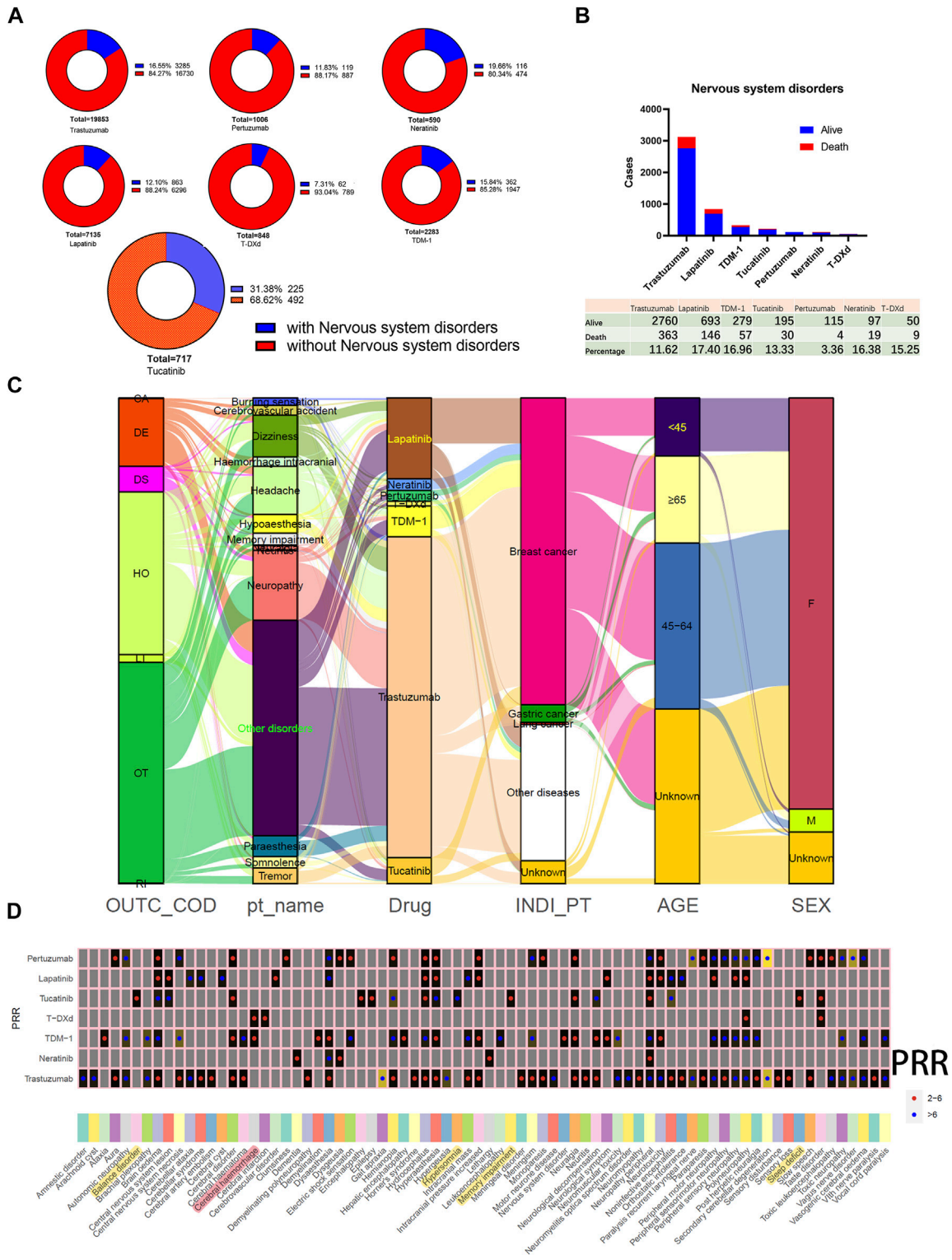


FIGURE 5
Adverse events involving nervous system disorders. **(A)** Distribution of the total number and percentage of patients with concomitant nervous system disorders in reports of HER2 monotherapy. **(B)** Bar graph statistics of the proportion and number of cases of living and dead patients presenting with nervous system disorders, and those not explicitly labeled in the outcome list have been excluded. **(C)** Mulberry map of clinical characteristics of patients with nervous system disorders. **(D)** Comparison of positive signal with nervous system disorders obtained by different HER2 inhibitors based on the Proportional Reporting Ratio (PRR) method. Red dots indicate PRR values in the 2.0–6.0 range. Blue dots indicate PRR values above 5.0.

drug safety), and cannot prove the causal relationship between drug events.

4.2 Conclusion

The types and reporting rates of AEs associated with different HER2 inhibitor treatments vary across multiple systems. In addition, hemorrhagic events concomitant with TDM-1 treatment and nervous system disorders concomitant with tucatinib treatment may be worthy of attention.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the [patients/participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YB: Conceptualization, Formal Analysis, Methodology, Visualization, Writing–original draft. JC: Conceptualization, Formal Analysis, Methodology, Writing–original draft. Conceptualization, Formal Analysis, Methodology, Writing–original draft. LD: Conceptualization, Formal Analysis, Methodology, Writing–original draft. FW: Conceptualization, Writing–original draft. HL: Conceptualization, Writing–original draft. ZM: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Software, Validation, Visualization, Project administration, Writing–original draft, Writing–review & editing, and Funding acquisition. WZ: Supervision, Validation, Visualization, Writing–review & editing, Funding acquisition.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Natural Science Foundation of Guangdong Province (Grant No. 2021A1515012593) and Science and Technology Fund of Guizhou Provincial Health Commission (gzwjkj2019-1-081).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer LZ declared a shared parent affiliation with the author ZM to the handling editor at the time of review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1288362/full#supplementary-material

References

Banys-Paluchowski, M., Krawczyk, N., Stickeler, E., Müller, V., and Fehm, T. (2023). New treatment strategies for human epidermal growth factor receptor 2-positive breast cancer in 2023. *Curr. Opin. Obstet. Gynecol.* 35 (1), 54–61. doi:10.1097/gco.0000000000000830

Battisti, N. M. L., Rogerson, F., Lee, K., Shepherd, S., Mohammed, K., Turner, N., et al. (2020). Safety and efficacy of T-DM1 in patients with advanced HER2-positive breast cancer the Royal Marsden experience. *Cancer Treat. Res. Commun.* 24, 100188. doi:10.1016/j.ctarc.2020.100188

Berchuck, A., Kamel, A., Whitaker, R., Kerns, B., Olt, G., Kinney, R., et al. (1990). Overexpression of HER-2/neu is associated with poor survival in advanced epithelial ovarian cancer. *Cancer Res.* 50 (13), 4087–4091.

Brunson, J. C. (2020). Ggalluvial: layered grammar for alluvial plots. *J. Open Source Softw.* 5 (49), 2017. doi:10.21105/joss.02017

Chari, A., Vogl, D. T., Gavriatopoulou, M., Nooka, A. K., Yee, A. J., Huff, C. A., et al. (2019). Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N. Engl. J. Med.* 381 (8), 727–738. doi:10.1056/NEJMoa1903455

Chuma, M., Nakamoto, A., Bando, T., Niimura, T., Kondo, Y., Hamano, H., et al. (2022). Association between statin use and daptomycin-related musculoskeletal adverse events: a mixed approach combining a meta-analysis and a disproportionality analysis. *Clin. Infect. Dis.* 75 (8), 1416–1422. doi:10.1093/cid/ciac128

Cianfrocca, M., and Goldstein, L. J. (2004). Prognostic and predictive factors in early-stage breast cancer. *Oncologist* 9 (6), 606–616. doi:10.1634/theoncologist.9-6-606

Conway, J. R., Lex, A., and Gehlenborg, N. (2017). UpSetR: an R package for the visualization of intersecting sets and their properties. *Bioinformatics* 33 (18), 2938–2940. doi:10.1093/bioinformatics/btx364

Delgado, J., Vleminckx, C., Sarac, S., Sosa, A., Bergh, J., Giuliani, R., et al. (2021). The EMA review of trastuzumab emtansine (T-DM1) for the adjuvant treatment of adult patients with HER2-positive early breast cancer. *ESMO Open* 6 (2), 100074. doi:10.1016/j.esmoop.2021.100074

Elting, L. S., Rubenstein, E. B., Martin, C. G., Kurtin, D., Rodriguez, S., Laiho, E., et al. (2001). Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. *J. Clin. Oncol.* 19 (4), 1137–1146. doi:10.1200/jco.2001.19.4.1137

Ferrario, C., Christofides, A., Joy, A. A., Laing, K., Gelmon, K., and Brezden-Masley, C. (2022). Novel therapies for the treatment of HER2-positive advanced breast cancer: a Canadian perspective. *Curr. Oncol.* 29 (4), 2720–2734. doi:10.3390/curroncol29040222

ggVennDiagram, G. C.-H. (2023). *A 'ggplot2' implement of venn diagram.*

Giordano, G., Griguolo, G., Landriscina, M., Meattini, I., Carbone, F., Leone, A., et al. (2023). Multidisciplinary management of HER2-positive breast cancer with brain metastases:

an evidence-based pragmatic approach moving from pathophysiology to clinical data. *Crit. Rev. Oncol. Hematol.* 192, 104185. doi:10.1016/j.critrevonc.2023.104185

Giordano, S. H., Franzoi, M. A. B., Temin, S., Anders, C. K., Chandarlapaty, S., Crews, J. R., et al. (2022). Systemic therapy for advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO guideline update. *J. Clin. Oncol.* 40 (23), 2612–2635. doi:10.1200/jco.22.00519

Grieb, B. C., and Agarwal, R. (2021). HER2-Directed therapy in advanced gastric and gastroesophageal adenocarcinoma: triumphs and troubles. *Curr. Treat. Options Oncol.* 22 (10), 88. doi:10.1007/s11864-021-00884-7

Gu, Z., Eils, R., and Schlesner, M. (2016). Complex heatmaps reveal patterns and correlations in multidimensional genomic data. *Bioinformatics* 32 (18), 2847–2849. doi:10.1093/bioinformatics/btw313

Guntner, A. S., Peyrl, A., Mayr, L., Englinger, B., Berger, W., Slavc, I., et al. (2020). Cerebrospinal fluid penetration of targeted therapeutics in pediatric brain tumor patients. *Acta Neuropathol. Commun.* 8 (1), 78. doi:10.1186/s40478-020-00953-2

Hedhli, N., and Russell, K. S. (2011). Cardiotoxicity of molecularly targeted agents. *Curr. Cardiol. Rev.* 7 (4), 221–233. doi:10.2174/157340311799960636

Kassambara, A. (2023). *Ggpubr: 'ggplot2' based publication ready plots.*

Mo, Z., Deng, Y., Bao, Y., Liu, J., and Jiang, Y. (2023). Evaluation of cardiotoxicity of anthracycline-containing chemotherapy regimens in patients with bone and soft tissue sarcomas: a study of the FDA adverse event reporting system joint single-center real-world experience. *Cancer Med.* 12, 21709–21724. doi:10.1002/cam4.6730

Najminejad, Z., Dehghani, F., Mirzaei, Y., Mer, A. H., Saghi, S. A., Abdolvahab, M. H., et al. (2023). Clinical perspective: antibody-drug conjugates for the treatment of HER2-positive breast cancer. *Mol. Ther.* 31 (7), 1874–1903. doi:10.1016/j.ymthe.2023.03.019

Oh, D. Y., and Bang, Y. J. (2020). HER2-targeted therapies - a role beyond breast cancer. *Nat. Rev. Clin. Oncol.* 17 (1), 33–48. doi:10.1038/s41571-019-0268-3

Patil, I. (2021). Visualizations with statistical details: the 'ggstatsplot' approach. *J. Open Source Softw.* 6, 3167. doi:10.21105/joss.03167

Rakhshani, N., Kalantari, E., Bakhti, H., Sohrabi, M. R., and Mehrazma, M. (2014). Evaluation of HER-2/neu overexpression in gastric carcinoma using a tissue microarray. *Asian Pac J. Cancer Prev.* 15 (18), 7597–7602. doi:10.7314/apjcp.2014.15.18.7597

Raschi, E., Fusaroli, M., La Placa, M., Ardizzoni, A., Zamagni, C., Poluzzi, E., et al. (2022). Skin toxicities with cyclin-dependent kinase 4/6 inhibitors in breast cancer: signals from disproportionality analysis of the FDA adverse event reporting system. *Am. J. Clin. Dermatol* 23 (2), 247–255. doi:10.1007/s40257-021-00645-0

Schlam, I., and Swain, S. M. (2021). HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. *NPJ Breast Cancer* 7 (1), 56. doi:10.1038/s41523-021-00265-1

Singh, D. D., Lee, H. J., and Yadav, D. K. (2022). Clinical updates on tyrosine kinase inhibitors in HER2-positive breast cancer. *Front. Pharmacol.* 13, 1089066. doi:10.3389/fphar.2022.1089066

Stemmler, H. J., Schmitt, M., Willems, A., Bernhard, H., Harbeck, N., and Heinemann, V. (2007). Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. *Anticancer Drugs* 18 (1), 23–28. doi:10.1097/01.cad.0000236313.50833.ee

Swain, S. M., Miles, D., Kim, S. B., Im, Y. H., Im, S. A., Semiglazov, V., et al. (2020). Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 21 (4), 519–530. doi:10.1016/s1470-2045(19)30863-0

Swain, S. M., Nishino, M., Lancaster, L. H., Li, B. T., Nicholson, A. G., Bartholmai, B. J., et al. (2022). Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)-related interstitial lung disease/pneumonitis-Focus on proactive monitoring, diagnosis, and management. *Cancer Treat. Rev.* 106, 102378. doi:10.1016/j.ctrv.2022.102378

Thuss-Patience, P. C., Shah, M. A., Ohtsu, A., Van Cutsem, E., Ajani, J. A., Castro, H., et al. (2017). Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol.* 18 (5), 640–653. doi:10.1016/s1470-2045(17)30111-0

Wang, T. F., Carrier, M., Carney, B. J., Kimpton, M., and Delluc, A. (2023). Anticoagulation management and related outcomes in patients with cancer-associated thrombosis and thrombocytopenia: a systematic review and meta-analysis. *Thromb. Res.* 227, 8–16. doi:10.1016/j.thromres.2023.05.012

Wickham, H. (2016). *ggplot2: elegant graphics for data analysis*. New York: Springer-Verlag.

Wuerstlein, R., Ellis, P., Montemurro, F., Antón Torres, A., Delaloge, S., Zhang, Q., et al. (2022). Final results of the global and Asia cohorts of KAMILLA, a phase IIIB safety trial of trastuzumab emtansine in patients with HER2-positive advanced breast cancer. *ESMO Open* 7 (5), 100561. doi:10.1016/j.esmoop.2022.100561

Yan, H., Endo, Y., Shen, Y., Rotstein, D., Dokmanovic, M., Mohan, N., et al. (2016). Ado-trastuzumab emtansine targets hepatocytes via human epidermal growth factor receptor 2 to induce hepatotoxicity. *Mol. Cancer Ther.* 15 (3), 480–490. doi:10.1158/1535-7163.Mct-15-0580

Zambelli, A., Della Porta, M. G., Eleuteri, E., De Giuli, L., Catalano, O., Tondini, C., et al. (2011). Predicting and preventing cardiotoxicity in the era of breast cancer targeted therapies. Novel molecular tools for clinical issues. *Breast* 20 (2), 176–183. doi:10.1016/j.breast.2010.11.002

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 31 January 2024
DOI 10.3389/fphar.2024.1329409

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Carolina Dagli Hernandez,
Independent Researcher, Sao Paulo, Brazil
Marcela Forgerini,
São Paulo State University, Brazil

*CORRESPONDENCE
Xinyuan Yang,
xinyuanyang2022@163.com

†These authors share first authorship

RECEIVED 30 October 2023
ACCEPTED 15 January 2024
PUBLISHED 31 January 2024

CITATION
Cui Z, Zhai Z, Xie D, Wang L, Cheng F, Lou S, Zou F, Pan R, Chang S, Yao H, She J, Zhang Y and Yang X (2024), From genomic spectrum of NTRK genes to adverse effects of its inhibitors, a comprehensive genome-based and real-world pharmacovigilance analysis.
Front. Pharmacol. 15:1329409.
doi: 10.3389/fphar.2024.1329409

From genomic spectrum of NTRK genes to adverse effects of its inhibitors, a comprehensive genome-based and real-world pharmacovigilance analysis

Zhiwei Cui[1†], Zhen Zhai[2†], De Xie[3†], Lihui Wang[1], Feiyan Cheng[1], Siyu Lou[4], Fan Zou[4], Rumeng Pan[1], Shixue Chang[5], Haoyan Yao[1], Jing She[1], Yidan Zhang[1] and Xinyuan Yang[1]*

[1]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3]Department of Endocrinology, Xiang'an Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian, China, [4]Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China, [5]Center for Translational Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Introduction: The discovery of neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions has facilitated the development of precision oncology. Two first-generation *NTRK* inhibitors (larotrectinib and entrectinib) are currently approved for the treatment of patients with solid tumors harboring *NTRK* gene fusions. Nevertheless, comprehensive *NTRK* profiling at the pan-cancer genomic level and real-world studies pertaining to the adverse events of *NTRK* inhibitors are lacking.

Methods: We characterize the genome of *NTRK* at the pan-cancer level through multi-omics databases such as The Cancer Genome Atlas (TCGA). Through the FDA Adverse Event Reporting System (FAERS) database, we collect reports of entrectinib and larotrectinib-induced adverse events and perform a pharmacovigilance analysis using various disproportionality methods.

Results: *NTRK1/2/3* expression is lower in most tumor tissues, while they have higher methylation levels. *NTRK* gene expression has prognostic value in some cancer types, such as breast invasive carcinoma (BRCA). The cancer type with highest *NTRK* alteration frequency is skin cutaneous melanoma (SKCM) (31.98%). Thyroid carcinoma (THCA) has the largest number of *NTRK* fusion cases, and the most common fusion pair is *ETV6-NTRK3*. Adverse drug events (ADEs) obtained from the FAERS database for larotrectinib and entrectinib are 524 and 563, respectively. At the System Organ Class (SOC) level, both drugs have positive signal value for "nervous system disorder". Other positive signals for entrectinib include "cardiac disorders", "metabolism and nutrition disorders", while for larotrectinib, it is "hepatobiliary disorders". The unexpected signals are also listed in detail. ADEs of the two *NTRK* inhibitors mainly occur in the first month. The median onset time of ADEs for entrectinib and larotrectinib was 16 days (interquartile range [IQR] 6–86.5) and 44 days ([IQR] 7–136), respectively.

Conclusion: Our analysis provides a broad molecular view of the *NTRK* family. The real-world adverse drug event analysis of entrectinib and larotrectinib contributes to more refined medication management.

KEYWORDS

NTRK, gene fusion, entrectinib, larotrectinib, FAERS, adverse drug event, pharmacovigilance

1 Introduction

Members of the tropomyosin receptor kinase (TRK) family include the TRKA, TRKB, and TRKC proteins, encoded by the neurotrophic tyrosine kinase receptor 1 (*NTRK1*), *NTRK2*, and *NTRK3* genes, respectively (Khotskaya et al., 2017). Activation of neurotrophic factors, which are specific ligands for TRK receptors, triggers the activation of various downstream signaling cascades. These cascades include the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), and phospholipase C-γ (PLC-γ) pathways. These pathways have significant effects on essential biological processes such as neuronal cell differentiation, survival, and proliferation (Bhangoo and Sigal, 2019; Jiang et al., 2022). Alterations in *NTRK* genes are closely associated with both tumor initiation and progression. Among these alterations, *NTRK* gene fusions are the most well-characterized aberrations. These gene fusions possess oncogenic properties as they promote tumorigenesis by constitutively activating downstream cell growth and proliferation pathways (Khotskaya et al., 2017; Cocco et al., 2018; Okamura et al., 2018). In addition to gene fusions, several studies have also characterized the genomic profile of *NTRK*. Light et al. reported that *NTRK1/3* were highly expressed in neuroblastoma patients with a better prognosis, whereas *NTRK2* was highly expressed in neuroblastoma patients with a poor prognosis (Light et al., 2012). Additionally, in 83 clinical samples of triple-negative breast cancers, *NTRK1/2/3* were found to exhibit varying degrees of copy number gain and amplification (Zito Marino et al., 2023). However, these aforementioned studies are limited by focusing on specific cancer types and small sample sizes, highlighting the critical need for comprehensive analyses across multiple tumor types to investigate their functions.

The US Food and Drug Administration (FDA) has approved the first generation of *NTRK* inhibitors, which have shown favorable clinical outcomes. One such inhibitor is larotrectinib, a potent and highly selective small molecule inhibitor targeting three TRK proteins. Larotrectinib is prescribed for the treatment of patients with solid tumors who have *NTRK* gene fusions and have experienced disease progression after alternative therapies (Scott, 2019). Its recommended phase 2 dose is 100 mg twice daily (Laetsch et al., 2018). Whereas entrectinib is mainly used for the treatment of locally advanced or metastatic solid tumors harboring fusion mutations in the *NTRK1/2/3*, C-ros oncogene 1 (*ROS1*) and anaplastic lymphoma kinase (*ALK*) genes. The recommended adult dose of entrectinib is 600 mg/d, while the pediatric dose is based on body surface area (Frampton, 2021). The main difference between the two drugs is that entrectinib is indicated for adult and pediatric patients aged ≥12 years, while larotrectinib is indicated for adult and pediatric patients of all ages (Frampton, 2021). Both drugs prolong metastasis-free survival and overall survival and maintain health-related quality of life in patients with solid tumors (Drilon et al., 2022; Jiang et al., 2022). Adverse events were predominantly reported during clinical trials for both drugs, primarily in grades 1–2, such as fatigue and dizziness. Additionally, a variable proportion of patients (ranging from 2% to 40%) also experienced grade 3–4 adverse events, including anaemia and elevated aminotransferases (Doebele et al., 2020; Hong et al., 2020). However, the majority of clinical trials were unable to identify new signals of adverse drug reactions due to the limited number of patients included and the short duration of follow-up (Doz et al., 2022). Liguori et al. recently collected and descriptively analyzed reports of adverse events following the introduction of two first-generation *NTRK* inhibitors (Liguori et al., 2023). Nevertheless, there is still a lack of disproportionality analysis of the adverse reaction signals of the two first-generation *NTRK* inhibitors, identification of new adverse reaction signals, and detailed comparisons of the safety of the two drugs.

Evidence at the genomic level plays a crucial role in the foundation of drug design. Drugs with confirmed targets from human genetic studies are more likely to be successfully marketed than those lacking such evidence (Roden et al., 2019). Furthermore, mutations and epigenetic modifications of drug target genes can significantly and consistently alter cellular gene expression patterns and are strongly associated with drug efficacy and adverse drug reactions (Brockmöller and Tzvetkov, 2008; Borges et al., 2021). For instance, fibroblast growth factor receptor 2 (*FGFR2*) rearrangements in cholangiocarcinoma predict tumor sensitivity to *FGFR2* inhibitors (Vogel et al., 2023). Clinical trials serve as a vital pre-market assessment of drugs and represent an important step in translating genomic evidence into clinical practice (Joffe et al., 2017). However, due to the relatively low exposure of clinical trials with clear inclusion criteria and drug treatment conditions, rare but serious adverse drug reactions are usually detected after marketing authorization and increased population exposure (Ehmann et al., 2014). Therefore, post-market real-world vigilance data on drugs are of paramount importance, complementing evidence from pharmacoepidemiology (Sabaté and Montané, 2023). By integrating data from three sources-genomics, clinical trials, and real-world pharmacovigilance, a comprehensive view is provided, which is not available from any independent data source (Figure 1). This approach also effectively overcomes the limitations of analyzing each data type separately (Jing et al., 2021).

This study aimed to characterize the molecular signature of *NTRK* using a large genomic dataset covering diverse tumor types, and to conduct a comprehensive analysis of the safety of first-generation *NTRK* inhibitors based on real-world adverse drug event (ADE) data. Firstly, we conducted a systematic analysis of *NTRK*

10.3389/fphar.2024.1329409

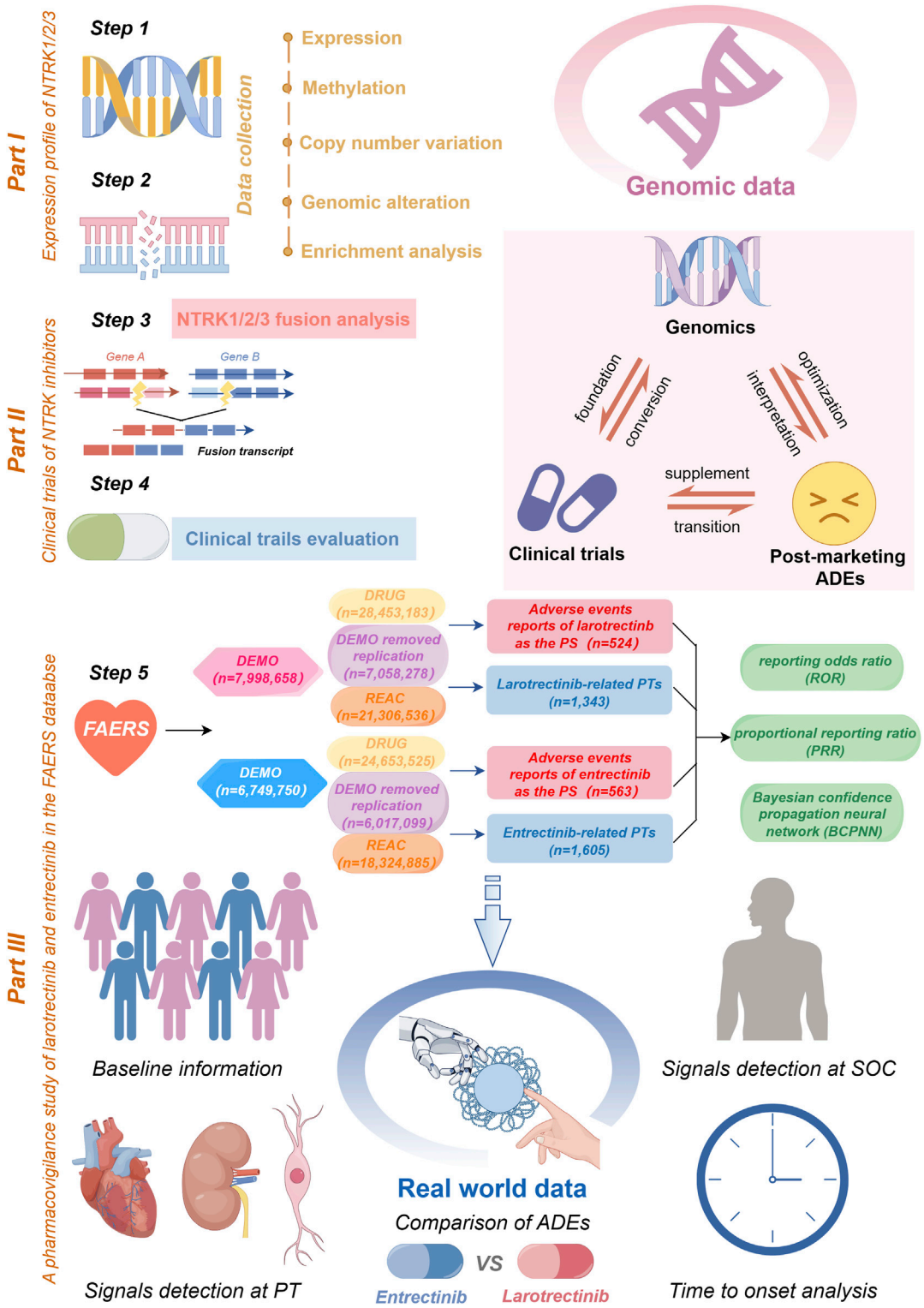


FIGURE 1
A flow chart of the whole study. In part I, we acquired *NTRK* expression profiling data and conducted an analysis of its mRNA expression, methylation, and CNV (step 1). Subsequently, we delved into the genomic alterations of *NTRK*, co-mutation pathways (step 2), and emphasized *NTRK* fusions (step 3). The part II involved a comprehensive review of the clinical trials of *NTRK* inhibitors (step 4). In part III, a safety assessment of the first-generation *NTRK* inhibitors was carried out utilizing real-world ADE reports sourced from the FAERS database (step 5). This encompassed data cleaning, baseline information description, signal detection, and time to onset analysis. Furthermore, we provided a summarization of the interrelationships between the three different data sources (top right of figure). CNV, copy number variation; FAERS, FDA Adverse Event Reporting System; SOC, System Organ Class; PT, preferred term; ADE, adverse drug event; PS, primary suspect.

expression, methylation, and genomic alterations across various cancer types. Additionally, we investigated *NTRK* fusions and examined the current status of clinical trials for the first-generation *NTRK* inhibitors, including larotrectinib and entrectinib. Lastly, we compared the differences in ADEs between the two drugs and assessed the time of onset for these ADEs. The integration of data from various sources in our study offers a comprehensive perspective on the *NTRK* gene.

2 Materials and methods

2.1 Genomics data collection and processing

The RNA sequencing data from a pan-cancer microarray (n = 15,776) was obtained from the UCSC Xena browser (https://xenabrowser.net/datapages/) on 1 August 2023. This dataset integrates various cancerous and normal tissues obtained from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) (Goldman et al., 2020). Secondly, these data were filtered and normalized before subsequent analyses were performed (Vivian et al., 2017; Zhao et al., 2020). For detailed procedures, please refer to a previously published article of us (Cui et al., 2023).

To assess the correlation between *NTRK1/2/3* gene expression (with the median value as the cut-off) and patient prognosis, we utilized univariate Cox proportional hazards regression analysis to calculate hazard ratios (HR) and corresponding *p*-values. Patient survival indicators examined in this study comprised overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI). OS was defined as death from any cause, with surviving patients censored at the last follow-up. DSS was determined based on deaths attributed to a specific disease, and PFI represented the duration between the date of initial treatment in the randomized group and disease recurrence (Ekmekcioglu et al., 2016; Liu et al., 2018). During this process, key R packages was utilized, including "survival (version 3.3.1)" and "ggplot (version 3.3.6)".

2.2 Genomic alteration and enrichment analysis

Gene Set Cancer Analysis (GSCA) (http://bioinfo.life.hust.edu.cn/GSCA/#/) is an integrative platform for genomic cancer analysis (Liu et al., 2023). We employed the "Mutation" module to investigate the association between *NTRK1/2/3* mRNA expression and copy number variation (CNV) as well as methylation across various tumor types. Additionally, we utilized the "Expression" module to explore the correlation between gene expression and pathway activity. All analyses were conducted on 1 August 2023.

The cBioPortal (https://www.cbioportal.org/) provides an open access to the interactive exploration of multidimensional cancer genomics data (Cerami et al., 2012; Gao et al., 2013). To systematically analyze the genomic alterations of *NTRK1/2/3* genes across 32 different cancer types, we selected the "TCGA Pan Cancer Atlas Studies" cohort, which consisted of a total of 10,953 patients (including 10,967 samples) for further investigation. This cohort was chosen from the "Cancer Types Summary" and "Mutations" modules. To identify the most frequently altered genes, we utilized the "Genomic alterations" option under the "Comparison/Survival" module. Specifically, we focused on genes with alteration cases surpassing 100 in the altered group (totaling 2,799 genes) that were found to have q-values<0.01. The top 20 genes with the highest alteration frequencies in the altered group were subsequently visualized using a bar graph. To gain insights into the potential functions of these genes, a functional enrichment analysis was conducted. This analysis was performed using the R packages "clusterProfiler" (version 4.4.4) for enrichment analysis and "org.Hs.e.g.,.db" (version 3.1.0) for ID conversion (Yu et al., 2012). The *p*-values were adjusted using BH correction. All operational processes were conducted on 4 August 2023.

2.3 Fusion gene analysis

The fusion gene data of *NTRK1/2/3* were retrieved from the TCGA Fusion Gene Database (https://www.tumorfusions.org/) on 5 August 2023. The database's pipeline for RNA sequencing Data Analysis (PRADA) allowed us to identify fusion transcripts comprehensively and with high confidence, and provided a list of authentic fusion genes across 33 TCGA cancer types (Hu et al., 2018). The database defines four tiers to rank the screened fusion transcripts according to the abundance of supporting evidence. From tier 1 to tier 4 indicates strong to weak confidence levels.

2.4 My cancer genome

The My Cancer Genome (MCG) database were launched in 2011 to guide clinicians in applying genomic test results to the treatment of cancer patients (Jain et al., 2020; Jain et al., 2021). Under the "Drugs" module, we selected two first-generation *NTRK* inhibitors (including larotrectinib and entrectinib) and systematically surveyed the top biomarker inclusion criteria for open clinical trials investigating these two drugs (5 August 2023).

2.5 Adverse drug event data collection and deduplication

Adverse drug events (ADEs) are unintended and harmful effects of medication use, and they commonly result in unplanned hospitalizations and fatalities (Bailey et al., 2016; Visacri et al., 2022). To assess the post-marketing safety of entrectinib and larotrectinib, we conducted a retrospective pharmacovigilance study with ADEs data extracted from the FAERS database. The FAERS data consists of seven datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse drug reaction information (REAC), patient outcomes information (OUCT), reported sources (RPSR), drug therapy start dates and end dates (THER), and indications for drug administration (INDI). Considering the different timing of FDA approval for marketing of the two drugs, we collected information on all ADEs from the FAERS database from 2018 Q4 to 2023 Q1 (for larotrectinib, approved for marketing in 2018 Q4), and from 2019 Q3 to 2023 Q1 (for entrectinib, approved for marketing in

TABLE 1 Three disproportionality algorithms for assessing potential associations between *NTRK* inhibitors and ADEs.

Algorithms	Equation	Criteria
ROR	ROR = ad/bc, 95%CI = $e^{\ln(ROR)\pm1.96\ (1/a+1/b+1/c+1/d)0.5}$	lower limit of 95% CI > 1, N ≥ 3
PRR	PRR = [a (c + d)]/[c (a+b)]	PRR≥2, $\chi^2 \geq 4$, N ≥ 3
	χ2 = [(ad-bc)2](a+b + c + d)/[(a+b)(c + d)(a+c)(b + d)]	
BCPNN	IC = $\log_2$a (a+b + c + d)/[(a+c)(a+b)], 95%CI = E (IC) ± 2V(IC)0.5	IC025 > 0

a, number of reports that contain both targeted drug and targeted drug adverse reactions; b, number of reports of other drug adverse reactions that contain the targeted drug; c, number of reports of targeted drug adverse reactions that contain other drugs; d, number of reports that contain other drugs and other drug adverse reactions. ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, Bayesian confidence propagation neural network; 95% CI, 95% confidence interval; N, reports number; χ2, chi-squared; IC, information component; IC025, the lower limit of the 95% CI of IC; E (IC), the IC expectations; V(IC), the variance of IC

2019 Q3), respectively. As the database is updated on a quarterly basis, it is inevitable that there will be duplicates of previous published reports. In accordance with FDA recommendations, we performed deduplication prior to statistical analyses based on the following criteria: if CASEIDs were the same, the most recent FDA_DT was selected; if CASEIDs and FDA_DTs were the same, the higher PRIMARYIDs were selected (Shu et al., 2022). In this study, "larotrectinib" (brand name: VITRAKVI), and "entrectinib" (brand name: ROZLYTREK) were used to recognize records related to the two *NTRK* inhibitors. To analyze the role of drugs in ADEs, the drugs involved in ADE reports were classified as: primary suspect (PS), which denotes the primary drug considered to have possibly caused the ADE; second suspect (SS), which denotes the secondary drug considered to have possibly caused the ADE; concomitant (C), indicating the concurrent use of other drugs associated with the ADE; and interacting (I), representing possible drug interactions associated with the ADE. To improve accuracy, role codes for ADEs are reserved for entrectinib and larotrectinib as the PS drugs only, which resulted in ADEs associated with entrectinib and larotrectinib dosing being 563 and 524, respectively (Wu et al., 2023). System Organ Class (SOC) was the highest level of terminology in the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). All ADEs in the report were coded according to the preferred terms (PTs). Consequently, 1,343 larotrectinib-related PTs and 1,605 entrectinib-related PTs were screened out.

2.6 Data mining algorithm and statistical analysis

In pharmacovigilance studies, the term "signal" denotes a statistical association between a drug and an adverse event or drug-related adverse event (Hauben and Aronson, 2009; Sakaeda et al., 2013). Disproportionality analysis is a vital analytical method used to identify signals of adverse reactions associated with drugs, as well as to compare the occurrence of adverse reactions between a specific drug and all other drugs. This analysis helps uncover drug-related adverse reactions by evaluating the proportion of these reactions in relation to the overall adverse reaction pool (Montastruc et al., 2011). Therefore, in this study, we employed disproportionality analysis to identify potential correlations between the use of two *NTRK* inhibitors and all ADEs. We utilized two non-Bayesian algorithms, namely, the reporting odds ratio (ROR) and the proportional reporting ratio (PRR), along with a Bayesian algorithm known as the Bayesian confidence propagation neural network (BCPNN) (Montastruc et al., 2011). The Bayesian method (BCPNN) have sufficient power to detect unique signals even when few ADEs are reported for a drug (Bate, 2007). Generally, a higher parameter value indicates a stronger signal value. The specific formulas and criteria for detecting positive safety signals using the three algorithms are presented in Table 1. To enhance the reliability of our findings, we considered only adverse drug events (ADEs) with positive signal values that satisfied all three algorithms simultaneously. Furthermore, we excluded ADEs related to drug indications to ensure clarity in our presentation. Unexpected signals were determined as positive ADEs that were detected but not listed in the drug instruction. The primary analyses of this study are depicted in Figure 1. All data processing and statistical analyses were performed using SAS 9.4, Microsoft Excel 2019, and R software (version 4.2.1).

2.7 Time to onset analysis

The time to onset (TTO) for ADEs associated with *NTRK* inhibitor dosing was calculated as the interval between the ADEs onset date (EVENT_DT) within the DEMO file, and the start date of *NTRK* inhibitor dosing (START_DT) within the THER file. The exclusion criteria involved removing inaccurate or missing dates and cases where the ADEs onset date (EVENT_DT) preceded the start date of *NTRK* inhibitor dosing (START_DT). By utilizing the Weibull distribution, we could identify and estimate the increase or decrease in the incidence of ADE risk over time. The Weibull distribution employs two parameters, scale (α) and shape (β), to determine its shape (Kazi et al., 2020).

3 Results

3.1 Expression and clinical analysis of *NTRK*1/2/3 in pan-cancer

To gain a comprehensive understanding of *NTRK* genomic mRNA expression, we initially employed data from the TCGA and GTEx databases. *NTRK* mRNA expression was generally downregulated in tumor tissues compared to corresponding normal tissues. For *NTRK1*, *NTRK2* and *NTRK3*, the number of tumors with significantly reduced expression was 20, 17, and 22,

10.3389/fphar.2024.1329409

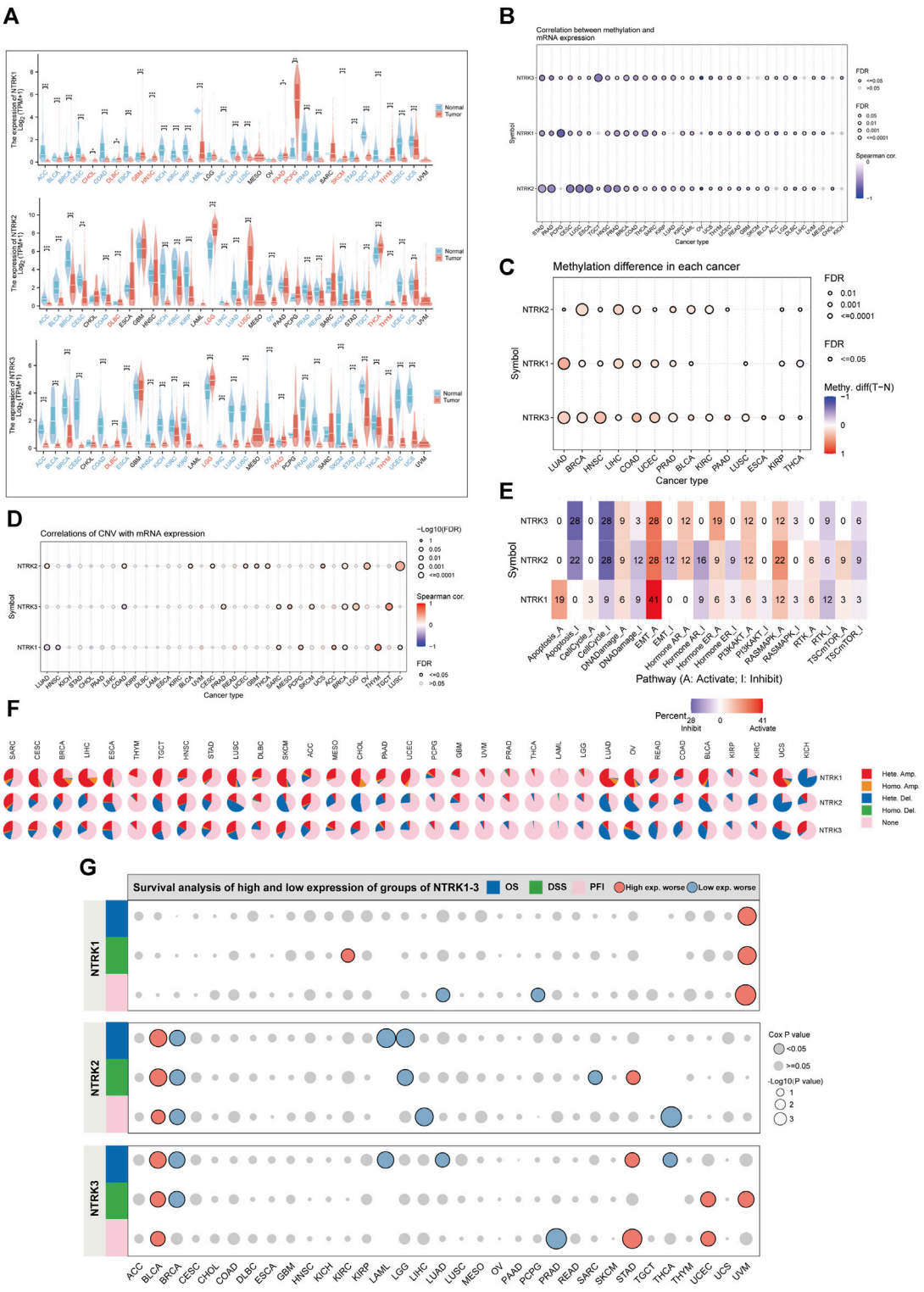


FIGURE 2
Genomic characterization of *NTRK* genes at the pan-cancer level. **(A)**. Differential mRNA expression of *NTRK1/2/3* in tumor and corresponding normal tissues. Gene expression is compared after Log2 (TPM+1) transformed. **(B)**. Bubble plots demonstrate the correlation between *NTRK* genes expression and methylation levels. The bubble size positively correlates with the significance of FDR. The black outline border indicates FDR≤0.05. **(C)**. Bubble plots depict the methylation differences of *NTRK* genes between tumor and normal samples. Blue dots and red color indicate methylation downregulation and upregulation in tumors, respectively. **(D)**. Figure summarizes the correlations between CNV and *NTRK* genes expression in pan-cancer. **(E)**. Percentage of cancers in which *NTRK1/2/3* expression has a potential impact on pathway activity is shown. Pathway A and I represent activation or inhibition of this pathway. **(F)**. Pie chart showing the percentage of different types of CNV in *NTRK1/2/3* in a given cancer, with different colors representing different CNV types. **(G)**. The relationship between *NTRK* genes expression and patient prognosis (OS, DSS, PFI) in pan-cancer. TPM, transcripts per million; FDR, false discovery rate; CNV, copy number variation; OS, overall survival; DSS, disease-specific survival; PFI, progression-free interval. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. ns, no significance.

10.3389/fphar.2024.1329409

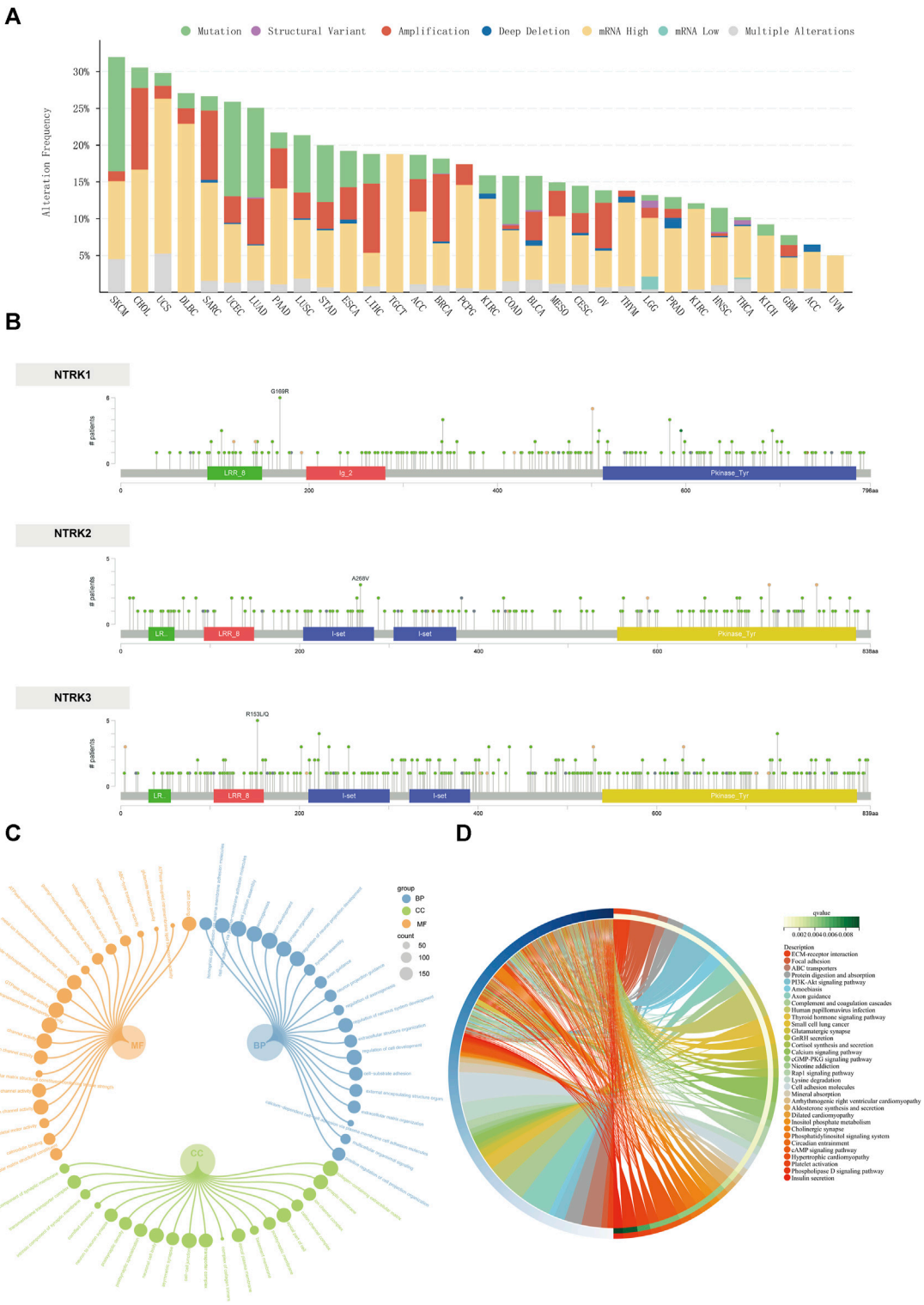


FIGURE 3
Genomic alterations of the *NTRK* genes at the pan-cancer level. **(A)**. The alteration frequency of *NTRK* genes across 32 TCGA tumor types. **(B)**. Amino acid mutation of in TCGA cancers. The GO and KEGG enrichment analyses of differentially altered genes between *NTRK*-gene-altered and unaltered groups are visualized using circular subgroup plot **(C)** and chord plot **(D)**. GO, gene ontology; BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

respectively (Figure 2A). Notably, there was a consistent trend towards significant downregulation of three *NTRK* genes expression in 15 tumor types ($p < 0.05$). However, in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC) and thymoma (THYM), they were significantly upregulated. The full names of the 33 cancer abbreviations were shown in Supplementary Table S1.

There is accumulating evidence indicating that both CNV and DNA methylation reshapes gene expression repertoire in cancers (Valsesia et al., 2012; Arechederra et al., 2018; Hammam et al., 2020; Ji et al., 2020). We therefore explored the relationship between *NTRK* genes expression and CNV, DNA methylation in different tumor types. Figure 2B indicated that in most tumor types, methylation levels and *NTRK1/2/3* gene expression values were significantly negatively correlated (Spearman's correlation<0, false discovery rate [FDR]<0.05). Moreover, we compared the methylation difference between tumor and normal and found that methylation of the *NTRK* genes was upregulated in various types, such as lung adenocarcinoma (LUAD), breast invasive carcinoma (BRCA), and head and neck squamous cell carcinoma (HNSC) (Figure 2C). Additionally, we evaluated the relationship between CNV and *NTRK* genes expression and observed a significant correlation in some tumors such as sarcoma (SARC), BRCA, and testicular germ cell tumors (TCGT) (Figure 2D). The comprehensive constitution of the heterozygous/homozygous CNV of *NTRK1/2/3* in each cancer was displayed in Figure 2F.

We also analyzed the roles of *NTRK* genes in cancer pathways. The results suggested that *NTRK1* had a relatively strong activation of apoptosis and a strong activation of epithelial-mesenchymal transition (EMT). *NTRK2* and *NTRK3* shared similar pathway activity. They exhibited strong inhibitory effect on apoptosis and cell cycle, and strong activation of EMT. Overall, *NTRK* genes had strong activating effect on EMT and potent inhibitory effect on the cell cycle (Figure 2E). The relationship between *NTRK* genes expression and patient prognosis was evaluated, as well. Increased *NTRK1* expression was a risk factor for uveal melanoma (UVM), and high *NTRK2* and *NTRK3* expression was associated deceased OS, DSS, and PFI in bladder urothelial carcinoma (BLCA). However, elevated *NTRK2* expression was protective in BRCA (Figure 2G).

3.2 Somatic mutation analysis of *NTRK* genes

As shown in Figure 3A, among the 32 cancer types observed, the frequency of mutations in the *NTRK* genes was not low overall. The frequency of mutations in the *NTRK* gene exceeded 15% in 19 cancer types. The mutation types were mainly composed of mRNA high, mutation, and amplification. The most frequent cancer types with *NTRK* genes alteration were skin cutaneous melanoma (SKCM) (31.98%), cholangiocarcinoma (CHOL) (30.56%), uterine carcinosarcoma (UCS) (29.82%), DLBC (27.08%), and SARC (26.67%). Instead, the mutation frequency of the *NTRK* genes in kidney chromophobe (KICH) (9.23%), glioblastoma multiforme (GBM) (7.77%), adrenocortical carcinoma (ACC) (6.5%), and UVM (5%) was relatively low, not exceeding 10%. Strikingly, all mutations in the *NTRK* gene in TCGT and UVM were mRNA high. In Figure 3B, the type, location and number of *NTRK1/2/3* genetic alterations could further be observed. The hot spot mutation sites G169R (located in the linker) of *NTRK1*, A268V (located in the I-set) of *NTRK2*, and R153L/Q (located in the LRR-8) of *NTRK3* were identified in 6, 3, and 5 patients. In general, the types of mutations at different amino acid sites of the *NTRK1/2/3* gene were primarily missense mutations (Figure 3B). Further analysis of the mutations (Supplementary Figure S1A) revealed that most of the *NTRK1/2/3* mutations were located in the structural domains of the Pkinase-Tyr and LRR-8. Moreover, the I-set domain in *NTRK2/3* also contained close to a quarter of the number of mutations. The Ig-2 domain was specific to *NTRK1* and contained about 5% of the mutations. In the final, we counted the genomic alterations of *NTRK1/2/3* in the TCGA pan-cancer cohort in each patient. Of these, 645, 451, and 584 patients contained alterations in only one of the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. There were still 21 individuals with genomic alteration for *NTRK1/2/3* simultaneously (Supplementary Figure S1B).

We also screened for altered genes that were significantly enriched in the *NTRK*-gene-altered group (compared to the unaltered group). The top 20 genes with the highest mutation frequencies in the *NTRK*-gene-altered group were displayed in Supplementary Figure S1C, and the full list of genes was provided in Supplementary Table S2. Genes with significant mutation differences were involved in biological processes including cell junctions, cell adhesion; involved in cellular components including extracellular matrix, synapses and ion channels; involved in molecular functions including cytoskeletal motility and ion channel activity (Figure 3C). Similarly, the signaling pathways and diseases in which these genes may be engaged included hormone synthesis and delivery (thyroid hormones, aldosterone hormone, insulin), some traditional signaling pathways (PI3K/Akt, cGMP-PKG, cAMP, etc.), as well as small-cell lung cancer, and human papillomavirus infection (Figure 3D). All enrichment analysis results were presented in Supplementary Table S3.

3.3 Fusion gene analysis

We detected fusion transcripts of the *NTRK1/2/3* genes in pan-cancer through the TCGA Fusion Gene Database with high credibility (Supplementary Figure S2). In total, transcripts of *NTRK* fusion genes were detected in 11 tumor types, especially in thyroid carcinoma (THCA, n = 15), and brain lower grade glioma (LGG, n = 5). The *NTRK3* gene had the highest number of fusion transcripts (n = 18). *NTRK3-ETV6* (n = 10) had the highest percentage of all fusion pairs, especially in THCA (n = 6). Chromosomes 12 and 15 were the major chromosomes for 5′gene junction and 3′gene junction, respectively. The great majority of these *NTRK* fusion transcripts were classified as in-frame transcripts, while two fusion transcripts (*NTRK2-RASEF*, and *FAT1-NTRK3*) were classified as out-of-frame and one (*PAN3-NTRK2*) was classified as 5UTR-CDS. The complete data was available in Supplementary Table S4.

3.4 Landscape analysis of clinical trials of larotrectinib and entrectinib

First-generation *NTRK* inhibitors (larotrectinib and entrectinib) treat patients with *NTRK* fusion-positive cancers with high remission rates, irrespective of tumor histology (Cocco et al., 2018). We have subsequently employed the MCG database to

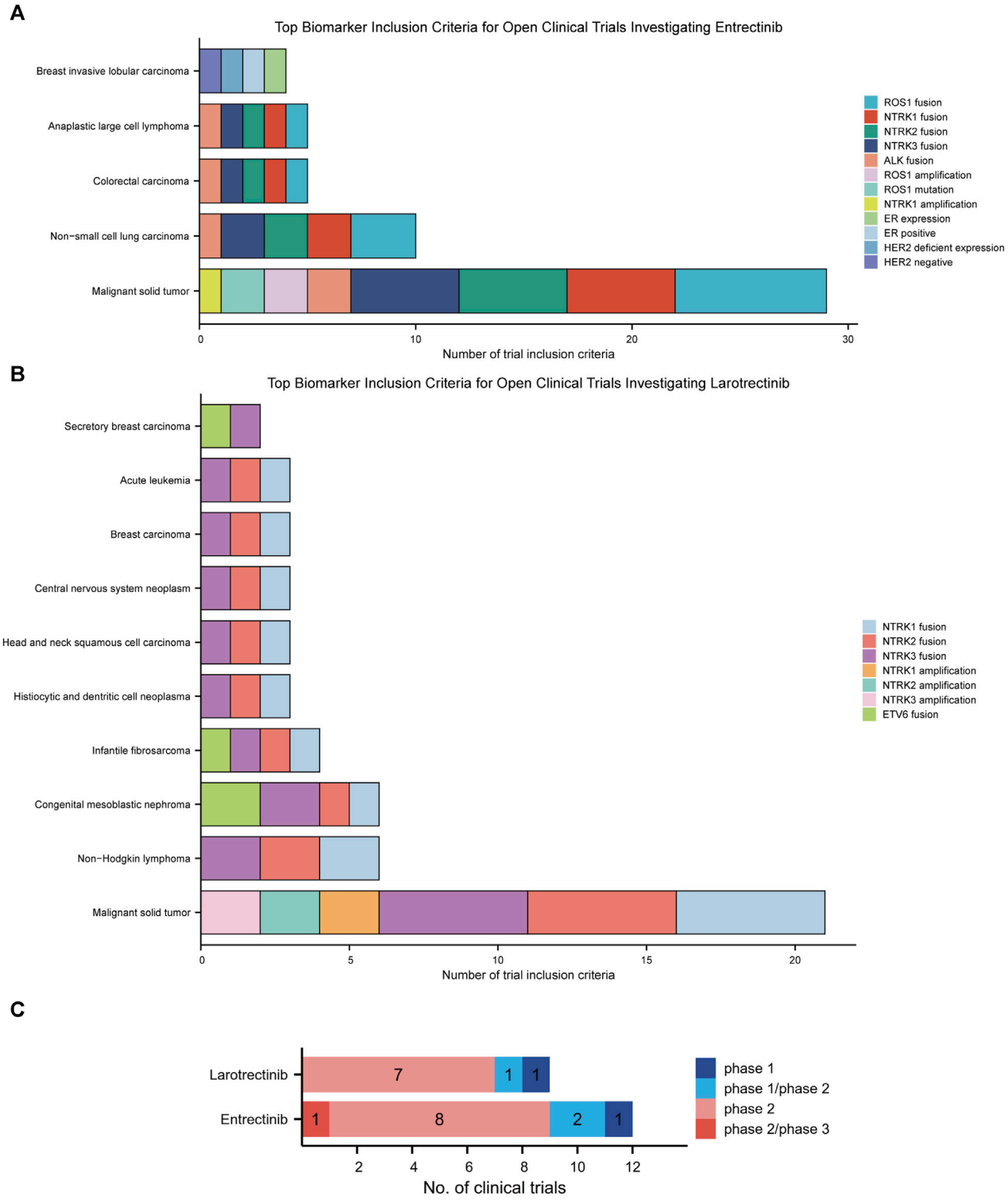


FIGURE 4
This chart shows the top biomarkers most frequently included in clinical trials investigating larotrectinib **(A)** and entrectinib **(B)**, and the types of cancers associated with those biomarkers. **(C)**. Current clinical trial status of larotrectinib and entrectinib.

explore the investigation of these two drugs in clinical trials. The most frequent biomarkers in clinical trials investigating entrectinib were *ROS1* fusion, *NTRK1* fusion, and *NTRK2* fusion (Figure 4A). For larotrectinib, they were *NTRK1* fusion, *NTRK2* fusion, and *NTRK3* fusion (Figure 4B). Malignant solid tumors (n = 29), non-small cell lung carcinoma (n = 10), and colorectal carcinoma (n = 5) were the most common diseases studied in entrectinib clinical trials (Figure 4A), while malignant solid tumor (n = 21),

10.3389/fphar.2024.1329409

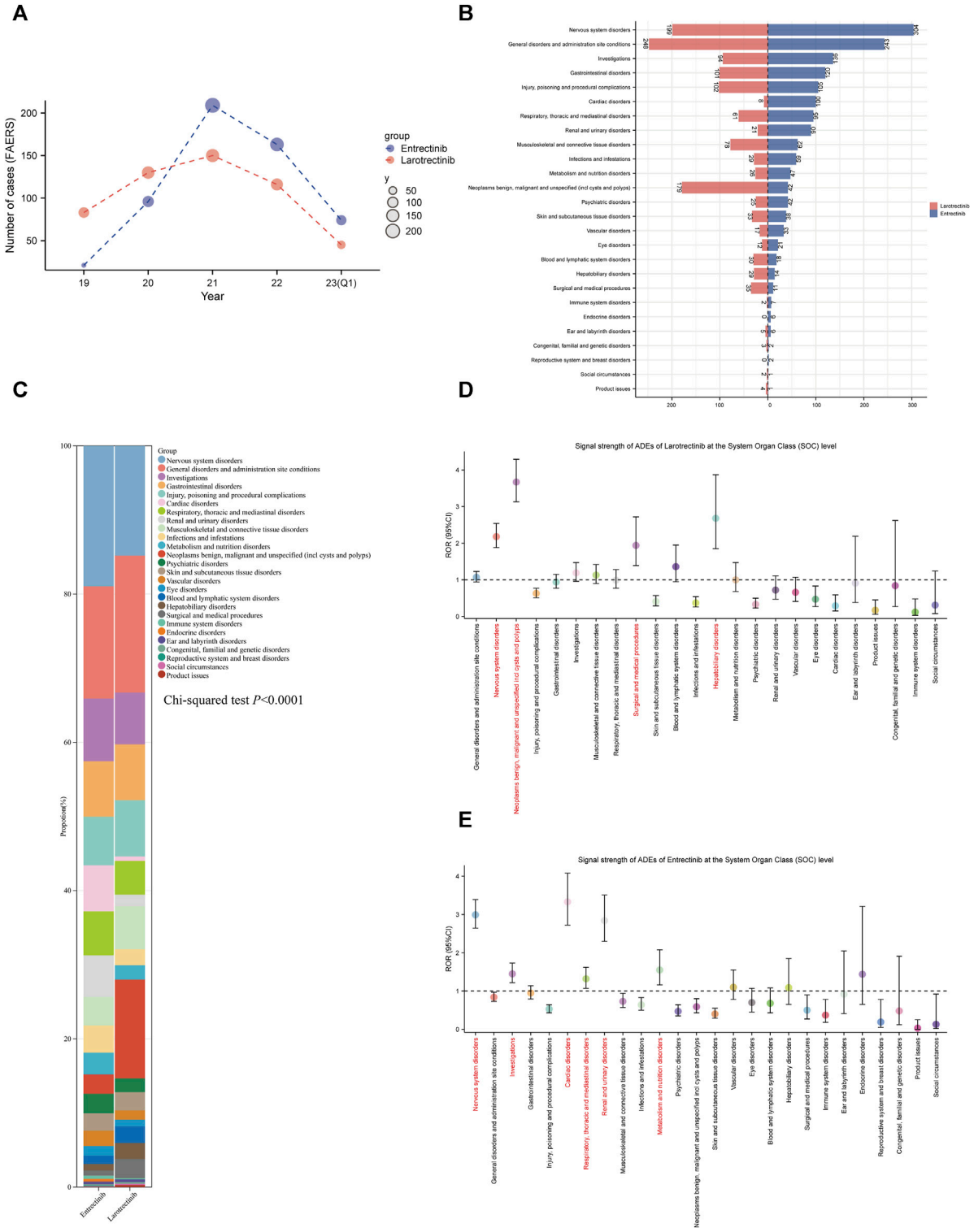


FIGURE 5
Signal detection at the SOC level. **(A)**. Annual distribution of ADE reports of the two first-generation *NTRK* inhibitors (entrectinib, blue; larotrectinib, red), from 2019 Q1 to 2023 Q1. **(B)**. Number of ADE reports for entrectinib and larotrectinib at the SOC level. **(C)**. The bar scale graph shows the percentage of ADEs at the SOC level. The ROR values and their corresponding 95% confidence intervals for larotrectinib **(D)** and entrectinib **(E)** are displayed for different levels of SOC. ADEs, adverse drug events; SOC, System Organ Class; Q1, first quarter; ROR, reporting odds ratio.

non-Hodgkin lymphoma (n = 6), and congenital mesoblastic nephroma (n = 6) were the most prevalent diseases studied in larotrectinib clinical trials (Figure 4B).

Nine clinical trials studied larotrectinib, of which 9 were open and 0 were terminated. Of the trials that studied larotrectinib, 1 was early phase 1, 1 was phase 1/phase 2, and 7 were phase 2. Twelve

10.3389/fphar.2024.1329409

TABLE 2 The demographic baseline data for adverse drug event (ADE) reports involving entrectinib and larotrectinib as the primary suspect (PS) drugs.

Characteristics	Entrectinib		Characteristics	Larotrectinib	
	Case number, n	Case proportion, %		Case number, n	Case proportion, %
Age (years)			Age (years)		
<18	32	5.7	<18	7	1.3
18–64	22	3.9	18–64	22	4.2
>64	2	0.3	>64	17	3.3
Unknown	507	90.1	Unknown	478	91.2
Gender			Gender		
Female	286	50.8	Female	222	42.4
Male	237	42.1	Male	220	42.0
Unknown	40	7.1	Unknown	82	15.6
Weight			Weight		
<80	163	29.0	<80	18	3.4
80–100	23	4.1	80–100	5	1.0
>100	13	2.3	>100	1	0.2
Unknown	364	64.6	Unknown	500	95.4
Reported Countries (top five)			Reported Countries (top five)		
US	278	49.4	US	308	58.8
JP	139	24.7	FR	38	7.3
DE	14	2.5	MX	25	4.8
IL	13	2.3	CA	18	3.4
FR	12	2.1	CH	15	2.9
Reported person			Reported person		
Consumer	180	32.0	Consumer	139	26.5
Health professional	369	65.5	Health professional	384	73.3
Unknown	14	2.5	Unknown	1	0.2
Indications (Top five)			Indications (Top five)		
Non-small cell lung cancer	167	29.7	Thyroid cancer	28	5.3
Lung neoplasm malignant	107	19.0	Neoplasm malignant	19	3.6
Neoplasm	37	6.6	Lung neoplasm malignant	18	3.4
Neoplasm malignant	23	4.1	Neoplasm	17	3.2
Lung adenocarcinoma	14	2.5	Sarcoma	14	2.7
Serious Outcomes			Serious Outcomes		
Other serious outcomes (OT)	229	44.2	Other serious outcomes (OT)	238	56.7
Hospitalization (HO)	166	32.0	Hospitalization (HO)	95	22.6
Death (DE)	103	19.9	Death (DE)	80	19.0
Life-threatening (LT)	14	2.7	Life-threatening (LT)	5	1.2
Disability (DS)	6	1.2	Disability (DS)	2	0.5

clinical trials have studied entrectinib, 12 of which were open trials and 0 of which were closed trials. Of these trails, 1 was phase 1, 2 were phase 1/phase 2, 8 were phase 2, and 1 was phase 2/phase 3 (Figure 4C).

3.5 Adverse drug events (ADEs) related to entrectinib and larotrectinib in the FAERS database

Subsequently, we conducted pharmacovigilance analyses in the FAERS database to investigate the signals of ADEs closely associated with the use of two first-generation *NTRK* inhibitors. In terms of the annual ADEs reported, entrectinib exhibited a steeper increase compared to larotrectinib, with both reaching their peaks in 2021. From that point, entrectinib continued to receive more ADE reports than larotrectinib (Figure 5A). Analysis of the baseline information for these ADEs revealed that the age group with the highest proportion of entrectinib users was below 18 years (5.7%), while for larotrectinib, it was the age group of 18–64 years (4.2%) (Table 2). However, it is important to note that approximately 90% of the reports had unknown age group information for both drugs. Regarding gender distribution, entrectinib had a higher proportion of female reports for ADEs (50.8%), whereas larotrectinib had a similar percentage of reports from males (42.0%) and females (42.4%). The top three countries contributing the highest number of reports were the United States (49.4%), Japan (24.7%), and Germany (2.5%) for entrectinib, and the United States (58.8%), France (7.3%), and Mexico (4.8%) for larotrectinib. In terms of report sources, health professionals accounted for the majority of reports for both drugs (65.5% for entrectinib and 73.3% for larotrectinib). While the primary indication for entrectinib was non-small cell lung carcinoma (29.7%), thyroid cancer (5.3%) was the main indication for larotrectinib. It is noteworthy that entrectinib (32.0%) had a higher proportion of reports of hospitalization compared to larotrectinib (22.6%) in cases of serious outcomes. However, both drugs exhibited similar proportions of reports for death, life-threatening events, and disability (Table 2).

3.6 Signals detection at the System Organ Class (SOC) level

Figure 5B presented the reported numbers of the two *NTRK* inhibitors at the SOC level. For entrectinib and larotrectinib, ADEs were reported at 26 and 24 organ systems, respectively. Interestingly, no ADEs were reported for larotrectinib at the "endocrine disorder" and "reproductive system and breast disorders" SOCs (n = 0). In larotrectinib, the top three SOCs in terms of ADEs numbers were nervous system disorders (n = 304), general disorders and administration site conditions (n = 243), and investigations (n = 136). In entrectinib, they were, general disorders and administration site conditions (n = 248), nervous system disorders (n = 199), and neoplasms benign, malignant and unspecified (n = 179) (Figure 5B). Comparing the composition of each SOC between the two drugs, we found that entrectinib had a higher percentage of "nervous system disorders" (18.94% *versus* [vs.] 14.82%), "cardiac disorders" (6.23% vs. 0.60%), and "renal and urinary disorders" (5.61% vs. 1.56%) than larotrectinib, while "general disorders and administration site conditions" (18.47% vs. 15.14%) and "neoplasms benign, malignant and unspecified" (13.33% vs. 2.62%) were higher for larotrectinib. Statistical analyses also suggested that there was a significant difference in the proportion of SOCs between the two drugs ($p < 0.0001$, Figure 5C).

The disproportionality results of the three different algorithms at various SOC levels were shown in Table 3. Wherein, the number of SOCs meeting at least one algorithm signal value threshold was 4 and 6 for larotrectinib and entrectinib, respectively. For larotrectinib, they were nervous system disorders (SOC code: 10029205, ROR 2.18 [1.88–2.54]), neoplasms benign, malignant and unspecified (SOC code:10029104, ROR 3.67 [3.13–4.29]), hepatobiliary disorders (SOC code:10019805, ROR 2.68 [1.85–3.87]), and surgical and medical procedures (SOC code:10042613, ROR 1.94 [1.39–2.72]). For entrectinib, they were nervous system disorders (SOC code:10029205, ROR 2.99 [2.64–3.39]), investigations (SOC code:10022891, ROR 1.45 [1.22–1.73]), cardiac disorders (SOC code:10007541, ROR 3.33 [2.72–4.08]), respiratory, thoracic and mediastinal disorders (SOC code:10038738, ROR 1.32 [1.07–1.62]), renal and urinary disorders (SOC code:10038359, ROR 2.84 [2.30–3.51]), and metabolism and nutrition disorders (SOC code:10027433, ROR 1.55 [1.16–2.08]). To improve visualization, Figures 5D,E depicted the signal strength (ROR, with 95% confidence interval [CI]) at the SOC level for larotrectinib and entrectinib, respectively.

3.7 Differences in ADEs of entrectinib and larotrectinib at the preferred term (PT) level

After satisfying the thresholds of the three algorithms simultaneously, we detected 67 entrectinib-related ADEs and 57 larotrectinib-related ADEs at the PT level, respectively. We sorted these screened ADEs by case number and IC025 value, respectively. For entrectinib, signals including dizziness (n = 58), renal impairment (n = 35), and taste disorder (n = 26) had the highest reported cases, which suggested that they were more common in reports of ADEs following entrectinib dosing (Figure 6A). Dysplasia (6.13), ataxia (4.57), and troponin I increased (4.14) had the highest IC025 values, indicating that they were more associated with entrectinib dosing than the other drugs (Figure 6D). For larotrectinib, dizziness (n = 35), neuropathy peripheral (n = 26), and paraesthesia (n = 17) had the largest number of reports (Figure 6B), while adenocarcinoma of salivary gland (9.43), astrocytoma (7.51), and glioblastoma multiforme (6.98) had the highest IC025 values (Figure 6E).

Besides, a large number of unexpected signals were identified and highlighted in prominent colors. These signals need to be refined in subsequent updates of the drug instruction. After taking the intersection of ADEs for both drugs, we found a total of 11 overlapping signals (Figure 6C). Of them, renal impairment, taste disorder, disease progression, oedema, and ascites were intersected unexpected signals, which needed to be given sufficient attention in subsequent clinical studies. All signals and calculations that satisfied the thresholds of the three algorithms were listed in Supplementary Table S5.

TABLE 3 Signal detection at the SOC level. Lower right marker 1, entrectinib vs all other drugs; Lower right marker 2, larotrectinib vs all other drugs. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of the 95% CI of IC; SOC, System Organ Class.

SOC name	Case number1	Case number2	ROR1 (95 CI%)	ROR2 (95 CI%)	PRR1	PRR2	χ21	χ22	ICO251	ICO252
Nervous system disorders	304	199	2.99 (2.64–3.39)	2.18 (1.88–2.54)	2.61	2.01	326.03	108.46	−0.28	−0.66
General disorders and administration site conditions	243	248	0.84 (0.73–0.97)	1.07 (0.94–1.23)	0.87	1.06	6.12	1.03	−1.88	−1.58
Investigations	136	94	1.45 (1.22–1.73)	1.19 (0.96–1.47)	1.41	1.17	17.43	2.60	−1.17	−1.44
Gastrointestinal disorders	120	101	0.95 (0.79–1.14)	0.94 (0.77–1.15)	0.95	0.94	0.32	0.38	−1.74	−1.75
Injury, poisoning and procedural complications	105	102	0.53 (0.43–0.64)	0.63 (0.51–0.77)	0.56	0.65	41.83	21.04	−2.51	−2.28
Cardiac disorders	100	8	3.33 (2.72–4.08)	0.29 (0.15–0.59)	3.18	0.30	152.70	13.48	0.01	−3.41
Respiratory, thoracic and mediastinal disorders	95	61	1.32 (1.07–1.62)	0.99 (0.77–1.28)	1.30	0.99	6.77	0	−1.29	−1.68
Renal and urinary disorders	90	21	2.84 (2.30–3.51)	0.72 (0.47–1.11)	2.74	0.73	101.26	2.20	−0.22	−2.13
Musculoskeletal and connective tissue disorders	62	78	0.73 (0.57–0.94)	1.13 (0.90–1.42)	0.74	1.12	6.03	1.11	−2.10	−1.50
Infections and infestations	59	29	0.64 (0.50–0.83)	0.37 (0.26–0.54)	0.66	0.39	11.22	29.68	−2.27	−3.03
Metabolism and nutrition disorders	47	26	1.55 (1.16–2.08)	1.00 (0.68–1.47)	1.54	1.00	9.02	0	−1.05	−1.67
Psychiatric disorders	42	25	0.47 (0.35–0.64)	0.33 (0.23–0.50)	0.49	0.35	24.18	32.39	−2.71	−3.19
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	42	179	0.59 (0.43–0.80)	3.67 (3.13–4.29)	0.60	3.31	11.94	300.84	−2.41	0.06
Skin and subcutaneous tissue disorders	38	33	0.40 (0.29–0.55)	0.41 (0.29–0.57)	0.41	0.42	33.70	28.10	−2.94	−2.92
Vascular disorders	33	17	1.10 (0.78–1.55)	0.66 (0.41–1.07)	1.09	0.67	0.27	2.88	−1.54	−2.25
Eye disorders	21	12	0.70 (0.45–1.07)	0.47 (0.27–0.83)	0.70	0.48	2.70	7.02	−2.18	−2.74
Blood and lymphatic system disorders	18	30	0.68 (0.43–1.08)	1.36 (0.95–1.95)	0.68	1.35	2.70	2.80	−2.22	−1.23
Hepatobiliary disorders	14	29	1.09 (0.65–1.85)	2.68 (1.85–3.87)	1.09	2.64	0.11	29.83	−1.54	−0.27
Surgical and medical procedures	11	35	0.50 (0.27–0.90)	1.94 (1.39–2.72)	0.50	1.92	5.59	15.55	−2.67	−0.73
Immune system disorders	7	2	0.37 (0.18–0.78)	0.12 (0.03–0.48)	0.38	0.12	7.38	12.92	−3.08	−4.71
Ear and labyrinth disorders	6	5	0.92 (0.41–2.05)	0.91 (0.38–2.19)	0.92	0.91	0.04	0.05	−1.79	−1.81
Endocrine disorders	6	0	1.44 (0.65–3.21)	NA	1.44	NA	0.80	NA	−1.14	NA
Reproductive system and breast disorders	2	0	0.19 (0.05–0.78)	NA	0.20	NA	6.64	NA	−4.02	NA

(Continued on following page)

TABLE 3 (*Continued*) Signal detection at the SOC level. Lower right marker 1, entrectinib vs all other drugs; Lower right marker 2, larotrectinib vs all other drugs. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of the 95% CI of IC; SOC, System Organ Class.

SOC name	Case number1	Case number2	ROR1 (95 CI%)	ROR2 (95 CI%)	PRR1	PRR2	χ21	χ22	ICO251	ICO252
Congenital, familial and genetic disorders	2	3	0.48 (0.12–1.91)	0.84 (0.27–2.62)	0.48	0.84	1.14	0.09	−2.73	−1.91
Product issues	1	4	0.03 (0.00–0.25)	0.17 (0.06–0.45)	0.04	0.17	26.60	16.32	−6.48	−4.21
Social circumstances	1	2	0.13 (0.02–0.92)	0.31 (0.08–1.24)	0.13	0.31	5.82	3.08	−4.61	−3.35

3.8 Time to onset (TTO) analysis of all ADEs

Recognizing the onset time of these ADEs can enable healthcare professionals better target their post-medication monitoring. After data filtering (removing missing and incorrect reporting times), 243 and 113 TTO reports were collected related to entrectinib and larotrectinib, respectively. The median TTO for entrectinib and larotrectinib was 16 days (Figure 7E) and 44 days (Figure 7F). Observing these TTO at the SOC level, we noticed that the SOCs with longer onset after entrectinib administration included "blood and lymphatic system disorders" (median TTO: 23 days), and "neoplasms benign, malignant and unspecified" (median TTO: 17 days), while "psychiatric disorders" (median TTO: 1 day), "eye disorders" (median TTO: 4 days), and "gastrointestinal disorders" (median TTO: 4 days) had shorter onset (Figure 7A). For larotrectinib, "infections and infestations" (median TTO: 242 days) and "neoplasms benign, malignant and unspecified" (median TTO: 101 days) had longer onset time, while "psychiatric disorders" (median TTO: 4 days), "skin and subcutaneous tissue disorders" (median TTO: 8 days), and "nervous system disorders" (median TTO: 9 days) had shorter onset time (Figure 7B). The specific statistical description of TTO was in Supplementary Table S6.

Concerning the distribution of ADEs over time, Figures 7C,D indicated that the majority of ADEs occurred within the first month after *NTRK* inhibitors use (n = 147, 60.5% for entrectinib; n = 53, 46.9% for larotrectinib). As time was delayed, the number of ADEs decreased but leveled off. Of note, our data showed that ADEs could still occur after 1 year of drug administration (n = 25, 10.3% for entrectinib; n = 10, 8.9% for larotrectinib) (Supplementary Table S6). The Weibull shape parameter analysis revealed calculated shape parameters β) of 0.56 (0.51–0.61) for entrectinib (Figure 7E) and 0.73 (0.62–0.84) for larotrectinib (Figure 7F), both with β values <1, indicating an early failure type. This suggested that for both *NTRK* inhibitors, the incidence of ADE decreased over time.

4 Discussion

Precision medicine endeavors to develop medical interventions personalized to an individual's genetic, environmental, and lifestyle factors (Wahida et al., 2023). In recent years, with the rapid advancement of precision medicine, there has been a shift in clinical trials from being focused on specific tumor types to being oriented towards the genome and agnostic to histology (Fountzilas et al., 2022). In this broader context, genomics offers valuable insights into identifying dysregulated genes, associated pathways, and histological knowledge within complex disease pathology. Clinical trials play a crucial role in translating genomic evidence into effective drug treatments, bridging the gap between bench research and bedside application (Knoepfler, 2015). Pharmacovigilance, as a critical component of drug safety regulation, is essential in identifying ADEs that occur during clinical trials and post-marketing, ensuring medication safety. Conversely, analyzing ADEs in isolation without understanding the underlying molecular etiology of the observed signals can lead to "fragmentation" in the relationship between ADEs and genomic alterations. By integrating genomic-level evidence and participant target data from clinical trials, this fragmentation can be partially mitigated, aiding in the identification of high-risk individuals and populations for ADEs, thus enhancing drug safety, efficacy, and overall public health (Zhou et al., 2023). Recently, studies have emerged linking genomics and pharmacovigilance. For instance, Jing et al. assessed the relationship between multiple genomic factors and immune-associated adverse events in various cancer types by combining genomic data with pharmacovigilance data (Jing et al., 2020). In our study, we conducted a comprehensive mapping of the *NTRK* genome, utilizing multi-omics data from TCGA, followed by a review of clinical trials involving *NTRK* inhibitors and an extensive pharmacovigilance analysis using the FAERS database. Our genomic evidence provides valuable insights into mitigating adverse effects of first-generation *NTRK* inhibitors, such as drug resistance, while pharmacovigilance analyses offer crucial additions by uncovering undetected adverse effects in clinical trials and aiding in optimal drug design at the genomic level.

4.1 *NTRK* genes expression and genomic alteration

After analyzing the expression profiles of *NTRK* genes, we observed that the mRNA expression of *NTRK1/2/3* was generally downregulated in tumor tissues compared to normal tissues across most cancers. Additionally, we identified a significant negative correlation between the hypermethylation state of the *NTRK* gene promoters and their mRNA expression in multiple cancer types. Previous studies have also reported aberrant methylation patterns in the *NTRK* genes in various cancers. For instance, Yamada et al. demonstrated elevated methylation levels in PRAD cell lines for

10.3389/fphar.2024.1329409

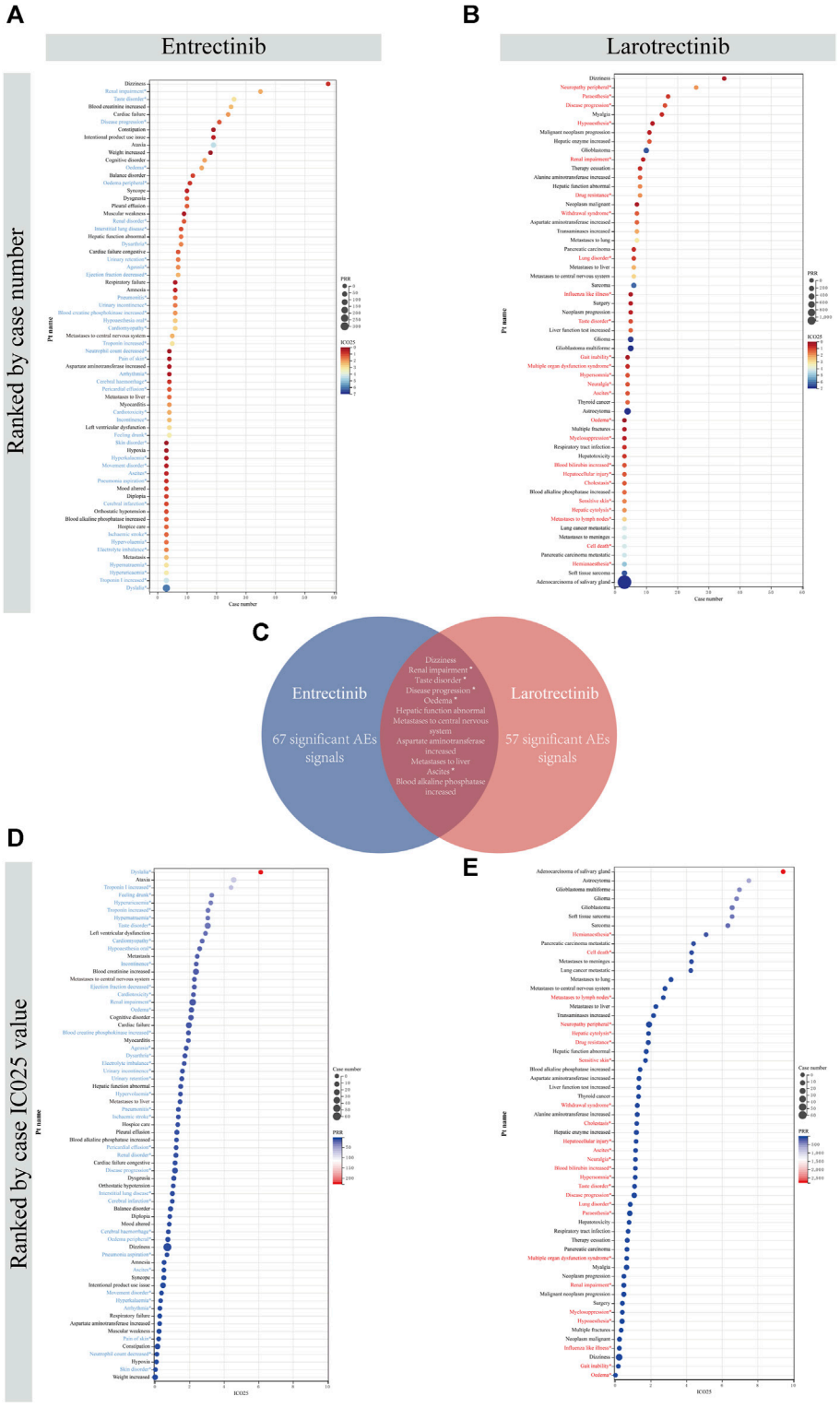
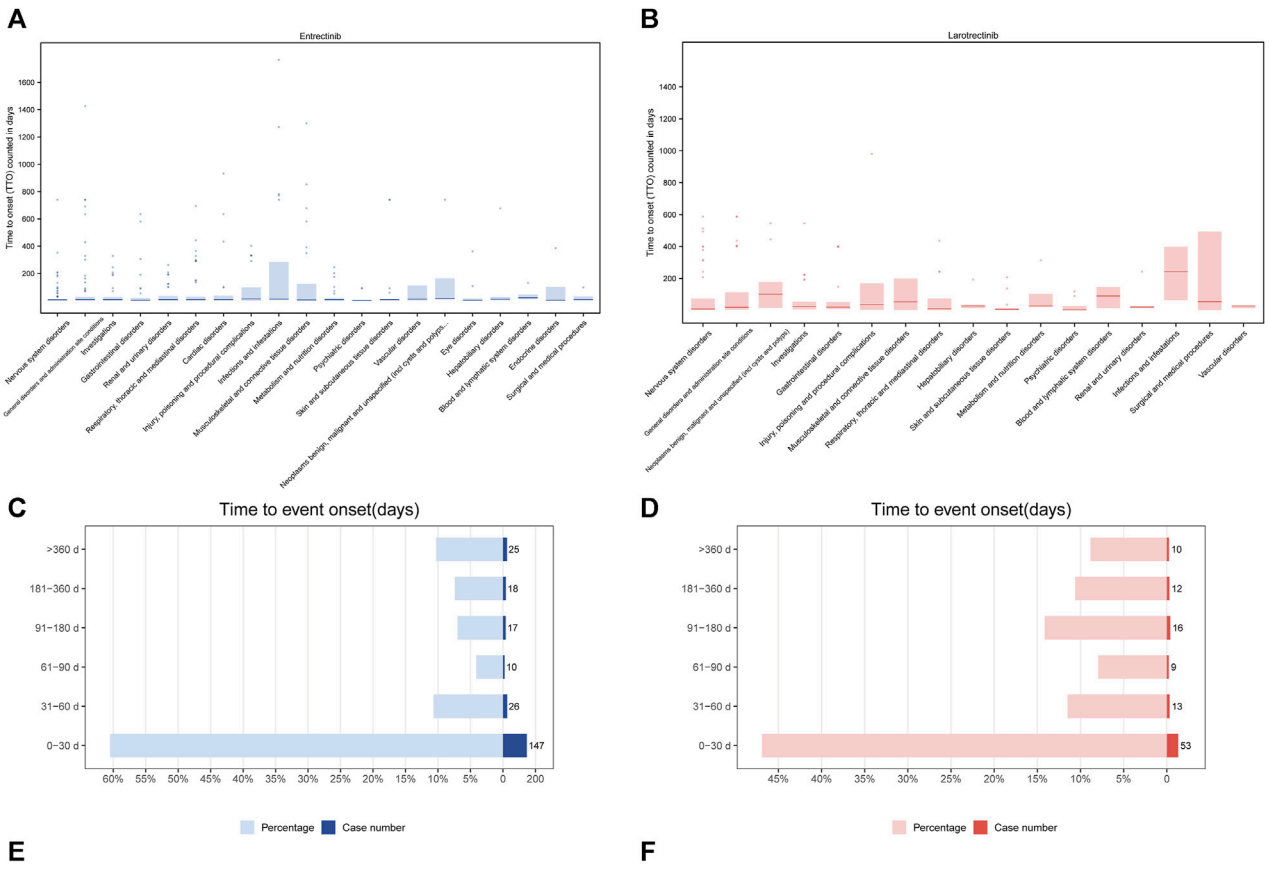


FIGURE 6
Comparison of signal values of the two first-generation *NTRK* inhibitors for ADEs at the PT level. All positive signals for entrectinib **(A)** and larotrectinib **(B)** are ranked by case number. **(C)**. Intersection of positive signals of two drugs. All positive signals for entrectinib **(D)** and larotrectinib **(E)** are ranked by IC025 value. An asterisk indicates that the signal is not indicated in the drug instruction. PRR, proportional reporting ratio; PT, preferred term; IC, information component; IC025, the lower limit of the 95% confidence interval of IC.

NTRK2, which resulted in decreased mRNA expression (Yamada et al., 2004). Similarly, hypermethylation status of *NTRK3* was reported in cervical cancer through analyzing sequencing data and further validated in clinical samples (Ji et al., 2021). Considering that epigenetic changes are an essential mechanism for regulating gene expression, aberrant DNA methylation might be



E

Cases	Weibull distribution						
	TTO (days)		Scale parameter		Shape parameter		Failure type
n	Media (IQR)	Min-Max	α	95% CI	β	95% CI	
243	16 (6-86.5)	0-1765	69.13	52.01-86.24	0.56	0.51-0.61	Early failure

F

Cases	Weibull distribution						
	TTO (days)		Scale parameter		Shape parameter		Failure type
n	Media (IQR)	Min-Max	α	95% CI	β	95% CI	
113	44 (7-136)	0-980	95.73	68.77-122.69	0.73	0.62-0.84	Early failure

FIGURE 7
Time to onset (TTO) analysis (counted in days). Box plot of the TTO at the SOC level for entrectinib **(A)** and larotrectinib **(B)**. Bold bar within the stick: median TTO; Lower end of the stick: 1/4 quantile of the TTO; Upper end of the stick: 3/4 quantile of the TTO. Number and proportion of all TTO reports in different time periods for entrectinib **(C)** and larotrectinib **(D)**. Weibull distribution test of TTO for entrectinib **(E)** and larotrectinib **(F)**. A TTO of 0 days signifies that the adverse event occurred on the same day as the start of treatment. IQR, interquartile range.

a plausible explanation for the dysregulation of *NTRK* gene expression (Arechederra et al., 2018). Moreover, CNV of DNA sequences can remodel gene structure, regulate gene expression, and facilitate significant phenotypic variation, including *NTRK* genes (Zhou et al., 2011; Tsai et al., 2016; Yu et al., 2021). Our study also uncovered the presence of CNVs in *NTRK* genes in many cancers, particularly in UCS and LUAD. This observation suggests that CNVs might influence the mRNA expression and function of these genes. However, further experiments are needed to validate this hypothesis, as there is limited evidence available from previous studies. Additionally, we observed a protective role of *NTRK3* in BRCA and PRAD, as well as a protective role of *NTRK2* in LGG. These findings are consistent with previous research and suggest that these genes may exert a protective effect through mechanisms such as immune cell recruitment, angiogenesis inhibition, and apoptosis induction (Bouzas-Rodriguez et al., 2010; Luo et al., 2013; Bagherabadi et al., 2022; Fang et al., 2023). However, we also noticed that high *NTRK* expression was hazardous for patients with BLCA and UVM. The varying prognoses in different types of tumors may be attributed to the fact that the function of *NTRK* genes is receptor-dependent. In the presence of a ligand, these genes transmit positive, proliferative signals, whereas they induce apoptosis in the absence of a ligand (Tauszig-Delamasure et al., 2007; Luo et al., 2013). Also, the effect of tumor heterogeneity and different splicing patterns on its function cannot be overlooked (Bagherabadi et al., 2022).

In our further exploration of the genomic alterations of *NTRK* genes, we discovered that in pan-cancer, alterations in these genes were predominantly characterized by high mRNA expression, amplifications, and mutations. The most frequently mutated amino acid sites in *NTRK1/2/3* were G169R, A268V, and R153L/Q, respectively. Prior research has indicated that non-fusion *NTRK* alterations, such as mutations and amplifications, are associated with the response to *NTRK* inhibitors and their therapeutic efficacy (Okamura et al., 2018; Amatu et al., 2019; Zito Marino et al., 2023). In particular, mutations at the G595R and G667C sites of *NTRK1*, and at G696A and G623R of *NTRK3*, have been associated with the acquisition of resistance to first-generation *NTRK* inhibitors, possibly due to the fact that these point mutations alter the three-dimensional conformation of the kinase's structural

domains, thereby reducing or abolishing binding to the inhibitors (Russo et al., 2016; Drilon et al., 2017; Somwar et al., 2020). In contrast, in a case report by Hempel et al., a patient with ESCA with *NTRK1* gene amplification experienced shrinkage of primary and metastatic tumors within 6 weeks after treatment with the *NTRK* inhibitor larotrectinib, accompanied by a decrease in tumor markers (Hempel et al., 2020). Finally, we also explored potential signaling pathways for genes co-altered with *NTRK* genes, which included PI3K/Akt, cGMP-PKG, and cAMP, etc. Mutational pathways co-activated with target genes are frequently observed in targeted therapies (Moore et al., 2020). For example, resistance to BRAF inhibitors is linked to the activation of the MAPK pathway, necessitating the co-administration of MEK inhibitors under certain circumstances (Yi et al., 2022). Likewise, combining *NTRK* inhibitors with co-mutational pathway inhibitors (such as PI3K inhibitors) could represent a potential therapeutic strategy for patients resistant to first-generation *NTRK* inhibitors. In conclusion, our study offers a comprehensive understanding of *NTRK* genomic alterations. While non-fusion alterations have not yet demonstrated consistent and long-lasting response to targeted therapies, they may still yield valuable insights into mechanisms of drug resistance.

4.2 Fusion mutations of *NTRK* genes

Structural rearrangements of the genome can lead to the formation of fusion genes, which possess oncogenic properties and subsequently result in the overexpression of aberrant proteins. These abnormal proteins are known to drive tumorigenesis and present potential targets for therapeutic intervention (Mitelman et al., 2007; Bastus et al., 2010; Best et al., 2018). While *NTRK* gene fusions occur at a low frequency in common cancer types like lung and colorectal cancers (<25%), they are observed at a high frequency in specific rare tumor types (>80%). These fusions activate downstream cell growth and proliferative pathways, thereby promoting tumorigenesis (Vaishnavi et al., 2015; Amatu et al., 2016; Amatu et al., 2019). Moreover, constitutively active TRK kinase generated by gene fusion becomes a target for the action of *NTRK* inhibitors (Wang et al., 2015; Khotskaya et al., 2017). Our study provided a comprehensive analysis of fusion mutations involving *NTRK* genes across various cancer types. We observed that the majority of these fusion mutations occurred in *NTRK3*, with THCA having the highest reported incidence. Among the fusion pairs, *ETV6-NTRK3* was found to have the highest percentage. Furthermore, most of these fusion mutations were in-frame mutations. Consistent with our findings, research studies have increasingly demonstrated the presence of the *ETV6-NTRK3* fusion in various tumor types, including glioblastoma, ductal carcinoma, fibrosarcoma, and THCA (Tognon et al., 2002; Bastos et al., 2018; Biswas et al., 2022; Jiang, 2022). Interestingly, the study by Kinnunen et al. employed proximity-labeled mass spectrometry to establish a stable, reliable association of the *ETV6-NTRK3* fusion with several key signaling pathways, including ERBB, IRS-1, and JAK/STAT (Kinnunen et al., 2023). As another of the more common and first reported *NTRK* fusion mutations, *TPM3-NTRK1* was initially identified in colorectal cancer (CRC) samples, and subsequent studies have confirmed that chromosomal rearrangements in this manner make patients with CRC highly sensitive to TRKA inhibitors (Martin-Zanca et al., 1986; Ardini et al., 2014; Créancier et al., 2015). Other fusion types, such as *SQSTM1-NTRK1*, although carried by only one patient with THCA in our study, a recent case report demonstrated that patients carrying *SQSTM1-NTRK1* had a 51% reduction in tumor burden after 18 months of treatment with larotrectinib, and this impressive efficacy continued (Bargas et al., 2022). Of course, we have identified other novel fusion types including *SQSTM1-NTRK2*, *FAT1-NTRK3*, and *AKAP13-NTRK3*, however the relevant reports are very limited so far. Whether they could become new targets for *NTRK* inhibitors needs to be validated in subsequent clinical trials (Bargas et al., 2022).

4.3 Detection of adverse drug event

Genomic evidence indicates that both larotrectinib and entrectinib are pan-TRK inhibitors, targeting TRKA, TRKB, and TRKC. However, it is important to note that these TRK receptors also play essential roles in neurodevelopment. Consequently, the use of these pan-TRK inhibitors may lead to treatment-related side effects due to the inhibition of TRK signaling in normal tissues (Bhangoo and Sigal, 2019). Our pharmacovigilance study revealed that entrectinib had positive signaling values at six SOC levels compared to four for larotrectinib. Of particular note, both entrectinib (ROR: 2.99 [2.64–3.39]) and larotrectinib (ROR: 2.18 [1.88–2.54]) had positive signal values at the “nervous system disorders”. Generally, neurological ADEs are primarily thought to be related to the on-target effects of TRK inhibitors (Kummar et al., 2023). Considering the critical role of *NTRK1* and *NTRK3* in the normal functioning of sensory neurons, their loss-of-function mutations may lead to dizziness, sensory abnormalities, headaches and gait disturbances (Cocco et al., 2018; Amatu et al., 2019). Another anticipated ADE is weight gain, due to the vital role of *NTRK2* in controlling energy balance and appetite (An et al., 2020; Houtz et al., 2021) Consistently, at the PT level, we also identified several common, drug-related on-target adverse reactions, including dizziness, constipation, ataxia, weight increased, balance disorder, and dysgeusia. These ADEs we identified are generally in line with previously reported adverse events in clinical trials of entrectinib. Although the majority of these treatment-related adverse events (TRAEs) were grade 1/2, weight gain (5%–10%) was considered the most common grade 3/4 event, and central nervous system toxicity was reported as the most severe TRAE (3%–4%) (Al-Salama and Keam, 2019; Doebele et al., 2020; Drilon et al., 2020; Dziadziuszko et al., 2021). Therefore, it is crucial to implement timely monitoring and provide appropriate guidance to patients. However, it is interesting to note that entrectinib has shown a potential protective effect in patients with tumors that may have a higher risk of central nervous system metastasis. This could be attributed to its ability to more easily penetrate the blood-brain barrier (Dziadziuszko et al., 2021; Frampton, 2021). How to balance adverse effects and potential benefits to optimize drug selection in the future also needs to be explored in depth.

Although previous clinical trials have shown similar safety profiles for both drugs, in our study we demonstrated that entrectinib had stronger signal values for “cardiac disorders”, “respiratory, thoracic and mediastinal disorders”, “renal and

urinary disorders" and "metabolism and nutrition disorders", while larotrectinib had stronger signal values for "neoplasms benign, malignant and unspecified", and "hepatobiliary disorders". For entrectinib, cardiac problem is the other most common type of severe TRAE (Drilon et al., 2020; Marcus et al., 2021). In a case of NSCLC with *ROS1* rearrangement, the patient developed drug-induced heart failure after treatment with entrectinib, and the symptoms improved after drug discontinuation (Otsu et al., 2022). Results from another previous pharmacovigilance analysis also revealed that *ALK* and *ROS1* inhibitors induced higher odds of cardiac conduction disease than other targeted therapies (Waliany et al., 2021). Moreover, at the PT level, we also detected positive signal values including "interstitial lung disease", "respiratory failure", and "pneumonitis" with a relatively high number of cases at the respiratory level, which may be due to the rich blood supply of the lungs, causing accumulation of the drug, or the release of toxic substances (Long and Suresh, 2020; Spagnolo et al., 2022). Elevated aminotransferase occurred in half of the adverse event reports during the clinical trials of larotrectinib and was also a primary cause of drug dose reductions (Drilon et al., 2018; Laetsch et al., 2018; Hong et al., 2020; Le et al., 2022). In light of these findings, it is important to conduct regular and dynamic monitoring of the patient's liver function and to administer suitable hepatoprotective agents. Additionally, we observed several ADEs related to neoplasm progression for larotrectinib, including "malignant neoplasm progression," "neoplasm malignant," and "metastases to lung". These adverse signals may be more associated with disease progression rather than being solely attributed to adverse reactions caused by larotrectinib. This is supported by the fact that a significant majority of patients experienced objective remission following treatment with the larotrectinib (Doebele et al., 2020; Doz et al., 2022; Drilon et al., 2022). In conclusion, our analysis has provided a comparative evaluation of the signal strength in different organs for both larotrectinib and entrectinib. This comprehensive assessment can contribute to a more detailed and proactive clinical medication monitoring approach, enhancing patient safety and optimizing the effectiveness of treatment.

4.4 Unexpected signals

Furthermore, our study revealed some unexpected signals. For entrectinib, we observed unexpected signals with a high number of cases, such as taste disorder and renal impairment. Furthermore, we identified unexpected signals with a low number of cases but a high signal intensity, including dyslalia and hyperuricemia. It is worth noting that taste disorder and dyslalia have been hypothesized to be a result of the potential on-target effects of *NTRK* inhibitors (Naik et al., 2010; Ma et al., 2011; Szobota et al., 2019). Hyperuricemia has been recognized in previous clinical trials as a serious toxicity induced by entrectinib treatment that required intervention, but the exact cause is unknown (Dziadziuszko et al., 2021; Marcus et al., 2021). Similarly, regarding larotrectinib, there were more case reports of neuropathy peripheral, paresthesia, and stronger signal strength for hemianesthesia, and drug-resistance. Regarding the mechanism of resistance to larotrectinib, in addition to being associated with mutations or altered pathway activation as described above, it may also relate to the mode of administration (e.g., intermittent dosing), which may require a combination of other drugs to overcome (Amatu et al., 2016; Cocco et al., 2019; Kummar et al., 2023). Remarkably, unexpected signals found in both drugs included, renal impairment, taste disorder, disease progression, edema, and ascites. Some previous clinical trials failed to detect the new signals, whereas our results complement the previous studies and are indicative of subsequent updates of drug instruction (Doebele et al., 2020; Hong et al., 2020; Doz et al., 2022). Furthermore, as both *NTRK* inhibitors are predominantly metabolized by the enzyme cytochrome P450 (CYP450), which has been strongly linked to hepatic and renal drug toxicity, investigating CYP450 site variation at the pharmacogenomic level could yield distinctive insights into the toxicity of *NTRK* inhibitors (Quintanilha et al., 2017; Wang et al., 2020).

It is important to note that while we have made certain genomic insights regarding the adverse effects (e.g., drug resistance) of first-generation *NTRK* inhibitors, more reliable conclusions about causality may require higher-level genetic evidence in the future. This could involve identifying single nucleotide polymorphism (SNP) loci significantly associated with ADEs through genome-wide association studies (Ghouse et al., 2022; Giles et al., 2022). Such an approach could enable the screening and identification of patients susceptible to adverse effects, thereby improving efficacy and concurrently mitigating adverse effects.

4.5 Time to onset analysis

Some ADEs can occur shortly after starting treatment, ranging from minutes to hours. However, other ADEs may manifest days, weeks, months, or even years after exposure. The timing of these events can vary depending on various factors, including the drug's pharmacokinetics and its metabolites, as well as the underlying pathophysiological mechanism of action (Leroy et al., 2014). Previous studies have provided information on various ADEs, but the precise timing of these events remains largely unknown. In our study, we found that both drugs exhibited earlier onset of ADEs in the SOC categories of "psychiatric disorders" and "nervous system disorders," while ADEs related to "infections and infestations" and "neoplasms benign, malignant, and unspecified" occurred later. However, there were notable differences between the two drugs. For instance, ADEs in the category of "musculoskeletal and connective tissue disorders" had a median time to onset of 6 days in entrectinib and 53 days in larotrectinib. In both drugs, these ADEs predominantly occurred within the first month of administration, with a progressive decrease in their probability of occurrence over time. This highlights the significance of early medication surveillance. Overall, our analysis provided valuable insights into the onset timing of ADEs for two *NTRK* inhibitors, facilitating a more meticulous approach to preventing or diagnosing the occurrence of ADEs.

Our study exhibits several strengths. Firstly, the comprehensive analysis of data from multiple sources contributes to a more thorough understanding of the *NTRK* genes. Secondly, the precise application of multiple analysis methods and the depth of the results further underscore the strength of this study. However, it is crucial to acknowledge certain limitations. Firstly, the small

sample sizes for specific cancer types may introduce bias into the analyses concerning these types of cancer. Moreover, the FAERS database does not establish a causal relationship between drug use and ADEs, and limited drug dosage information hindered our analysis of the correlation between ADEs and drug dosage. Lastly, due to the recent introduction of the two *NTRK* inhibitors to the market, reported ADEs were limited, necessitating further validation of our results with larger sample sizes in future studies.

5 Conclusion

This study delineated the genomic features of *NTRK*, encompassing expression, methylation, and gene fusion, through the analysis of multi-omics data. Subsequently, comprehensive analyses were conducted to compare the safety profiles of two first-generation *NTRK* inhibitors using the FAERS database. These analyses offer valuable insights for healthcare professionals, aiding their understanding of the mechanisms of resistance to *NTRK* inhibitors and facilitating the monitoring of adverse effects associated with entrectinib and larotrectinib.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

ZC: Conceptualization, Writing–original draft, Writing–review and editing. ZZ: Conceptualization, Writing–original draft, Writing–review and editing. DX: Formal Analysis, Writing–original draft. LW: Formal Analysis, Writing–original draft. FC: Formal Analysis, Writing–original draft. SL: Visualization, Writing–original draft. FZ: Visualization, Writing–original draft. RP: Visualization, Writing–original draft. SC: Visualization, Writing–original draft. HY: Visualization, Writing–original draft. JS: Writing–review and editing. YZ: Writing–review and editing. XY: Funding acquisition, Supervision, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the fund of "Project A of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU-2021-01)."

Acknowledgments

We are very grateful to the developers and maintainers of the various databases mentioned in the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1329409/full#supplementary-material

References

Al-Salama, Z. T., and Keam, S. J. (2019). Entrectinib: first global approval. *Drugs* 79 (13), 1477–1483. doi:10.1007/s40265-019-01177-y

Amatu, A., Sartore-Bianchi, A., Bencardino, K., Pizzutilo, E. G., Tosi, F., and Siena, S. (2019). Tropomyosin receptor kinase (TRK) biology and the role of NTRK gene fusions in cancer. *Ann. Oncol.* 30 (8), viii5–viii15. doi:10.1093/annonc/mdz383

Amatu, A., Sartore-Bianchi, A., and Siena, S. (2016). NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. *ESMO Open* 1 (2), e000023. doi:10.1136/esmoopen-2015-000023

An, J. J., Kinney, C. E., Tan, J.-W., Liao, G.-Y., Kremer, E. J., and Xu, B. (2020). TrkB-expressing paraventricular hypothalamic neurons suppress appetite through multiple neurocircuits. *Nat. Commun.* 11 (1), 1729. doi:10.1038/s41467-020-15537-w

Ardini, E., Bosotti, R., Borgia, A. L., De Ponti, C., Somaschini, A., Cammarota, R., et al. (2014). The TPM3-NTRK1 rearrangement is a recurring event in colorectal carcinoma and is associated with tumor sensitivity to TRKA kinase inhibition. *Mol. Oncol.* 8 (8), 1495–1507. doi:10.1016/j.molonc.2014.06.001

Arechederra, M., Daian, F., Yim, A., Bazai, S. K., Richelme, S., Dono, R., et al. (2018). Hypermethylation of gene body CpG islands predicts high dosage of functional oncogenes in liver cancer. *Nat. Commun.* 9 (1), 3164. doi:10.1038/s41467-018-05550-5

Bagherabadi, A., Hooshmand, A., Shekari, N., Singh, P., Zolghadri, S., Stanek, A., et al. (2022). Correlation of NTRK1 downregulation with low levels of tumor-infiltrating immune cells and poor prognosis of prostate cancer revealed by gene network analysis. *Genes* 13 (5), 840. doi:10.3390/genes13050840

Bailey, C., Peddie, D., Wickham, M. E., Badke, K., Small, S. S., Doyle-Waters, M. M., et al. (2016). Adverse drug event reporting systems: a systematic review. *Br. J. Clin. Pharmacol.* 82 (1), 17–29. doi:10.1111/bcp.12944

Bargas, S., Mc Leer, A., Mondet, J., Chabre, O., and Laramas, M. (2022). An impressive response with larotrectinib in a patient with a papillary thyroid carcinoma harboring an SQSTM1-NTRK1 fusion. *Eur. J. Endocrinol.* 186 (4), K5–K8. doi:10.1530/EJE-21-0509

Bastos, A. U., de Jesus, A. C., and Cerutti, J. M. (2018). ETV6-NTRK3 and STRN-ALK kinase fusions are recurrent events in papillary thyroid cancer of adult population. *Eur. J. Endocrinol.* 178 (1), 83–91. doi:10.1530/EJE-17-0499

Bastus, N. C., Boyd, L. K., Mao, X., Stankiewicz, E., Kudahetti, S. C., Oliver, R. T. D., et al. (2010). Androgen-induced TMPRSS2:ERG fusion in nonmalignant prostate epithelial cells. *Cancer Res.* 70 (23), 9544–9548. doi:10.1158/0008-5472.CAN-10-1638

Bate, A. (2007). Bayesian confidence propagation neural network. *Drug Saf.* 30 (7), 623–625. doi:10.2165/00002018-200730070-00011

Best, S. A., Harapas, C. R., Kersbergen, A., Rathi, V., Asselin-Labat, M.-L., and Sutherland, K. D. (2018). FGFR3-TACC3 is an oncogenic fusion protein in respiratory epithelium. *Oncogene* 37 (46), 6096–6104. doi:10.1038/s41388-018-0399-5

Bhangoo, M. S., and Sigal, D. (2019). TRK inhibitors: clinical development of larotrectinib. *Curr. Oncol. Rep.* 21 (2), 14. doi:10.1007/s11912-019-0761-y

Biswas, A., Rajesh, Y., Das, S., Banerjee, I., Kapoor, N., Mitra, P., et al. (2022). Therapeutic targeting of RBPJ, an upstream regulator of ETV6 gene, abrogates ETV6-NTRK3 fusion gene transformations in glioblastoma. *Cancer Lett.* 544, 215811. doi:10.1016/j.canlet.2022.215811

Borges, J. B., Oliveira, V. F. d., Ferreira, G. M., Los, B., Barbosa, T. K. A. A., Marçal, E. d.S. R., et al. (2021). Genomics, epigenomics and pharmacogenomics of familial hypercholesterolemia (FHBGEP): a study protocol. *Res. Soc. Adm. Pharm. RSAP* 17 (7), 1347–1355. doi:10.1016/j.sapharm.2020.10.007

Bouzas-Rodriguez, J., Cabrera, J. R., Delloye-Bourgeois, C., Ichim, G., Delcros, J.-G., Raquin, M.-A., et al. (2010). Neurotrophin-3 production promotes human neuroblastoma cell survival by inhibiting TrkC-induced apoptosis. *J. Clin. Investigation* 120 (3), 850–858. doi:10.1172/JCI41013

Brockmöller, J., and Tzvetkov, M. V. (2008). Pharmacogenetics: data, concepts and tools to improve drug discovery and drug treatment. *Eur. J. Clin. Pharmacol.* 64 (2), 133–157. doi:10.1007/s00228-007-0424-z

Cerami, E., Gao, J., Dogrusoz, U., Gross, B. E., Sumer, S. O., Aksoy, B. A., et al. (2012). The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2 (5), 401–404. doi:10.1158/2159-8290.CD-12-0095

Cocco, E., Scaltriti, M., and Drilon, A. (2018). NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat. Rev. Clin. Oncol.* 15 (12), 731–747. doi:10.1038/s41571-018-0113-0

Cocco, E., Schram, A. M., Kulick, A., Misale, S., Won, H. H., Yaeger, R., et al. (2019). Resistance to TRK inhibition mediated by convergent MAPK pathway activation. *Nat. Med.* 25 (9), 1422–1427. doi:10.1038/s41591-019-0542-z

Créancier, L., Vandenberghe, I., Gomes, B., Dejean, C., Blanchet, J.-C., Meilleroux, J., et al. (2015). Chromosomal rearrangements involving the NTRK1 gene in colorectal carcinoma. *Cancer Lett.* 365 (1), 107–111. doi:10.1016/j.canlet.2015.05.013

Cui, Z., Zou, F., Wang, R., Wang, L., Cheng, F., Wang, L., et al. (2023). Integrative bioinformatics analysis of WDHD1: a potential biomarker for pan-cancer prognosis, diagnosis, and immunotherapy. *World J. Surg. Oncol.* 21 (1), 309. doi:10.1186/s12957-023-03187-3

Doebele, R. C., Drilon, A., Paz-Ares, L., Siena, S., Shaw, A. T., Farago, A. F., et al. (2020). Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet. Oncol.* 21 (2), 271–282. doi:10.1016/S1470-2045(19)30691-6

Doz, F., van Tilburg, C. M., Geoerger, B., Højgaard, M., Øra, I., Boni, V., et al. (2022). Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. *Neuro-oncology* 24 (6), 997–1007. doi:10.1093/neuonc/noab274

Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D., et al. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N. Engl. J. Med.* 378 (8), 731–739. doi:10.1056/NEJMoa1714448

Drilon, A., Nagasubramanian, R., Blake, J. F., Ku, N., Tuch, B. B., Ebata, K., et al. (2017). A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. *Cancer Discov.* 7 (9), 963–972. doi:10.1158/2159-8290.CD-17-0507

Drilon, A., Siena, S., Dziadziuszko, R., Barlesi, F., Krebs, M. G., Shaw, A. T., et al. (2020). Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet. Oncol.* 21 (2), 261–270. doi:10.1016/S1470-2045(19)30690-4

Drilon, A., Tan, D. S. W., Lassen, U. N., Leyvraz, S., Liu, Y., Patel, J. D., et al. (2022). Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase fusion-positive lung cancers. *JCO Precis. Oncol.* 6, e2100418. doi:10.1200/PO.21.00418

Dziadziuszko, R., Krebs, M. G., De Braud, F., Siena, S., Drilon, A., Doebele, R. C., et al. (2021). Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer. *J. Clin. Oncol.* 39 (11), 1253–1263. doi:10.1200/JCO.20.03025

Ehmann, F., Caneva, L., and Papaluca, M. (2014). European Medicines Agency initiatives and perspectives on pharmacogenomics. *Br. J. Clin. Pharmacol.* 77 (4), 612–617. doi:10.1111/bcp.12319

Ekmekcioglu, S., Davies, M. A., Tanese, K., Roszik, J., Shin-Sim, M., Bassett, R. L., et al. (2016). Inflammatory marker testing identifies CD74 expression in melanoma tumor cells, and its expression associates with favorable survival for stage III melanoma. *Clin. Cancer Res.* 22 (12), 3016–3024. doi:10.1158/1078-0432.CCR-15-2226

Fang, Y., Zhang, Q., Chen, C., Chen, Z., Zheng, R., She, C., et al. (2023). Identification and comprehensive analysis of epithelial-mesenchymal transition related target genes of miR-222-3p in breast cancer. *Front. Oncol.* 13, 1189635. doi:10.3389/fonc.2023.1189635

Fountzilas, E., Tsimberidou, A. M., Vo, H. H., and Kurzrock, R. (2022). Clinical trial design in the era of precision medicine. *Genome Med.* 14 (1), 101. doi:10.1186/s13073-022-01102-1

Frampton, J. E. (2021). Entrectinib: a review in NTRK+ solid tumours and ROS1+ NSCLC. *Drugs* 81 (6), 697–708. doi:10.1007/s40265-021-01503-3

Gao, J., Aksoy, B. A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S. O., et al. (2013). Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* 6 (269), pl1. doi:10.1126/scisignal.2004088

Ghouse, J., Tragante, V., Muhammad, A., Ahlberg, G., Skov, M. W., Roden, D. M., et al. (2022). Polygenic risk score for ACE-inhibitor-associated cough based on the discovery of new genetic loci. *Eur. Heart J.* 43 (45), 4707–4718. doi:10.1093/eurheartj/ehac322

Giles, J. B., Steiner, H. E., Rollin, J., Shaffer, C. M., Momozawa, Y., Mushiroda, T., et al. (2022). Genome-wide association study of platelet factor 4/heparin antibodies in heparin-induced thrombocytopenia. *Blood Adv.* 6 (14), 4137–4146. doi:10.1182/bloodadvances.2022007673

Goldman, M. J., Craft, B., Hastie, M., Repečka, K., McDade, F., Kamath, A., et al. (2020). Visualizing and interpreting cancer genomics data via the Xena platform. *Nat. Biotechnol.* 38 (6), 675–678. doi:10.1038/s41587-020-0546-8

Hammam, E., Ananda, G., Sinha, A., Scheidig-Benatar, C., Bohec, M., Preiser, P. R., et al. (2020). Discovery of a new predominant cytosine DNA modification that is linked to gene expression in malaria parasites. *Nucleic Acids Res.* 48 (1), 184–199. doi:10.1093/nar/gkz1093

Hauben, M., and Aronson, J. K. (2009). Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Saf.* 32 (2), 99–110. doi:10.2165/00002018-200932020-00003

Hempel, D., Wieland, T., Solfrank, B., Grossmann, V., Steinhard, J., Frick, A., et al. (2020). Antitumor activity of larotrectinib in esophageal carcinoma with NTRK gene amplification. *Oncol.* 25 (6), e881–e886. doi:10.1634/theoncologist.2019-0641

Hong, D. S., DuBois, S. G., Kummar, S., Farago, A. F., Albert, C. M., Rohrberg, K. S., et al. (2020). Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet. Oncol.* 21 (4), 531–540. doi:10.1016/S1470-2045(19)30856-3

Houtz, J., Liao, G.-Y., An, J. J., and Xu, B. (2021). Discrete TrkB-expressing neurons of the dorsomedial hypothalamus regulate feeding and thermogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 118 (4), e2017218118. doi:10.1073/pnas.2017218118

Hu, X., Wang, Q., Tang, M., Barthel, F., Amin, S., Yoshihara, K., et al. (2018). TumorFusions: an integrative resource for cancer-associated transcript fusions. *Nucleic Acids Res.* 46 (D1), D1144–D1149. doi:10.1093/nar/gkx1018

Jain, N., Mittendorf, K. F., Holt, M., Lenoue-Newton, M., Maurer, I., Miller, C., et al. (2020). The My Cancer Genome clinical trial data model and trial curation workflow. *J. Am. Med. Inf. Assoc.* 27 (7), 1057–1066. doi:10.1093/jamia/ocaa066

Jain, N. M., Holt, M., Micheel, C., and Levy, M. (2021). Landscape analysis of breast cancer and acute myeloid leukemia trials using the my cancer genome clinical trial data model. *JCO Clin. Cancer Inf.* 5, 975–984. doi:10.1200/CCI.21.00082

Ji, A. L., Rubin, A. J., Thrane, K., Jiang, S., Reynolds, D. L., Meyers, R. M., et al. (2020). Multimodal analysis of composition and spatial architecture in human squamous cell carcinoma. *Cell* 182 (2), 1661–1662. doi:10.1016/j.cell.2020.08.043

Ji, H., Li, K., Jiang, W., Li, J., Zhang, J.-A., and Zhu, X. (2021). MRVI1 and NTRK3 are potential tumor suppressor genes commonly inactivated by DNA methylation in cervical cancer. *Front. Oncol.* 11, 802068. doi:10.3389/fonc.2021.802068

Jiang, H. (2022). A novel ETV6-NTRK3 gene fusion in primary renal fibrosarcoma. *Eur. Rev. Med. Pharmacol. Sci.* 26 (13), 4705–4708. doi:10.26355/eurrev_202207_29195

Jiang, Q., Li, M., Li, H., and Chen, L. (2022). Entrectinib, a new multi-target inhibitor for cancer therapy. *Biomed. Pharmacother. = Biomedecine Pharmacother.* 150, 112974. doi:10.1016/j.biopha.2022.112974

Jing, Y., Liu, J., Ye, Y., Pan, L., Deng, H., Wang, Y., et al. (2020). Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat. Commun.* 11 (1), 4946. doi:10.1038/s41467-020-18742-9

Jing, Y., Zhang, Y., Wang, J., Li, K., Chen, X., Heng, J., et al. (2021). Association between sex and immune-related adverse events during immune checkpoint inhibitor therapy. *J. Natl. Cancer Inst.* 113 (10), 1396–1404. doi:10.1093/jnci/djab035

Joffe, E., Iasonos, A., and Younes, A. (2017). Clinical trials in the genomic era. *J. Clin. Oncol. Official J. Am. Soc. Clin. Oncol.* 35 (9), 1011–1017. doi:10.1200/JCO.2016.70.8891

Kazi, D. S., Bellows, B. K., Baron, S. J., Shen, C., Cohen, D. J., Spertus, J. A., et al. (2020). Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation* 141 (15), 1214–1224. doi:10.1161/CIRCULATIONAHA.119.045093

Khotskaya, Y. B., Holla, V. R., Farago, A. F., Mills Shaw, K. R., Meric-Bernstam, F., and Hong, D. S. (2017). Targeting TRK family proteins in cancer. *Pharmacol. Ther.* 173, 58–66. doi:10.1016/j.pharmthera.2017.02.006

Kinnunen, M., Liu, X., Niemelä, E., Öhman, T., Gawriyski, L., Salokas, K., et al. (2023). The impact of ETV6-NTRK3 oncogenic gene fusions on molecular and signaling pathway alterations. *Cancers* 15 (17), 4246. doi:10.3390/cancers15174246

Knoepfler, P. S. (2015). From bench to FDA to bedside: US regulatory trends for new stem cell therapies. *Adv. Drug Deliv. Rev.* 82-83, 192–196. doi:10.1016/j.addr.2014.12.001

Kummar, S., Shen, L., Hong, D. S., McDermott, R., Keedy, V. L., Casanova, M., et al. (2023). Larotrectinib efficacy and safety in adult patients with tropomyosin receptor kinase fusion sarcomas. *Cancer* 129, 3772–3782. doi:10.1002/cncr.35036

Laetsch, T. W., DuBois, S. G., Mascarenhas, L., Turpin, B., Federman, N., Albert, C. M., et al. (2018). Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. *Lancet. Oncol.* 19 (5), 705–714. doi:10.1016/S1470-2045(18)30119-0

Le, X., Baik, C., Bauman, J., Gilbert, J., Brose, M. S., Grilley-Olson, J. E., et al. (2022). Larotrectinib treatment for patients with TRK fusion-positive salivary gland cancers. *Oncol.*, oyac080. doi:10.1093/oncolo/oyac080

Leroy, F., Dauxois, J.-Y., Théophile, H., Haramburu, F., and Tubert-Bitter, P. (2014). Estimating time-to-onset of adverse drug reactions from spontaneous reporting databases. *BMC Med. Res. Methodol.* 14, 17. doi:10.1186/1471-2288-14-17

Light, J. E., Koyama, H., Minturn, J. E., Ho, R., Simpson, A. M., Iyer, R., et al. (2012). Clinical significance of NTRK family gene expression in neuroblastomas. *Pediatr. Blood Cancer* 59 (2), 226–232. doi:10.1002/pbc.23343

Liguori, V., Gaio, M., Zinzi, A., Cagnotta, C., Riccardi, C., Docimo, G., et al. (2023). The safety profiles of two first-generation NTRK inhibitors: analysis of individual case safety reports from the FDA adverse event reporting system (FAERS) database. *Biomedicines* 11 (9), 2538. doi:10.3390/biomedicines11092538

Liu, C.-J., Hu, F.-F., Xie, G.-Y., Miao, Y.-R., Li, X.-W., Zeng, Y., et al. (2023). GSCA: an integrated platform for gene set cancer analysis at genomic, pharmacogenomic and immunogenomic levels. *Briefings Bioinforma.* 24 (1), bbac558. doi:10.1093/bib/bbac558

Liu, J., Lichtenberg, T., Hoadley, K. A., Poisson, L. M., Lazar, A. J., Cherniack, A. D., et al. (2018). An integrated TCGA pan-cancer clinical data resource to drive high-quality survival outcome analytics. *Cell* 173 (2), 400–416.e11. doi:10.1016/j.cell.2018.02.052

Long, K., and Suresh, K. (2020). Pulmonary toxicity of systemic lung cancer therapy. *Respirol. Carlt. Vic.)* 25 (2), 72–79. doi:10.1111/resp.13915

Luo, Y., Kaz, A. M., Kanngurn, S., Welsch, P., Morris, S. M., Wang, J., et al. (2013). NTRK3 is a potential tumor suppressor gene commonly inactivated by epigenetic mechanisms in colorectal cancer. *PLoS Genet.* 9 (7), e1003552. doi:10.1371/journal.pgen.1003552

Ma, L., Wang, D.-D., Zhang, T.-Y., Yu, H., Wang, Y., Huang, S.-H., et al. (2011). Region-specific involvement of BDNF secretion and synthesis in conditioned taste aversion memory formation. *J. Neurosci.* 31 (6), 2079–2090. doi:10.1523/JNEUROSCI.5348-10.2011

Marcus, L., Donoghue, M., Aungst, S., Myers, C. E., Helms, W. S., Shen, G., et al. (2021). FDA approval summary: entrectinib for the treatment of NTRK gene fusion solid tumors. *Clin. Cancer Res.* 27 (4), 928–932. doi:10.1158/1078-0432.CCR-20-2771

Martin-Zanca, D., Hughes, S. H., and Barbacid, M. (1986). A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. *Nature* 319 (6056), 743–748. doi:10.1038/319743a0

Mitelman, F., Johansson, B., and Mertens, F. (2007). The impact of translocations and gene fusions on cancer causation. *Nat. Rev. Cancer* 7 (4), 233–245. doi:10.1038/nrc2091

Montastruc, J.-L., Sommet, A., Bagheri, H., and Lapeyre-Mestre, M. (2011). Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br. J. Clin. Pharmacol.* 72 (6), 905–908. doi:10.1111/j.1365-2125.2011.04037.x

Moore, A. R., Rosenberg, S. C., McCormick, F., and Malek, S. (2020). RAS-targeted therapies: is the undruggable drugged? *Nat. Rev. Drug Discov.* 19 (8), 533–552. doi:10.1038/s41573-020-0068-6

Naik, B. S., Shetty, N., and Maben, E. V. S. (2010). Drug-induced taste disorders. *Eur. J. Intern. Med.* 21 (3), 240–243. doi:10.1016/j.ejim.2010.01.017

Okamura, R., Boichard, A., Kato, S., Sicklick, J. K., Bazhenova, L., and Kurzrock, R. (2018). Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. *JCO Precis. Oncol.* 2018, 1–20. doi:10.1200/PO.18.00183

Otsu, Y., Kata, Y., Takayasu, H., Inoue, S., and Kaneko, T. (2022). Entrectinib-induced heart failure in a patient with metastatic lung adenocarcinoma: a case report. *Cureus* 14 (12), e32174. doi:10.7759/cureus.32174

Quintanilha, J. C. F., de Sousa, V. M., Visacri, M. B., Amaral, L. S., Santos, R. M. M., Zambrano, T., et al. (2017). Involvement of cytochrome P450 in cisplatin treatment: implications for toxicity. *Cancer Chemother. Pharmacol.* 80 (2), 223–233. doi:10.1007/s00280-017-3358-x

Roden, D. M., McLeod, H. L., Relling, M. V., Williams, M. S., Mensah, G. A., Peterson, J. F., et al. (2019). Pharmacogenomics. *Lancet (London, Engl.* 394 (10197), 521–532. doi:10.1016/S0140-6736(19)31276-0

Russo, M., Misale, S., Wei, G., Siravegna, G., Crisafulli, G., Lazzari, L., et al. (2016). Acquired resistance to the TRK inhibitor entrectinib in colorectal cancer. *Cancer Discov.* 6 (1), 36–44. doi:10.1158/2159-8290.CD-15-0940

Sabaté, M., and Montané, E. (2023). Pharmacoepidemiology: an overview. *J. Clin. Med.* 12 (22), 7033. doi:10.3390/jcm12227033

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Scott, L. J. (2019). Larotrectinib: first global approval. *Drugs* 79 (2), 201–206. doi:10.1007/s40265-018-1044-x

Shu, Y., Ding, Y., Liu, Y., Wu, P., He, X., and Zhang, Q. (2022). Post-marketing safety concerns with secukinumab: a disproportionality analysis of the FDA adverse event reporting system. *Front. Pharmacol.* 13, 862508. doi:10.3389/fphar.2022.862508

Somwar, R., Hofmann, N. E., Smith, B., Odintsov, I., Vojnic, M., Linkov, I., et al. (2020). NTRK kinase domain mutations in cancer variably impact sensitivity to type I and type II inhibitors. *Commun. Biol.* 3 (1), 776. doi:10.1038/s42003-020-01508-w

Spagnolo, P., Bonniaud, P., Rossi, G., Sverzellati, N., and Cottin, V. (2022). Drug-induced interstitial lung disease. *Eur. Respir. J.* 60 (4), 2102776. doi:10.1183/13993003.02776-2021

Szobota, S., Mathur, P. D., Siegel, S., Black, K., Saragovi, H. U., and Foster, A. C. (2019). BDNF, NT-3 and Trk receptor agonist monoclonal antibodies promote neuron survival, neurite extension, and synapse restoration in rat cochlea *ex vivo* models relevant for hidden hearing loss. *PloS One* 14 (10), e0224022. doi:10.1371/journal.pone.0224022

Tauszig-Delamasure, S., Yu, L.-Y., Cabrera, J. R., Bouzas-Rodriguez, J., Mermet-Bouvier, C., Guix, C., et al. (2007). The TrkC receptor induces apoptosis when the dependence receptor notion meets the neurotrophin paradigm. *Proc. Natl. Acad. Sci. U. S. A.* 104 (33), 13361–13366. doi:10.1073/pnas.0701243104

Tognon, C., Knezevich, S. R., Huntsman, D., Roskelley, C. D., Melnyk, N., Mathers, J. A., et al. (2002). Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell* 2 (5), 367–376. doi:10.1016/s1535-6108(02)00180-0

Tsai, C.-T., Hsieh, C.-S., Chang, S.-N., Chuang, E. Y., Ueng, K.-C., Tsai, C.-F., et al. (2016). Genome-wide screening identifies a KCNIP1 copy number variant as a genetic predictor for atrial fibrillation. *Nat. Commun.* 7, 10190. doi:10.1038/ncomms10190

Vaishnavi, A., Le, A. T., and Doebele, R. C. (2015). TRKing down an old oncogene in a new era of targeted therapy. *Cancer Discov.* 5 (1), 25–34. doi:10.1158/2159-8290.CD-14-0765

Valsesia, A., Stevenson, B. J., Waterworth, D., Mooser, V., Vollenweider, P., Waeber, G., et al. (2012). Identification and validation of copy number variants using SNP genotyping arrays from a large clinical cohort. *BMC Genomics* 13, 241. doi:10.1186/1471-2164-13-241

Visacri, M. B., Duarte, N. C., Lima, T. d.M., de Souza, R. N., Cobaxo, T. S., Teixeira, J. C., et al. (2022). Adverse reactions and adherence to capecitabine: a prospective study in patients with gastrointestinal cancer. *J. Oncol. Pharm. Pract.* 28 (2), 326–336. doi:10.1177/1078155221989420

Vivian, J., Rao, A. A., Nothaft, F. A., Ketchum, C., Armstrong, J., Novak, A., et al. (2017). Toil enables reproducible, open source, big biomedical data analyses. *Nat. Biotechnol.* 35 (4), 314–316. doi:10.1038/nbt.3772

Vogel, A., Segatto, O., Stenzinger, A., and Saborowski, A. (2023). FGFR2 inhibition in cholangiocarcinoma. *Annu. Rev. Med.* 74, 293–306. doi:10.1146/annurev-med-042921-024707

Wahida, A., Buschhorn, L., Fröhling, S., Jost, P. J., Schneeweiss, A., Lichter, P., et al. (2023). The coming decade in precision oncology: six riddles. *Nat. Rev. Cancer* 23 (1), 43–54. doi:10.1038/s41568-022-00529-3

Waliany, S., Zhu, H., Wakelee, H., Padda, S. K., Das, M., Ramchandran, K., et al. (2021). Pharmacovigilance analysis of cardiac toxicities associated with targeted therapies for metastatic NSCLC. *J. Thorac. Oncol.* 16 (12), 2029–2039. doi:10.1016/j.jtho.2021.07.030

Wang, D., Li, D., Qin, G., Zhang, W., Ouyang, J., Zhang, M., et al. (2015). The structural characterization of tumor fusion genes and proteins. *Comput. Math. Methods Med.* 2015, 912742. doi:10.1155/2015/912742

Wang, Y., Sparidans, R. W., Li, W., Lebre, M. C., Beijnen, J. H., and Schinkel, A. H. (2020). OATP1A/1B, CYP3A, ABCB1, and ABCG2 limit oral availability of the NTRK inhibitor larotrectinib, while ABCB1 and ABCG2 also restrict its brain accumulation. *Br. J. Pharmacol.* 177 (13), 3060–3074. doi:10.1111/bph.15034

Wu, Y., Wei, M., and Zhang, J. (2023). A real-world pharmacovigilance analysis of FDA adverse event reporting system database for upadacitinib. *Front. Pharmacol.* 14, 1200254. doi:10.3389/fphar.2023.1200254

Yamada, Y., Toyota, M., Hirokawa, Y., Suzuki, H., Takagi, A., Matsuzaki, T., et al. (2004). Identification of differentially methylated CpG islands in prostate cancer. *Int. J. Cancer* 112 (5), 840–845. doi:10.1002/ijc.20335

Yi, Q., Peng, J., Xu, Z., Liang, Q., Cai, Y., Peng, B., et al. (2022). Spectrum of BRAF aberrations and its potential clinical implications: insights from integrative pan-cancer analysis. *Front. Bioeng. Biotechnol.* 10, 806851. doi:10.3389/fbioe.2022.806851

Yu, G., Wang, L.-G., Han, Y., and He, Q.-Y. (2012). clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics a J. Integr. Biol.* 16 (5), 284–287. doi:10.1089/omi.2011.0118

Yu, Z., Wang, H., Song, Q., Huang, J., Xu, J., Su, J., et al. (2021). Prognostic value and characterization of NTRK1 variation by fluorescence *in situ* hybridization in esophageal squamous cell carcinoma. *J. Cancer Res. Clin. Oncol.* 147 (10), 3113–3121. doi:10.1007/s00432-021-03578-7

Zhao, S., Ye, Z., and Stanton, R. (2020). Misuse of RPKM or TPM normalization when comparing across samples and sequencing protocols. *RNA (New York, N.Y.)* 26 (8), 903–909. doi:10.1261/rna.074922.120

Zhou, C., Peng, S., Lin, A., Jiang, A., Peng, Y., Gu, T., et al. (2023). Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* 59, 101967. doi:10.1016/j.eclinm.2023.101967

Zhou, J., Lemos, B., Dopman, E. B., and Hartl, D. L. (2011). Copy-number variation: the balance between gene dosage and expression in *Drosophila melanogaster*. *Genome Biol. Evol.* 3, 1014–1024. doi:10.1093/gbe/evr023

Zito Marino, F., Buono, S., Montella, M., Giannatiempo, R., Messina, F., Casaretta, G., et al. (2023). NTRK gene aberrations in triple-negative breast cancer: detection challenges using IHC, FISH, RT-PCR, and NGS. *J. Pathology. Clin. Res.* 9 (5), 367–377. doi:10.1002/cjp2.324

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 01 February 2024
DOI 10.3389/fphar.2024.1293468

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Liu Yang,
Heilongjiang University of Chinese Medicine, China
Wei Peng,
Chengdu University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Sheng-Fang Xie,
xieshengfang@163.com
Xue-Zhou Wang,
wxz007voa@126.com

RECEIVED 13 September 2023
ACCEPTED 22 January 2024
PUBLISHED 01 February 2024

CITATION
Zhu K-X, Wu M, Bian Z-L, Han S-L, Fang L-M, Ge F-F, Wang X-Z and Xie S-F (2024), Growing attention on the toxicity of Chinese herbal medicine: a bibliometric analysis from 2013 to 2022.
Front. Pharmacol. 15:1293468.
doi: 10.3389/fphar.2024.1293468

Growing attention on the toxicity of Chinese herbal medicine: a bibliometric analysis from 2013 to 2022

Ke-Xin Zhu[1,2], Min Wu[1,2], Zhi-Lin Bian[1,2], Shi-Liang Han[1,2], Li-Ming Fang[1,2], Feng-Feng Ge[1,2], Xue-Zhou Wang[3]* and Sheng-Fang Xie[1,2]*

[1]Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, China, [2]Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, China, [3]International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing, China

Introduction: Despite the clinical value of Chinese herbal medicine (CHM), restricted comprehension of its toxicity limits the secure and efficacious application. Previous studies primarily focused on exploring specific toxicities within CHM, without providing an overview of CHM's toxicity. The absence of a quantitative assessment of focal points renders the future research trajectory ambiguous. Therefore, this study aimed to reveal research trends and areas of concern for the past decade.

Methods: A cross-sectional study was conducted on publications related to CHM and toxicity over the past decade from Web of Science Core Collection database. The characteristics of the publication included publication year, journal, institution, funding, keywords, and citation counts were recorded. Co-occurrence analysis and trend topic analysis based on bibliometric analysis were conducted on keywords and citations.

Results: A total of 3,225 publications were analyzed. Number of annal publications increased over the years, with the highest number observed in 2022 (n = 475). The *Journal of Ethnopharmacology* published the most publications (n = 425). The most frequently used toxicity classifications in keywords were hepatotoxicity (n = 119) or drug-induced liver injury (n = 48), and nephrotoxicity (n = 40). Co-occurrence analysis revealed relatively loose connections between CHM and toxicity, and their derivatives. Keywords emerging from trend topic analysis for the past 3 years (2019–2022) included ferroptosis, NLRP3 inflammasome, machine learning, network pharmacology, traditional uses, and pharmacology.

Conclusion: Concerns about the toxicity of CHM have increased in the past decade. However, there remains insufficient studies that directly explore the intersection of CHM and toxicity. Hepatotoxicity and nephrotoxicity, as the most concerned toxicity classifications associated with CHM, warrant more in-depth investigations. Apoptosis was the most concerned toxicological mechanism. As a recent increase in attention, exploring the mechanisms of ferroptosis in

nephrotoxicity and NLRP3 inflammasome in hepatotoxicity could provide valuable insights. Machine learning and network pharmacology are potential methods for future studies.

KEYWORDS

Chinese herbal medicine, toxicity, safety, bibliometric analysis, crosssectional, pharmacology

1 Introduction

Herbal medicine is derived from traditional medical systems and serves as an extensively employed complementary therapy in clinical practice (Barnes et al., 2016). Particularly, Chinese herbal medicine (CHM) stands as a representative within this domain, boasting a long historical lineage and even contributed China's first Nobel Prize in natural sciences (Tu, 2016). Evidence supports the protentional efficacy of CHM in treating cardiovascular (Hao et al., 2017), nephritic (Zhong et al., 2015), immunologic (Jakobsson et al., 2022) and cancer-related disorders (Yao et al., 2021). As one of the most prevalent herbal medicines, CHM is exported to over 175 countries and regions (Teng et al., 2016). Despite these promising prospects, similar to other herbal remedies, CHM encounters the hurdle of toxicity. The toxicity of CHM typically presents as hepatotoxicity and nephrotoxicity (Ekor, 2014), which are the leading causes of drug development failure or market withdrawal (Hoppmann et al., 2020; Kulkarni, 2021). Given the World Health Organization's prioritization of drug safety (Donaldson et al., 2017), emphasizing the toxicity of CHM becomes imperative.

The underestimation of the toxicity of CHM is a longstanding issue. The prescription of CHM under the guidance of traditional toxicity theory is frequently considered to be completely safe. Following the first discovery of severe toxic aristolochic acids in some Chinese herbs (Vanhaelen et al., 1994), many toxic components were determined (Lv et al., 2012). However, before the prohibition of these CHMs and synthetic drugs by countries (Hashimoto et al., 1999; Lee et al., 2002; Gabardi et al., 2007; Zhou et al., 2013), the associated herbs had been used for thousands of years. Astonishingly, the modern toxicity of some CHMs contradicts the traditional theory. For instance, *Aristolochia manshuriensis* Kom was traditionally believed to possess diuretic properties for treating kidney disease but was proven to be nephrotoxic and carcinogenic (Wang L. et al., 2018). Recent studies revealed that the toxicity of certain CHMs were quite complex, particularly in terms of hepatotoxicity. The toxicity of these herbs exhibits a dose-independent pattern and displays significant inter-individual variability across different populations (Ma et al., 2023). In addition, the lack of quality control measures during production and sales exacerbates the risks associated with toxicity (Raynor et al., 2011; Liu et al., 2015). Such concerns prompted regulatory bodies including the Food and Drug Administration (FDA) to only approve limited CHMs (Qu et al., 2022; You et al., 2022).

Fortunately, the toxicity of CHM garnered increased attention in recent years, with various safety regulatory standards, clinical practice guidelines and manifestos highlighting the urgency of this issue (Yang et al., 2022). However, existing studies mainly focused on specific toxicities, resulting in a lack of overview to the overall safety of CHM. Additionally, there are still gaps in understanding the actual incidence rate and specific mechanisms (Teschke et al., 2014; Yang et al., 2018; Wang et al., 2022). Therefore, to provide a comprehensive understanding of the toxicity of CHM and identify potential avenues for future research, this cross-sectional study aimed to reveal research trends and areas of concern for the past decade through bibliometric analysis.

2 Materials and methods

2.1 Data collection

This study included publications concerning the toxicity of CHM, and were published between 2013 and 2022. The search was conducted by the Web of Science Core Collection (WOS) database using the following strategy:

#1 TS= "toxicity" OR "toxicology" OR "nephrotoxicity" OR "hepatotoxicity" OR "drug-induced injury" OR "cardiotoxicity" OR "neurotoxicity" OR "ototoxicity" OR "hematotoxicity" OR "immunotoxicity".

#2 TS= "traditional Chinese medicine" OR "Chinese herbal" OR "Chinese herb".

#3 FPY = 2013–2022.

#1 AND #2 AND #3.

An additional search was conducted within the CNKI database to examine the distinctions in publication characteristics across databases. The search strategy used for the CNKI database is provided in the Supplementary Material.

2.2 Analysis

After obtaining the data of all publications, basic characteristics including title, publication year, author, author's keyword, institution, funding agency and citation were counted. VOSviewer (version 1.6.19), Bibliometrix package of R (version 4.3.0) and Citespace (version 5.7. R5) software were used for visualized analysis (van Eck and Waltman, 2010). Bibliographic coupling analysis with timeline was performed in influential journals. Influential journals were defined as the top 25 journals (≥5 publications on this field per journal) with the most cite frequency by the included publications. Evaluation of hotspot and trend was conducted by co-occurrence analysis and trend topic analysis based on author's keywords. Co-occurrence analysis was conducted on the 40 keywords of the most records,

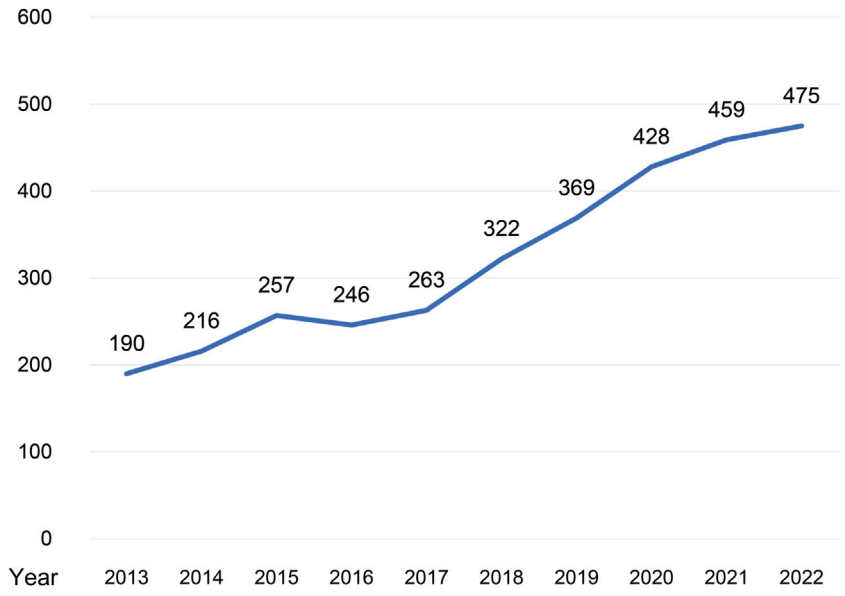


FIGURE 1
Number of annal publications on the toxicity of Chinese herbal medicine.

TABLE 1 Top 5 productive journals, institutions and funding agencies.

Category		Counts (%)
Journal	Journal of Ethnopharmacology (IF = 5.4, Q1)[a]	425 (13.18)
	Frontiers in Pharmacology (IF = 5.6, Q1)	226 (7.01)
	Evidence-Based Complementary and Alternative Medicine[b]	138 (4.28)
	Molecules (IF = 4.6, Q2)	77 (2.39)
	Phytomedicine (IF = 7.9, Q1)	76 (2.36)
Institution	Beijing University of Chinese Medicine	187 (5.80)
	Chengdu University of Traditional Chinese Medicine	152 (4.71)
	Shanghai University of Traditional Chinese Medicine	146 (4.52)
	Nanjing University of Chinese Medicine	132 (4.09)
	Chinese Academy of Medical Sciences and Peking Union Medical College	118 (3.66)
Funding agency	National Natural Science Foundation of China	1,489 (46.17)
	China Postdoctoral Science Foundation	87 (2.70)
	National Basic Research Program of China	78 (2.42)
	Fundamental Research Funds for the Central Universities	74 (2.29)
	National Natural Science Foundation of Guangdong Province	65 (2.02)

[a]Impact factor (IF) and quartile ranking were based on the Journal Citation Reports (JCR) data updates 18 Oct 2023.
[b]The journal no longer includes in Web of Science (WOS) journal list since 20 March 2023.

with varied colors showing the trends over time. Additional co-occurrence analysis was conducted on countries with more than 10 publications for exploring the cooperation between individual countries. Trend topic analysis was conducted on the 3 independent emerging keywords each year, with the duration of the hot topic. In trend topic analysis, keywords lasted for more than 5 years were defined as long-term concerned keywords, while the ones with the duration less than 2 years were defined as short-term concerned keywords. Co-occurrence analysis and trend topic analysis are complementary. The former selects the term of analysis by

TABLE 2 Top 5 productive authors.

Author	Counts[a]	H-index[b]
Xiao-He, Xiao	30	87
Jia-Bo, Wang[c]	25	36
Jin-Ao, Duan	24	51
Yu-Ping, Tang	22	51
Tomas, Efferth	17	79

[a]Due to the duplication of names, publications were counted by individual authors, rather than authors' name. After formatting all names manually, authors' information was verified in WOS to prevent mismatching.
[b]The h-index is an indicator based on a list of publications ranked in descending order by the Times Cited and reflects the productivity of authors based on their publication and citation records. H-index of the authors were recorded on 25 November 2023.
[c]Two author profiles appeared in WOS, that were verified to belong to the same individual author. Publications were combined counted and h-index was selected from the profile with more publications.

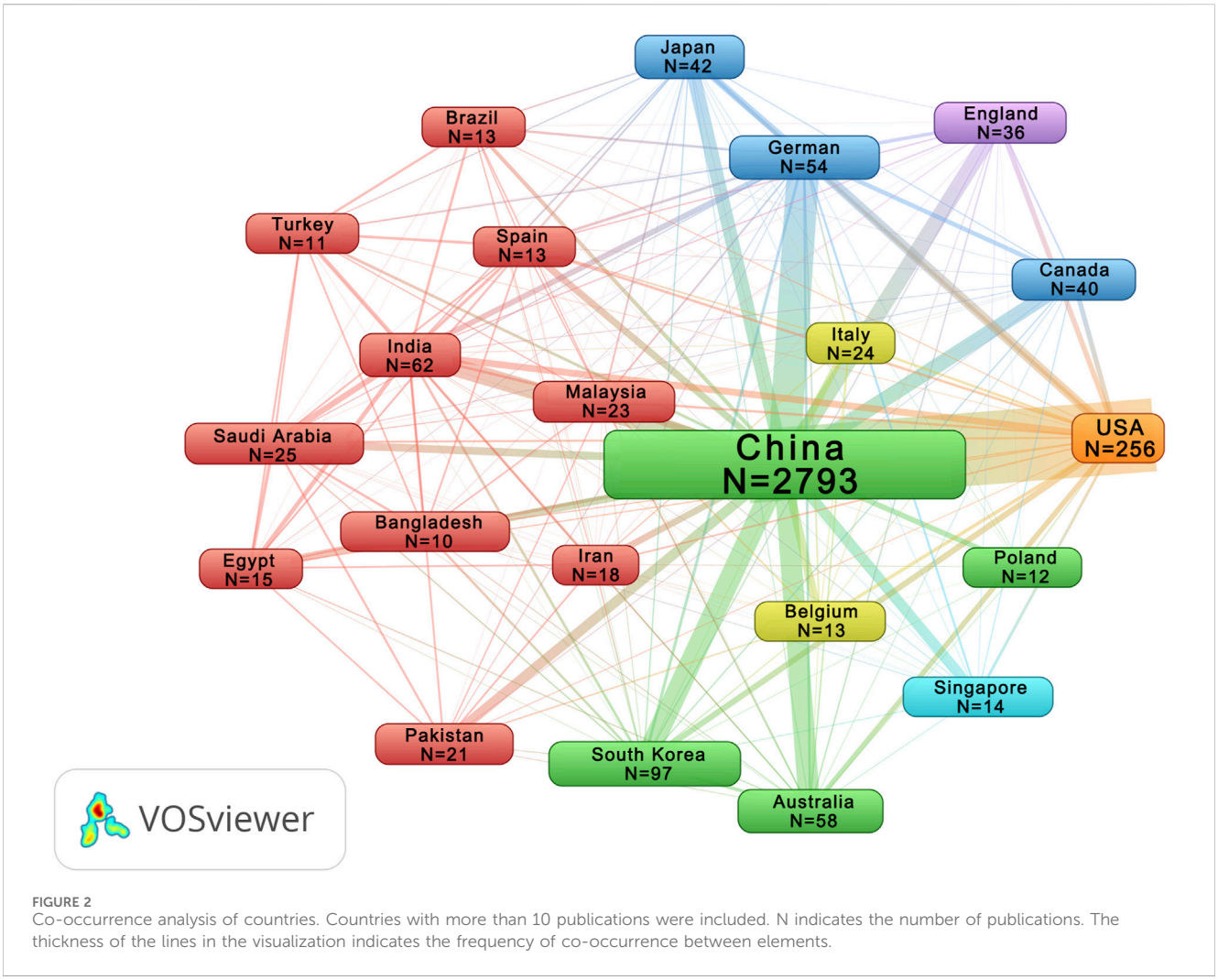


FIGURE 2
Co-occurrence analysis of countries. Countries with more than 10 publications were included. N indicates the number of publications. The thickness of the lines in the visualization indicates the frequency of co-occurrence between elements.

keyword frequency, which can show the connection between keywords, but may mask the recent emerging keywords. Trend topic analysis does not have the ability to show connections, but can better detect the potential hotspots. Citation burst analysis was conducted to discern emergent citations.

3 Results

The initial search yielded 3,242 records, and 17 of them were excluded for reasons including languages other than English (n = 12), retracted publication (n = 3) and correction (n = 2). A total of

TABLE 3 Top 10 publications with the most citations.

Title	Corresponding author[a]	Journal	Publication year	Cited frequency[b]
The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety	Ekor, M	Frontiers in Pharmacology	2014	1,416
Network Pharmacology Databases for Traditional Chinese Medicine: Review and Assessment	Ning, K	Frontiers in Pharmacology	2019	530
Puerarin: A Review of Pharmacological Effects	Peng, C	Phytotherapy Research	2014	427
Emodin: A Review of its Pharmacology, Toxicity and Pharmacokinetics	Ni, J	Phytotherapy Research	2016	364
From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy	Efferth, T	Seminars in Cancer Biology	2017	317
Apigenin in cancer therapy: anti-cancer effects and mechanisms of action	Shao, HJ	Cell and Bioscience	2017	267
Triptolide: Progress on research in pharmacodynamics and toxicology	Jiang, ZZ	Journal of Ethnopharmacology	2014	255
Traditional uses, botany, phytochemistry, pharmacology and toxicology of Panax notoginseng (Burk.) FH Chen: A review	Wang, ZJ	Journal of Ethnopharmacology	2016	254
Incidence and Etiology of Drug-Induced Liver Injury in Mainland China	Mao, YM	Gastroenterology	2019	244
Traditional usages, botany, phytochemistry, pharmacology and toxicology of Polygonum multiflorum Thunb.: A review	Ni, J	Journal of Ethnopharmacology	2015	239

[a]When a publication contains multiple corresponding authors, only the last one is presented.
[b]Cited frequency was counted on 13 July 2023.

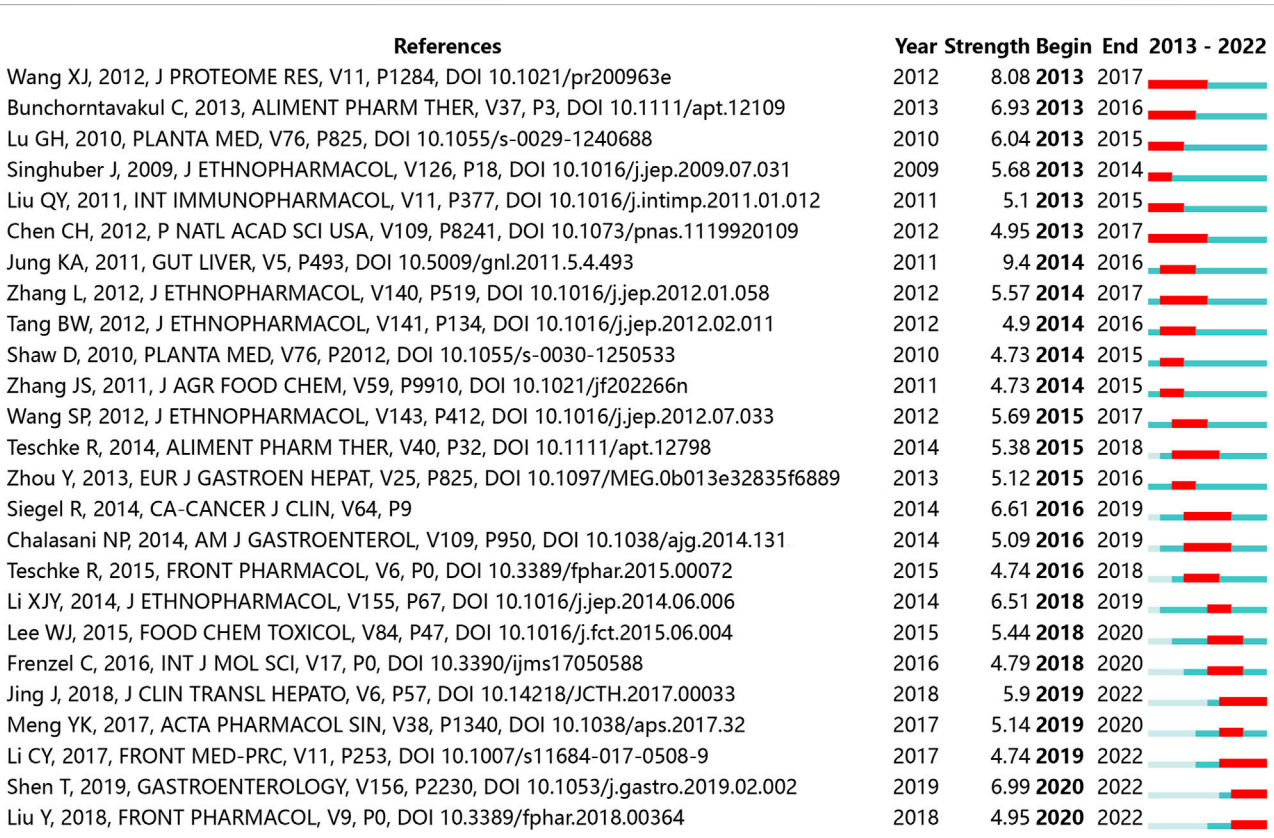


FIGURE 3
Top 25 citations with the strongest bursts.

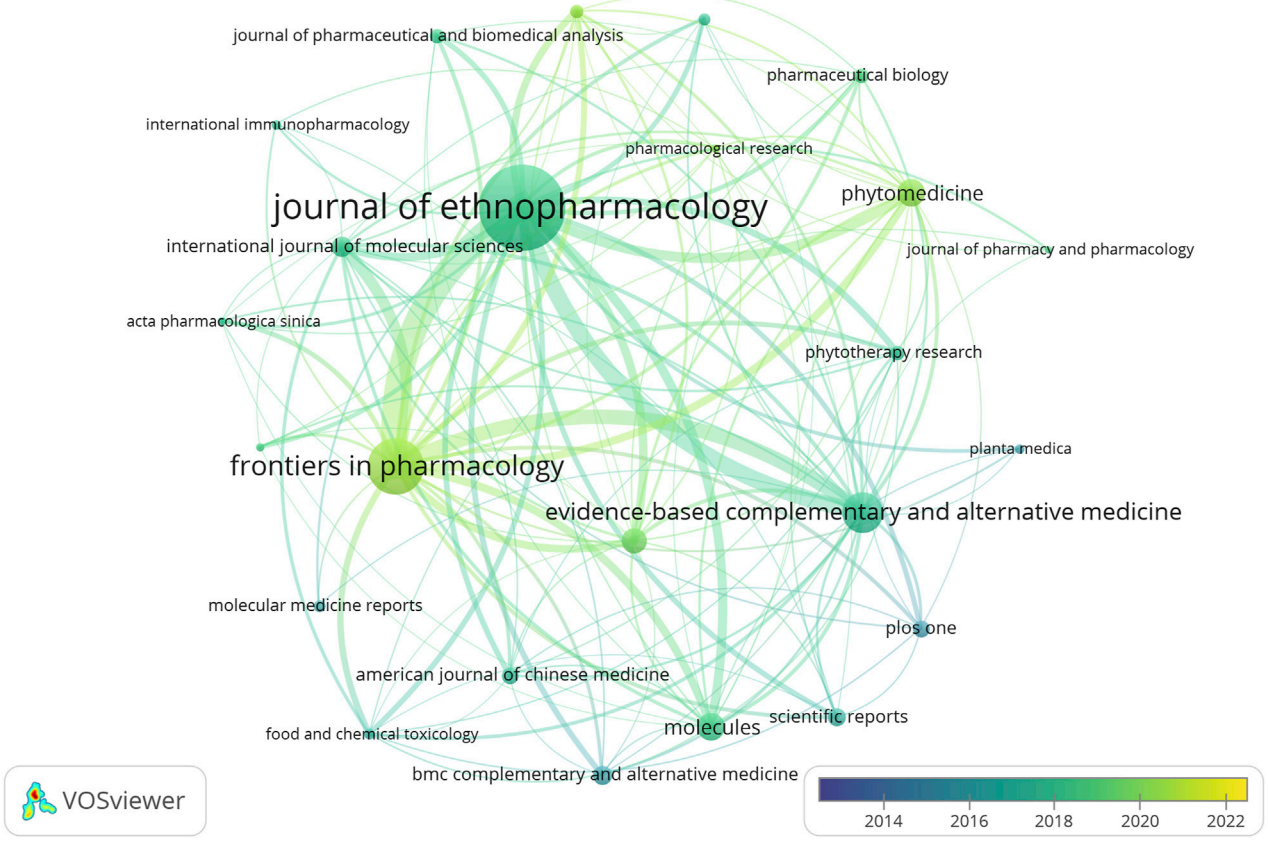


FIGURE 4
Coupling analysis of 25 influential journals. The thickness of the lines in the visualization indicates the frequency of co-occurrence between elements.

3,225 publications were included in the analysis, with 2,413 articles, 785 reviews, 12 meeting abstracts, 11 editorial materials and 4 letters.

3.1 Basic characteristics

From 2013 to 2022, with the exception of a slight decline in 2016 (n = 246), annual publications were increased by the year (Figure 1). The number of publications reached its highest in 2022 (n = 475). As showing in Table 1, the top 5 productive journals in this field were *Journal of Ethnopharmacology* (n = 425), *Frontiers in Pharmacology* (n = 226), *Evidence-Based Complementary and Alternative Medicine* (n = 138), *Molecules* and *Phytomedicine* (n = 76). Beijing University of Chinese Medicine (n = 187) contributed the most publications. National Natural Science Foundation of China (n = 1,489) is the agency that supported the most publications in this field. The top 5 institutions and funding agencies were all Chinese. Table 2 displays the leading 5 authors alongside their respective h-index values, representing the individuals with the highest number of publications. Xiao-He, Xiao had the most publications and the highest h-index among the authors listed. Figure 2 delineates the publication volume and cooperative connections among countries. China stands out as the most prolific region (n = 2,793), exhibiting collaboration primarily with the United States and Germany.

3.2 Most cited publications and journals

Table 3 lists the 10 most cited publications, with 9 reviews and 1 research article. The publication entitled "The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety (Ekor, 2014)" got the most citations (1,416 citations). Within these 10 publications, 8 were contributed by Chinese researches, 5 were published on the aforenamed top 5 journals. None was published on multidisciplinary journals. Figure 3 shows the temporal burst of cited publications over the last decade in the included publications. "Screening for main components associated with the idiosyncratic hepatotoxicity of a tonic herb, Polygonum multiflorum (Li et al., 2017)", "Incidence and Etiology of Drug-Induced Liver Injury in Mainland China (Shen et al., 2019)" and "Polygonum multiflorum Thunb.: A Review on Chemical Analysis, Processing Mechanism, Quality Evaluation, and Hepatotoxicity (Liu et al., 2018)" were emerged as focal points, garnering significant citations in recent years. The top 5 frequently cited journals by the included publications were *Journal of Ethnopharmacology* (n = 13,159), *Frontiers in Pharmacology* (n = 5,099), *Molecules* (n = 1,503), *Evidence-Based Complementary and Alternative Medicine* (n = 1,489), *International Journal of Molecular Sciences* (n = 1,347). Figure 4 shows the coupling result of the influential journals. The patterns of journal citations transferred over time, with a recent

TABLE 4 Top 25 keywords with the most frequencies.

Keyword	Count
Traditional Chinese medicine	263
Apoptosis	190
Pharmacology	168
Toxicity	167
Phytochemistry	143
Hepatotoxicity	119
Oxidative stress	115
Pharmacokinetics	93
Toxicology	93
Metabolomics	88
Inflammation	81
Alzheimer's disease	79
Chinese herbal medicine	75
Network pharmacology	71
Autophagy	66
Traditional uses	56
Triptolide	53
Drug-induced liver injury	48
Herbal medicine	47
Safety	47
Chemotherapy	45
Neuroprotection	43
Meta-analysis	42
Nephrotoxicity	40
Review	39

surge in the popularity of citing journals such as *Frontiers in Pharmacology* and *Phytomedicine*.

3.3 Hotspots and trends

Table 4 lists the top 25 keywords with the most frequencies. In terms of toxic classifications, hepatotoxicity (n = 119) or drug-induced liver injury (n = 48), and nephrotoxicity (n = 40) were focused on. In physiological and pathological manifestations, apoptosis (n = 190), oxidative stress (n = 115), inflammation (n = 81) and autophagy (n = 66) were focused on. In methods, pharmacokinetics (n = 93), metabolomics (n = 88), network pharmacology (n = 71), meta-analysis (n = 42) received great attentions.

After co-occurrence clustering of the top 40 keywords, 3 clusters were determined (Figure 5A). The keywords contained in cluster 1 (green cluster) were mainly CHM and its derivative words, which is characterized by the weak connection in-cluster and between-clusters. Cluster 2 (red cluster) contained the most keywords (n = 19). Among the most frequent words, apoptosis often co-occurred with oxidative stress and autophagy. Keywords in cluster 3 (blue cluster) were closely connected. Toxicity and toxicology often co-occurred with pharmacology or phytochemistry. The two keywords with the strongest correlation were pharmacology and phytochemistry. Figure 5B shows the change of keyword co-occurrence over time. Co-occurring keywords tended to shift from Cluster 1 and Cluster 2 to Cluster 3 between 2020 and 2022.

Figure 6 presents the results of trend topic analysis. Emerging keywords for the past 3 years (2019–2022) included ferroptosis, NLRP3 inflammasome, machine learning, network pharmacology, traditional uses and pharmacology. Long-term concerned keywords (>5 years) included toxicity, safety, angiogenesis and neuroprotection. Short-term concerned keywords (<2 years) included ferroptosis, repellency, LC-MS/MS, aristolochia and contamination.

3.4 Features of publications in the CNKI database

The search in CNKI database generated 5,880 records, comprising 3,306 journal articles, 1894 dissertations, 465 conference articles and 215 other types of publications. Supplementary Figure S1 and Supplementary Table S1 show the frequencies of the top 40 keywords and their co-occurrence network. A substantial portion of the top 40 words exhibited overlap, often conveying similar concepts. In contrast to the WOS database, publications within the CNKI database paid extra attention to the issues in CHM production process, while displaying less attention to the mechanism of CHM toxicity.

4 Discussion

Despite concerns about the toxicity of CHM, its social hazards persist. There is a misconception that CHM is non-toxic and universally applicable. Hence, adverse events caused by the toxicity of CHM occurs in both clinical practice and the public health field. Notably, China experiences a higher proportion of toxic incidents caused by herbs compared to other countries (Yang et al., 2022). As one of the oldest herbal remedies, CHM is often overused outside of prescription. In Asia, it is frequently used as a complementary treatment or health supplement, while in western countries, weight losing is an important purpose (Chen and Fontana, 2021). Therefore, in order to draw attention and provide research directions, it is important to evaluate current research trends.

The number of publications on CHM's toxicity increased in the past decade. The top 5 journals with the most publications have a great influence, with half of the highly cited publications (5/10) included. The *Journal of Ethnopharmacology* was considered the most influential journal within the field, exhibiting the highest publication and citation frequencies. Although most studies were funded and completed by Chinese institutions and authors, publications were concentrated in non-native journals. This highlights the need for more high-quality local journals to

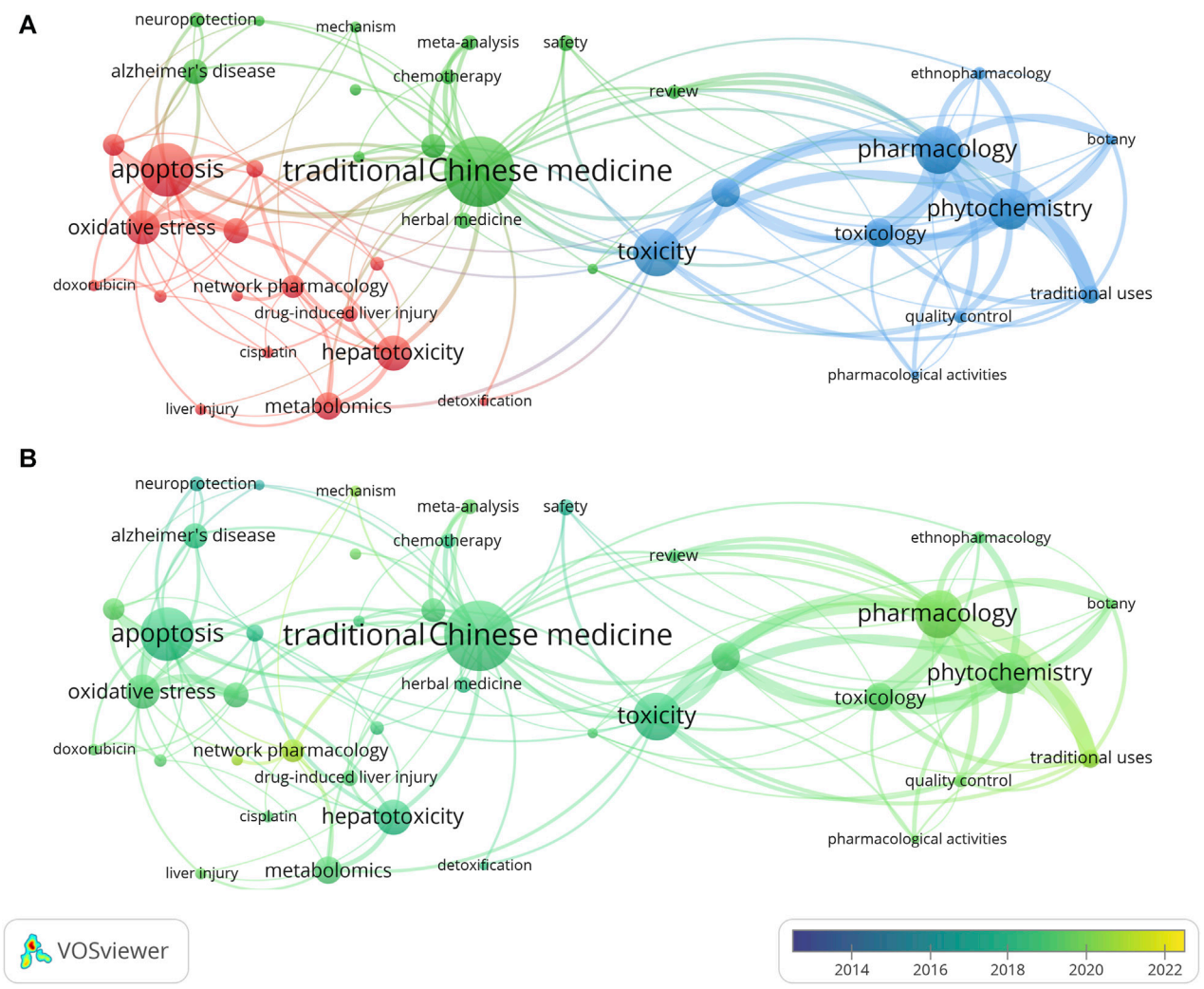


FIGURE 5
Co-occurrence analysis on the 40 keywords of the most records **(A)**, clustering result; **(B)**, clustering result with time-variation). The thickness of the lines in the visualization indicates the frequency of co-occurrence between elements.

accommodate the growing studies. Similar to other study on toxicity (He et al., 2022), this study found that 9 of the top 10 cited studies were reviews, with only 1 being original research. While reviews contribute to summarizing research progress, this phenomenon may indicate a lack of attention to original research.

In keywords, this study identified hepatotoxicity and nephrotoxicity as the most concerned toxicity categories associated with CHM. Hepatotoxicity is the most common toxicity observed, with over 40 CHMs being identified as potential causes of liver injury (Teschke et al., 2014; Frenzel and Teschke, 2016). Among these toxic substances, alkaloids and terpenoids represent the two primary groups associated with hepatotoxic effects (He et al., 2019). Nephrotoxic components in CHM, particularly aristolochic acid, were among the earliest lethal toxic components identified in CHM. Besides, additional components that cause nephrotoxicity include alkaloids and anthraquinones. Although certain toxicities related to CHM were reported, including neurotoxicity (e.g., *Tripterygium wilfordi* (Liu et al., 2019)), cardiotoxicity (e.g., *Aconitum carmichaeli* (Sun et al., 2018)), and reproductive toxicity (e.g., *Rhizoma Pinelliae* (Li et al., 2022)), these do not exhibit high keyword frequency. This could be attributed to the fact that many CHMs possess a multitoxic nature, including hepatotoxicity or nephrotoxicity. Apoptosis was the most concerned pathological mechanism, which is quite complex. Toxic components such as triptolide and aristolochic acid can induce apoptosis to cause damage (Romanov et al., 2015; Wang Y. et al., 2018). Conversely, oxymatrine in *Sophora flavescens* may promote apoptosis to provide anti-cancer effect (Lan et al., 2020). In addition, evidence suggest that emodin in several CHMs can reduce the toxicity of cisplatin by inhibiting apoptosis (Liu et al., 2016). In methodology, the diversity reflected in the keywords of high-frequency, including various experimental and statistical methods. Regarding toxic ingredients, triptolide (n = 53), flavonodis (n = 25) and aristolochic acid (n = 21) keywords used over 20 times each. Expect aristolochic acids, as the most classic toxic ingredient, the other two exhibit dual characteristics.

FIGURE 6
Trend topic analysis. The blue line signifies the duration of the keyword's status as a hot topic, while the size of the blue dot indicates the frequency.

Triptolide functions as both an active and toxic ingredient, showcasing antitumor properties alongside notable hepatotoxic, nephrotoxic, and cardiotoxic tendencies (Noel et al., 2019). Flavonoids exists in most plant species, yet certain members within this category carry nephrotoxic properties (Yang et al., 2018). Other classic toxic components received less attention in keyword mentions, likely attributable to the prohibition of corresponding CHM, consequently diminishing research focus.

Co-occurrence clustering analysis identified 3 clusters related to CHM, mechanism and pharmacology, respectively. Although all included publications involved both CHM and toxicity, the connection between these 2 words and their derivatives were relatively loose. This may be attributed to studies focusing predominantly on one keyword and giving less attention to the other, leading to a low frequency of co-occurrence. Therefore, there remains insufficient studies that directly explore the intersection of CHM and toxicity. Keywords with short-term durations indicate limited research importance in these topics. In long-term keywords, apart from toxicity and safety, angiogenesis and neuroprotection had weak correlation with CHM's toxicity itself. On the contrary, some low-toxicity CHMs were shown to possess neuroprotective or anti-angiogenic properties, thereby reducing neurotoxicity or cardiotoxicity induced by other drugs (Cheng et al., 2016; Li et al., 2019). These keywords could provide new insights into the relationship between CHM and toxicity. Emerging keywords in the past 3 years included 2 mechanism-related terms and 2 methodological terms. Within the mechanism category, ferroptosis is a non-apoptotic form of cell death, which is also an effective index for monitoring kidney injury (Jiang et al., 2021; Zeng et al., 2023). A recent study indicated that certain CHMs containing arsenic can induce kidney injury through the induction of ferroptosis (Zhang et al., 2022). The NLRP3 inflammasome was recognized as a trigger for liver injury (Mridha et al., 2017). In CHMs, *Epimedium brevicornu* and *Psoralea corylifolia* were proved to cause liver injury by enhancing NLRP3 inflammasome activation (Wang et al., 2020; Qin et al., 2021). Therefore, further studies concerning hepatotoxicity and nephrotoxicity in CHMs could take these 2 topics into consideration. Machine learning and network pharmacology were emerging technologies in the field of pharmacology. In the study of CHM, machine learning exists the potential in predicting toxicity (Zulkifli et al., 2023), while network pharmacology could be utilized to compensate for the limitations of traditional research methods in understanding the multi-component synergism of CHM (Yuan et al., 2017). Although landmark achievements in these 2 methods within CHM toxicity research are currently limited, they hold potential for future directions. It should be emphasized that these methods, based on existing evidence, rely on the accumulation of data from original studies.

One limitation is that the study was conducted on existing publications, which was unable to represent undiscovered research directions. Despite this common shortcoming of this type of research, this study attempted to explore future research directions by summarizing emerging keywords. Another limitation is that the influence of a journal or individual publication may not be fully consistent with the number of citations received. Aside from publication time and exposure, citation rate may even be affected by the popularity of the publisher or author (Hirsch, 2005). To mitigate this limitation, this study included only publications from the last 10 years to avoid diluting recent trends with outdated studies or methods. Additionally, potential bias may arise from the constraint of current software in merging database analyses. In order to mitigate this source of error, WOS was designated as the principal database for analysis, with supplementary examination of the CNKI database aimed at exploring divergences between the two databases.

5 Conclusion

Concerns about the toxicity of CHM have increased in the past decade. However, there remains insufficient studies that directly explore the intersection of CHM and toxicity. Hepatotoxicity and nephrotoxicity, as the most concerned toxicity classifications associated with CHM, warrant more in-depth investigations. Apoptosis was the most concerned toxicological mechanism. As a recent increase in attention, exploring the mechanisms of ferroptosis in nephrotoxicity and NLRP3 inflammasome in hepatotoxicity could provide valuable insights. Machine learning and network pharmacology are potential methods for future studies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

K-XZ: Data curation, Investigation, Methodology, Writing–original draft. MW: Investigation, Writing–original draft. Z-LB: Formal Analysis, Resources, Software, Visualization, Writing–review and editing. S-LH: Writing–review and editing. L-MF: Writing–review and editing. F-FG: Formal Analysis, Resources, Software, Visualization, Writing–review and editing. X-ZW: Conceptualization, Formal Analysis, Resources, Software, Supervision, Visualization, Writing–review and editing. S-FX: Project administration, Supervision, Validation, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the fifth batch of training objects of the national TCM clinical outstanding talents training program (National Letter of TCM Education [2022] No. 1), the Key Project of Jiangsu Provincial Health Commission (ZD2021042) and the Natural Science Foundation for Nanjing University of Chinese Medicine (XZR2020029).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1293468/full#supplementary-material

References

Barnes, J., McLachlan, A. J., Sherwin, C. M., and Enioutina, E. Y. (2016). Herbal medicines: challenges in the modern world. Part 1. Australia and New Zealand. *Expert Rev. Clin. Pharmacol.* 9, 905–915. doi:10.1586/17512433.2016.1171712

Chen, V. L., and Fontana, R. J. (2021). Are herbals more hepatotoxic than prescription medications. *Hepatol. Int.* 15, 1301–1304. doi:10.1007/s12072-021-10256-w

Cheng, J. H., Tsai, C. L., Lien, Y. Y., Lee, M. S., and Sheu, S. C. (2016). High molecular weight of polysaccharides from Hericium erinaceus against amyloid beta-induced neurotoxicity. *BMC Complement. Altern. Med.* 16, 170. doi:10.1186/s12906-016-1154-5

Donaldson, L. J., Kelley, E. T., Dhingra-Kumar, N., Kieny, M. P., and Sheikh, A. (2017). Medication without harm: WHO's third global patient safety challenge. *Lancet* 389, 1680–1681. doi:10.1016/S0140-6736(17)31047-4

Ekor, M. (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front. Pharmacol.* 4, 177. doi:10.3389/fphar.2013.00177

Frenzel, C., and Teschke, R. (2016). Herbal hepatotoxicity: clinical characteristics and listing compilation. *Int. J. Mol. Sci.* 17, 588. doi:10.3390/ijms17050588

Gabardi, S., Munz, K., and Ulbricht, C. (2007). A review of dietary supplement-induced renal dysfunction. *Clin. J. Am. Soc. Nephrol.* 2, 757–765. doi:10.2215/CJN.00500107

Hao, P., Jiang, F., Cheng, J., Ma, L., Zhang, Y., and Zhao, Y. (2017). Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. *J. Am. Coll. Cardiol.* 69, 2952–2966. doi:10.1016/j.jacc.2017.04.041

Hashimoto, K., Higuchi, M., Makino, B., Sakakibara, I., Kubo, M., Komatsu, Y., et al. (1999). Quantitative analysis of aristolochic acids, toxic compounds, contained in some medicinal plants. *J. Ethnopharmacol.* 64, 185–189. doi:10.1016/s0378-8741(98)00123-8

He, S., Zhang, C., Zhou, P., Zhang, X., Ye, T., Wang, R., et al. (2019). Herb-induced liver injury: phylogenetic relationship, structure-toxicity relationship, and herb-ingredient network analysis. *Int. J. Mol. Sci.* 20, 3633. doi:10.3390/ijms20153633

He, T., Ao, J., Duan, C., Yan, R., Li, X., Liu, L., et al. (2022). Bibliometric and visual analysis of nephrotoxicity research worldwide. *Front. Pharmacol.* 13, 940791. doi:10.3389/fphar.2022.940791

Hirsch, J. E. (2005). An index to quantify an individual's scientific research output. *Proc. Natl. Acad. Sci. U.S.A.* 102, 16569–16572. doi:10.1073/pnas.0507655102

Hoppmann, N. A., Gray, M. E., and McGuire, B. M. (2020). Drug-induced liver injury in the setting of chronic liver disease. *Clin. Liver Dis.* 24, 89–106. doi:10.1016/j.cld.2019.09.006

Jakobsson, P. J., Robertson, L., Welzel, J., Zhang, M., Zhihua, Y., Kaixin, G., et al. (2022). Where traditional Chinese medicine meets Western medicine in the prevention of rheumatoid arthritis. *J. Intern. Med.* 292, 745–763. doi:10.1111/joim.13537

Jiang, X., Stockwell, B. R., and Conrad, M. (2021). Ferroptosis: mechanisms, biology and role in disease. *Nat. Rev. Mol. Cell Biol.* 22, 266–282. doi:10.1038/s41580-020-00324-8

Kulkarni, P. (2021). Prediction of drug-induced kidney injury in drug discovery. *Drug Metab. Rev.* 53, 234–244. doi:10.1080/03602532.2021.1922436

Lan, X., Zhao, J., Zhang, Y., Chen, Y., Liu, Y., and Xu, F. (2020). Oxymatrine exerts organ- and tissue-protective effects by regulating inflammation, oxidative stress, apoptosis, and fibrosis: from bench to bedside. *Pharmacol. Res.* 151, 104541. doi:10.1016/j.phrs.2019.104541

Lee, T. Y., Wu, M. L., Deng, J. F., and Hwang, D. F. (2002). High-performance liquid chromatographic determination for aristolochic acid in medicinal plants and slimming products. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 766, 169–174. doi:10.1016/s0378-4347(01)00416-9

Li, C., Niu, M., Bai, Z., Zhang, C., Zhao, Y., Li, R., et al. (2017). Screening for main components associated with the idiosyncratic hepatotoxicity of a tonic herb, Polygonum multiflorum. *Front. Med.* 11, 253–265. doi:10.1007/s11684-017-0508-9

Li, J., Wu, Y., Wang, D., Zou, L., Fu, C., Zhang, J., et al. (2019). Oridonin synergistically enhances the anti-tumor efficacy of doxorubicin against aggressive breast cancer via pro-apoptotic and anti-angiogenic effects. *Pharmacol. Res.* 146, 104313. doi:10.1016/j.phrs.2019.104313

Li, Q., Yan, X., Zhang, Y., Zhou, J., Yang, L., Wu, S., et al. (2022). Risk compounds, potential mechanisms and biomarkers of traditional Chinese medicine-induced reproductive toxicity. *J. Appl. Toxicol.* 42, 1734–1756. doi:10.1002/jat.4290

Liu, C., Zhang, C., Wang, W., Yuan, F., He, T., Chen, Y., et al. (2019). Integrated metabolomics and network toxicology to reveal molecular mechanism of celastrol induced cardiotoxicity. *Toxicol. Appl. Pharmacol.* 383, 114785. doi:10.1016/j.taap.2019.114785

Liu, H., Gu, L. B., Tu, Y., Hu, H., Huang, Y. R., and Sun, W. (2016). Emodin ameliorates cisplatin-induced apoptosis of rat renal tubular cells *in vitro* by activating autophagy. *Acta Pharmacol. Sin.* 37, 235–245. doi:10.1038/aps.2015.114

Liu, S. H., Chuang, W. C., Lam, W., Jiang, Z., and Cheng, Y. C. (2015). Safety surveillance of traditional Chinese medicine: current and future. *Drug Saf.* 38, 117–128. doi:10.1007/s40264-014-0250-z

Liu, Y., Wang, Q., Yang, J., Guo, X., Liu, W., Ma, S., et al. (2018). Polygonum multiflorum Thunb.: a review on chemical analysis, processing mechanism, quality evaluation, and hepatotoxicity. *Front. Pharmacol.* 9, 364. doi:10.3389/fphar.2018.00364

Lv, W., Piao, J. H., and Jiang, J. G. (2012). Typical toxic components in traditional Chinese medicine. *Expert Opin. Drug Saf.* 11, 985–1002. doi:10.1517/14740338.2012.726610

Ma, Z. T., Shi, Z., Xiao, X. H., and Wang, J. B. (2023). New insights into herb-induced liver injury. *Antioxid. Redox Signal.* 38, 1138–1149. doi:10.1089/ars.2022.0134

Mridha, A. R., Wree, A., Robertson, A., Yeh, M. M., Johnson, C. D., Van Rooyen, D. M., et al. (2017). NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J. Hepatol.* 66, 1037–1046. doi:10.1016/j.jhep.2017.01.022

Noel, P., Von Hoff, D. D., Saluja, A. K., Velagapudi, M., Borazanci, E., and Han, H. (2019). Triptolide and its derivatives as cancer therapies. *Trends Pharmacol. Sci.* 40, 327–341. doi:10.1016/j.tips.2019.03.002

Qin, N., Xu, G., Wang, Y., Zhan, X., Gao, Y., Wang, Z., et al. (2021). Bavachin enhances NLRP3 inflammasome activation induced by ATP or nigericin and causes idiosyncratic hepatotoxicity. *Front. Med.* 15, 594–607. doi:10.1007/s11684-020-0809-2

Qu, L., Li, X., Xiong, Y., Wang, Z., Zhou, Y., Zou, W., et al. (2022). Opportunities and hurdles to European market access for multi-herbal traditional Chinese medicine products: an analysis of EU regulations for combination herbal medicinal products. *Pharmacol. Res.* 186, 106528. doi:10.1016/j.phrs.2022.106528

Raynor, D. K., Dickinson, R., Knapp, P., Long, A. F., and Nicolson, D. J. (2011). Buyer beware? Does the information provided with herbal products available over the counter enable safe use. *BMC Med.* 9, 94. doi:10.1186/1741-7015-9-94

Romanov, V., Whyard, T. C., Waltzer, W. C., Grollman, A. P., and Rosenquist, T. (2015). Aristolochic acid-induced apoptosis and G2 cell cycle arrest depends on ROS generation and MAP kinases activation. *Arch. Toxicol.* 89, 47–56. doi:10.1007/s00204-014-1249-z

Shen, T., Liu, Y., Shang, J., Xie, Q., Li, J., Yan, M., et al. (2019). Incidence and Etiology of drug-induced liver injury in mainland China. *Gastroenterology* 156, 2230–2241. doi:10.1053/j.gastro.2019.02.002

Sun, W., Yan, B., Wang, R., Liu, F., Hu, Z., Zhou, L., et al. (2018). *In vivo* acute toxicity of detoxified Fuzi (lateral root of Aconitum carmichaeli) after a traditional detoxification process. *EXCLI J.* 17, 889–899. doi:10.17179/excli2018-1607

Teng, L., Zu, Q., Li, G., Yu, T., Job, K. M., Yang, X., et al. (2016). Herbal medicines: challenges in the modern world. Part 3. China and Japan. *Expert Rev. Clin. Pharmacol.* 9, 1225–1233. doi:10.1080/17512433.2016.1195263

Teschke, R., Wolff, A., Frenzel, C., and Schulze, J. (2014). Review article: herbal hepatotoxicity--an update on traditional Chinese medicine preparations. *Aliment. Pharmacol. Ther.* 40, 32–50. doi:10.1111/apt.12798

Tu, Y. (2016). Artemisinin-A gift from traditional Chinese medicine to the world (Nobel lecture). *Angewandte Chemie Int. ed. Engl.* 55, 10210–10226. doi:10.1002/anie.201601967

van Eck, N. J., and Waltman, L. (2010). Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 84, 523–538. doi:10.1007/s11192-009-0146-3

Vanhaelen, M., Vanhaelen-Fastre, R., But, P., and Vanherweghem, J. L. (1994). Identification of aristolochic acid in Chinese herbs. *Lancet* 343, 174. doi:10.1016/s0140-6736(94)90964-4

Wang, J., Song, H., Ge, F., Xiong, P., Jing, J., He, T., et al. (2022). Landscape of DILI-related adverse drug reaction in China Mainland. *Acta Pharm. Sin. B* 12, 4424–4431. doi:10.1016/j.apsb.2022.04.019

Wang, L., Ding, X., Li, C., Zhao, Y., Yu, C., Yi, Y., et al. (2018a). Oral administration of Aristolochia manshuriensis Kom in rats induces tumors in multiple organs. *J. Ethnopharmacol.* 225, 81–89. doi:10.1016/j.jep.2018.07.001

Wang, Y., Guo, S. H., Shang, X. J., Yu, L. S., Zhu, J. W., Zhao, A., et al. (2018b). Triptolide induces Sertoli cell apoptosis in mice via ROS/JNK-dependent activation of the mitochondrial pathway and inhibition of Nrf2-mediated antioxidant response. *Acta Pharmacol. Sin.* 39, 311–327. doi:10.1038/aps.2017.95

Wang, Z., Xu, G., Wang, H., Zhan, X., Gao, Y., Chen, N., et al. (2020). Icariside II, a main compound in Epimedii Folium, induces idiosyncratic hepatotoxicity by enhancing NLRP3 inflammasome activation. *Acta Pharm. Sin. B* 10, 1619–1633. doi:10.1016/j.apsb.2020.03.006

Yang, B., Xie, Y., Guo, M., Rosner, M. H., Yang, H., and Ronco, C. (2018). Nephrotoxicity and Chinese herbal medicine. *Clin. J. Am. Soc. Nephrol.* 13, 1605–1611. doi:10.2215/CJN.11571017

Yang, Y., Ge, F. L., Tang, J. F., Qin, S. L., Zeng, R., Yao, M. L., et al. (2022). A review of herb-induced liver injury in mainland China. *Front. Pharmacol.* 13, 813073. doi:10.3389/fphar.2022.813073

Yao, C. L., Zhang, J. Q., Li, J. Y., Wei, W. L., Wu, S. F., and Guo, D. A. (2021). Traditional Chinese medicine (TCM) as a source of new anticancer drugs. *Nat. Prod. Rep.* 38, 1618–1633. doi:10.1039/d0np00057d

You, L., Liang, K., An, R., and Wang, X. (2022). The path towards FDA approval: a challenging journey for Traditional Chinese Medicine. *Pharmacol. Res.* 182, 106314. doi:10.1016/j.phrs.2022.106314

Yuan, H., Ma, Q., Cui, H., Liu, G., Zhao, X., Li, W., et al. (2017). How can synergism of traditional medicines benefit from network pharmacology. *Molecules* 22, 1135. doi:10.3390/molecules22071135

Zeng, F., Nijiati, S., Liu, Y., Yang, Q., Liu, X., Zhang, Q., et al. (2023). Ferroptosis MRI for early detection of anticancer drug-induced acute cardiac/kidney injuries. *Sci. Adv.* 9, eadd8539. doi:10.1126/sciadv.add8539

Zhang, S., Cao, S., Zhou, H., Li, L., Hu, Q., Mao, X., et al. (2022). Realgar-induced nephrotoxicity via ferroptosis in mice. *J. Appl. Toxicol.* 42, 1843–1853. doi:10.1002/jat.4362

Zhong, Y., Menon, M. C., Deng, Y., Chen, Y., and He, J. C. (2015). Recent advances in traditional Chinese medicine for kidney disease. *Am. J. Kidney Dis.* 66, 513–522. doi:10.1053/j.ajkd.2015.04.013

Zhou, J., Ouedraogo, M., Qu, F., and Duez, P. (2013). Potential genotoxicity of traditional Chinese medicinal plants and phytochemicals: an overview. *Phytother. Res.* 27, 1745–1755. doi:10.1002/ptr.4942

Zulkifli, M. H., Abdullah, Z. L., Mohamed Yusof, N., and Mohd Fauzi, F. (2023). *In silico* toxicity studies of traditional Chinese herbal medicine: a mini review. *Curr. Opin. Struct. Biol.* 80, 102588. doi:10.1016/j.sbi.2023.102588

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 15 February 2024
DOI 10.3389/fonc.2024.1340419

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Stephanie Dobersch,
Fred Hutchinson Cancer Center, United States
Charushila Kadam,
Sukh Sagar Medical College and Hospital, India

*CORRESPONDENCE
Eishi Baba
baba.eishi.889@m.kyushu-u.ac.jp

RECEIVED 17 November 2023
ACCEPTED 30 January 2024
PUBLISHED 15 February 2024

CITATION
Ohmura H, Tobo T, Ando Y, Masuda T, Mimori K, Akashi K and Baba E (2024) Case report: A rare case of triple negative breast cancer with development of acute pancreatitis due to dexamethasone during adjuvant chemotherapy.
Front. Oncol. 14:1340419.
doi: 10.3389/fonc.2024.1340419

Case report: A rare case of triple negative breast cancer with development of acute pancreatitis due to dexamethasone during adjuvant chemotherapy

Hirofumi Ohmura[1], Taro Tobo[2], Yuki Ando[3], Takaaki Masuda[3], Koshi Mimori[3], Koichi Akashi[4] and Eishi Baba[1]*

[1]Department of Oncology and Social Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan, [2]Department of Clinical Laboratory Medicine, Kyushu University Beppu Hospital, Beppu, Japan, [3]Department of Surgery, Kyushu University Beppu Hospital, Oita, Japan, [4]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Here, we present the case of a 42-year-old female who developed acute pancreatitis due to dexamethasone during adjuvant chemotherapy for early triple negative breast cancer (TNBC). The patient received partial mastectomy and sentinel lymph node biopsy for early TNBC (cT1N0M0, cStage I) of the left breast. Dose-dense doxorubicin plus cyclophosphamide (ddAC) was administered as the adjuvant-chemotherapy; however, epigastralgia appeared on the fifth day of the first administration. A blood test showed a remarkable increase of serum pancreatic enzyme levels and computed tomography (CT) showed the swelling of pancreas and surrounding effusion, and she was diagnosed with moderate acute pancreatitis. As she had no history of excessive alcohol consumption or complication of cholelithiasis, dyslipidemia, or pancreatic neoplasm, drug-induced pancreatitis was suspected. Dexamethasone, which was administered as an antiemetic, was the suspected drug based on the drug administration history and previous report, and dexamethasone was discontinued from the second administration of ddAC. There was subsequently no recurrence of pancreatitis with no increase in serum pancreatic enzyme levels, and it was possible to complete adjuvant-chemotherapy. Alcohol, gallstones, dyslipidemia, and drugs have been reported as causes of pancreatitis; however, steroid-induced acute pancreatitis is extremely rare. We present the first case of acute pancreatitis induced by dexamethasone as the antiemetic.

KEYWORDS

breast cancer, adjuvant-chemotherapy, pancreatitis, dexamethasone, adverse effects

1 Introduction

Breast cancer is the most common malignancy and a leading cause of cancer death in women worldwide (1). Early-stage breast cancer is treated with surgery, while multimodal therapy including radiation, perioperative chemotherapy is added according to the risk factors for recurrence. In operable breast cancer, adjuvant chemotherapy and neoadjuvant chemotherapy have shown no significant difference in overall survival (OS) and disease-free survival (DFS) (2). Pathologic complete response after neoadjuvant chemotherapy is associated with improved long-term outcomes (3–5). Standard perioperative chemotherapy options for HER2-negative breast cancer include anthracyclines and taxanes. A typical regimen is 4 cycles of doxorubicin plus cyclophosphamide (AC) followed by 4 cycles of paclitaxel (PTX). Compared to standard 3-week cycles, dose-dense chemotherapy with the support of granulocyte colony-stimulating factor and 2-week cycles significantly improved DFS and OS (6).

Acute pancreatitis is diagnosed based on at least two of the following revised Atlanta criteria: (1) abdominal pain suggestive of pancreatitis, (2) serum amylase or lipase >3 times the upper limit of normal, and (3) imaging findings of acute pancreatitis on CT or MRI (7, 8). Common causes are gallstones and alcohol, while genetic and drug-induced are less common. The pathogenesis involves damage to pancreatic acinar cells, inappropriate intra-acinar trypsinogen activation, and autodigestion of the pancreatic parenchyma. Activated pancreatic enzymes injure the pancreatic tissue, inducing inflammatory cytokines through NFκB signaling, resulting in inflammation and edema of the pancreas. In gallstone pancreatitis, increased pancreatic duct pressure from obstructed outflow is thought to be the main cause, while the pathogenesis of alcohol-induced pancreatitis has not been well elucidated (9). Genetic mutations have been identified as the cause of pancreatitis, including *PRSS1* mutations in cationic trypsinogen, and *SPINK1* mutations associated with inactivation of trypsin (10). Drug-induced pancreatitis is rare; however, more than 100 medications have been reported to be associated with pancreatitis. Direct toxicity for pancreas, accumulation of metabolites, ischemia of pancreatic tissue, and increased viscosity of pancreatic secretions have been suggested as the mechanisms for the onset of drug-induced pancreatitis; however, the mechanisms underlying drug-induced pancreatitis have not been well elucidated for most causative drugs (11, 12).

2 Case description

A 42-year-old woman presented to a local clinic in March 2019 with a complaint of left breast mass with the longest diameter of 15mm in the C region by ultrasound examination. The patient had undergone breast cancer screening in the previous year, and mammography revealed no abnormal findings. Core needle biopsy from the left breast mass showed invasive ductal carcinoma, solid tubular type, tumor size; invasive area 18×16mm, nuclear grade (NG) 3, hormone receptor (estrogen receptor, ER; and progesterone receptor, PgR) negative, and HER2 negative. The patient was referred to our surgical department in April for further treatment of TNBC cT1N0M0, cStage I. The patient had no family history of pancreatic cancer or pancreatitis, or history of excessive alcohol consumption, cholelithiasis, diabetes, dyslipidemia or hypertension. And she had no medication or food allergy. In May, partial mastectomy and sentinel lymph node biopsy were performed. Postoperative pathological diagnosis revealed TNBC, T1cN0, ly0, v0, NG3, ER (Allred score 0), PgR (Allred score 0), HER2 (IHC score 0), and MIB1 (78%) (Figures 1A–E). Postoperative dose-dense doxorubicin plus cyclophosphamide (ddAC; doxorubicin 60 mg/m2 day1, cyclophosphamide 600 mg/m2 day1, 2-week cycle)×4 cycles followed by dose-dense paclitaxel (ddPTX; paclitaxel 175 mg/m2 day1, 2-week cycle)×4 cycles, then radiation to the residual breast, was planned for the adjuvant therapy. Administration of ddAC was initiated in August. As antiemetics, dexamethasone (9.9mg/body day1, intravenous; 8mg/body day2-4, oral), aprepitant (125mg/body day1; 80mg/body day2-3, oral), and granisetron (3mg/body, day1, intravenous) were administered. On day 5 of the first cycle of ddAC, the patient developed epigastric pain, with marked elevation of pancreatic enzymes (amylase 1344 U/L (pancreatic amylase, 97.4%; salivary amylase, 2.6%), lipase 1895 U/L). Contrast-enhanced CT showed pancreatic enlargement and peri-pancreatic fluid, meeting criteria for mild acute pancreatitis by the revised Atlanta classification (Figure 2). With fasting and intravenous fluid administration, pancreatic enzymes rapidly decreased, and the abdominal pain resolved (Figure 3). Re-examination of CT after 3 days showed the resolution of the peri-pancreatic fluid, indicating improvement of the pancreatitis. The patient had no history of heavy alcohol intake, gallstones, dyslipidemia, or pancreatic tumor, implicating drug-induced pancreatitis. Among the medications, doxorubicin, cyclophosphamide, and antiemetics including dexamethasone, aprepitant, and granisetron were considered to be candidates for suspected drugs. There has been a previous report of acute pancreatitis due to dexamethasone, and with the Naranjo adverse drug reactions (ADR) probability scale (≥ 9 points, Definite; 5-8 points, Probable; 1-4 points, Possible; 0-3 points, Doubtful) (13), dexamethasone scored 6 indicating 'Probable', while other drugs scored 3 indicating 'Possible', and dexamethasone was considered as the suspected drug. Dexamethasone was omitted from cycle 2. The doses of other drugs remained unchanged. No further elevation of serum pancreatic enzymes or recurrence of pancreatitis was observed, allowing completion of 4 cycles of ddAC and 4 cycles of ddPTX. Steroid-induced acute pancreatitis is extremely rare, however, it should be recognized as a potential adverse event of chemotherapy.

3 Discussion

There is one previous case report of acute pancreatitis after administration of dexamethasone for spinal cord compression, with recurrence on re-challenge; however, the patient also had risk factors

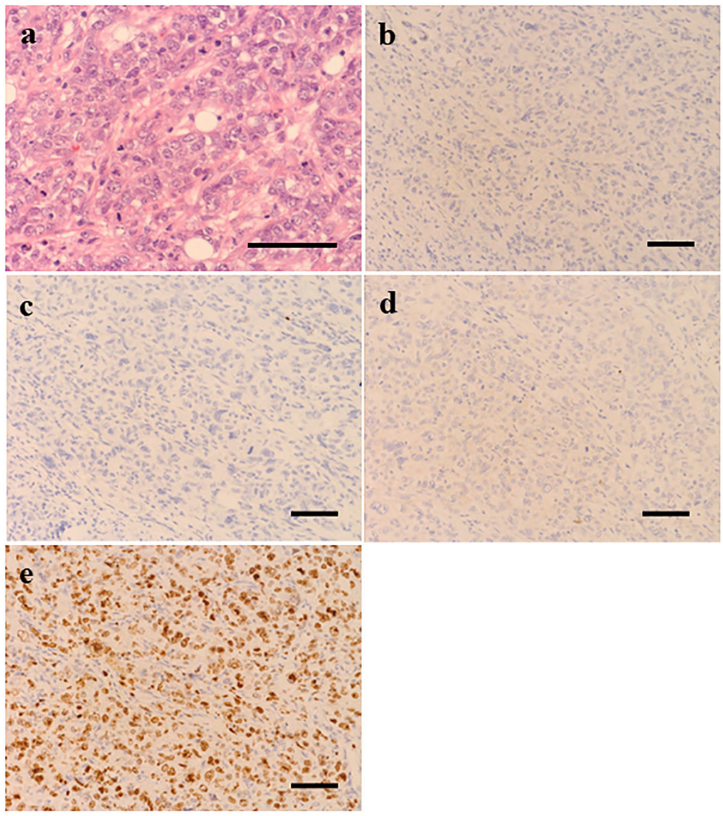


FIGURE 1
Histopathological examination (scale bar 50 μm) of the surgical specimen from the lesion of left breast showed invasive ductal carcinoma grade 3 **(A)**. Immunohistochemically, tumor cells were negative for estrogen receptor **(B)**, progesterone receptor **(C)** and HER2 **(D)** and Ki67 score was 78% **(E)**.

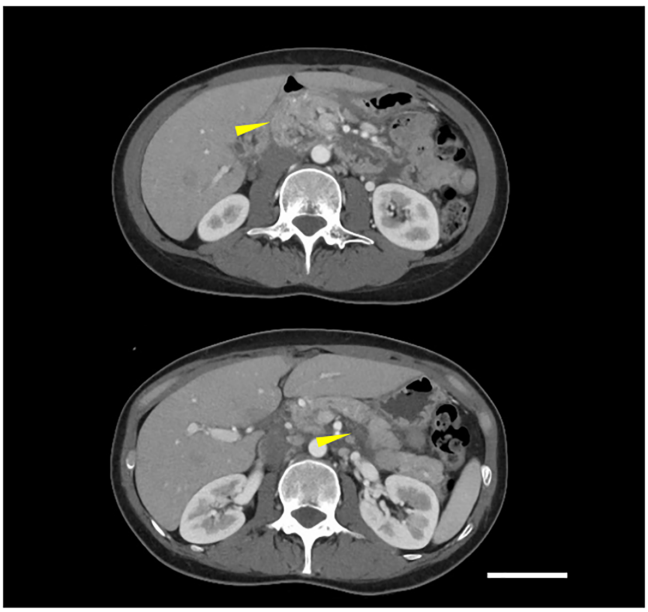


FIGURE 2
Contrast-enhanced CT showed pancreatic enlargement and peri-pancreatic fluid (indicated by yellow arrows), meeting criteria for mild acute pancreatitis according to the revised Atlanta classification (scale bar 5 cm).

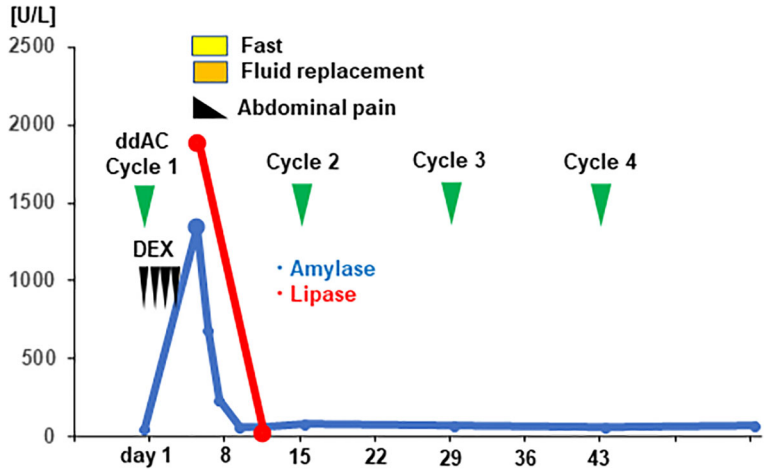


FIGURE 3
Clinical time course and the serum level of pancreatic enzymes of the patient are shown. The vertical axis of the graph shows the serum levels of pancreatic enzymes [U/mL], and the horizontal axis shows the days from initiation of dose-dense doxorubicin plus cyclophosphamide (ddAC). Dexamethasone (DEX) was administered on day1-4.

including alcohol intake (14). Khanna et al. reported a case of acute pancreatitis induced by re-administration of hydrocortisone for ulcerative colitis. Other steroids including prednisolone and cortisone acetate also may potentially cause acute pancreatitis (15). Glucocorticoids including dexamethasone have been reported to inhibit NFκB activation and suppress TNFα production of immune cells (16). As NFκB activation and inflammatory cytokine production are involved in the pathogenesis of pancreatitis (9), the mechanism of steroid-induced pancreatitis likely involves pathways other than NFκB activation. Previous reports have also suggested that steroids increase pancreatic juice viscosity and proliferate pancreatic ductal epithelium, delaying excretion and contributing to pancreatic autodigestion (12, 17). However, the detailed mechanisms of steroid-induced pancreatitis have not been elucidated. The association between side effects and suspected drug can be evaluated using the Naranjo ADR probability scale (13), and in this case, dexamethasone scored higher than other drugs, suggesting a stronger association with pancreatitis. By excluding gallstones, alcohol, and other common causes of pancreatitis, and based on the Naranjo score, dexamethasone-induced pancreatitis was diagnosed. In the previous case-control study by Sadr-Azodi et al., oral glucocorticoid (betamethasone and prednisolone) administration was associated with an increased risk of acute pancreatitis (OR, 1.53; 95% CI, 1.27-1.84) and the risk was highest 4 to 14 days after drug administration (OR, 1.73; 95% CI, 1.31-2.28). Dexamethasone had not been studied in this study, however, it should also be considered as a potential cause of pancreatitis as an oral glucocorticoid (18).

Although there has been one case report of pancreatitis caused by dexamethasone administered for spinal cord compression, no previous report of pancreatitis caused by dexamethasone administered for supportive therapy for chemotherapy. In this case, dexamethasone was considered to be the cause of acute pancreatitis, and by omitting dexamethasone, it was possible to complete perioperative chemotherapy for the present patient.

4 Conclusion

Although steroid-induced acute pancreatitis is extremely rare, it should be recognized as a potential adverse event observed during cancer chemotherapy due to use of dexamethasone as antiemetic.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Kyushu University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

HO: Conceptualization, Writing – original draft, Writing – review & editing. TT: Writing – review & editing. YA: Writing – review & editing. TM: Writing – review & editing. KM: Writing – review &

editing. KA: Writing – review & editing. EB: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to thank our patient for giving us permission to publish this case report.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* (2022) 72(1):7–33. doi: 10.3322/caac.21708

2. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National surgical adjuvant breast and bowel project B-18. *J Clin Oncol* (1997) 15(7):2483–93. doi: 10.1200/JCO.1997.15.7.2483

3. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol* (2008) 26(5):778–85. doi: 10.1200/JCO.2007.15.0235

4. van Nes JG, Putter H, Julien JP, Tubiana-Hulin M, van de Vijver M, Bogaerts J, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. *Breast Cancer Res Treat* (2009) 115(1):101–13. doi: 10.1007/s10549-008-0050-1

5. von Minckwitz G, Raab G, Caputo A, Schütte M, Hilfrich J, Blohmer JU, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German breast group. *J Clin Oncol* (2005) 23(12):2676–85. doi: 10.1200/JCO.2005.05.078

6. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* (2003) 21(8):1431–9. doi: 10.1200/JCO.2003.09.081

7. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester M, et al. Acute pancreatitis. *Lancet* (2020) 396(10252):726–34. doi: 10.1016/S0140-6736(20)31310-6

8. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* (2013) 62(1):102–11. doi: 10.1136/gutjnl-2012-302779

9. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: A review. *JAMA* (2021) 325(4):382–90. doi: 10.1001/jama.2020.20317

10. Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. Genetics, cell biology, and pathophysiology of pancreatitis. *Gastroenterology* (2019) 156(7):1951–68.e1. doi: 10.1053/j.gastro.2018.11.081

11. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. *N Engl J Med* (2016) 375(20):1972–81. doi: 10.1056/NEJMra1505202

12. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. *Ochsner J* (2015) 15(1):45–51.

13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* (1981) 30(2):239–45. doi: 10.1038/clpt.1981.154

14. Levine RA, McGuire RF. Corticosteroid-induced pancreatitis: a case report demonstrating recurrence with rechallenge. *Am J Gastroenterol* (1988) 83(10):1161–4.

15. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* (2007) 5(6):648–61. doi: 10.1016/j.cgh.2006.11.023

16. Crinelli R, Antonelli A, Bianchi M, Gentilini L, Scaramucci S, Magnani M. Selective inhibition of NF-kB activation and TNF-alpha production in macrophages by red blood cell-mediated delivery of dexamethasone. *Blood Cells Mol Dis* (2000) 26(3):211–22. doi: 10.1006/bcmd.2000.0298

17. Ranta F, Avram D, Berchtold S, Düfer M, Drews G, Lang F, et al. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. *Diabetes* (2006) 55(5):1380–90. doi: 10.2337/db05-1220

18. Sadr-Azodi O, Mattsson F, Bexlius TS, Lindblad M, Lagergren J, Ljung R. Association of oral glucocorticoid use with an increased risk of acute pancreatitis: a population-based nested case-control study. *JAMA Intern Med* (2013) 173(6):444–9. doi: 10.1001/jamainternmed.2013.2737

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 15 February 2024
DOI 10.3389/fphar.2024.1329220

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Simin Yan,
Nanjing Drum Tower Hospital, China
Haoxiao Chang,
Capital Medical University, China
Dayong Zheng,
North China University of Science and Technology, China
Xin Yue,
First Affiliated Hospital of Sun Yat-sen University, China

*CORRESPONDENCE
Bo Zhai,
etyyzb@163.com
Yang Zhou,
zyangcpu@163.com

RECEIVED 28 October 2023
ACCEPTED 29 January 2024
PUBLISHED 15 February 2024

CITATION
Yan H, Wang P, Yang F, Cheng W, Chen C, Zhai B and Zhou Y (2024), Anticancer therapy-induced adverse drug reactions in children and preventive and control measures.
Front. Pharmacol. 15:1329220.
doi: 10.3389/fphar.2024.1329220

Anticancer therapy-induced adverse drug reactions in children and preventive and control measures

Hui Yan[1,2], Penggao Wang[2], Fang Yang[2], Weyland Cheng[1], Congcong Chen[1], Bo Zhai[2]* and Yang Zhou[1,2]*

[1]Henan Provincial Clinical Research Center for Pediatric Diseases, Henan Key Laboratory of Pediatric Genetics and Metabolic Diseases, Children's Hospital Affiliated to Zhengzhou University, Henan Children's Hospital, Zhengzhou Children's Hospital, Zhengzhou, China, [2]Department of Cardiothoracic Surgery, Children's Hospital Affiliated to Zhengzhou University, Henan Children's Hospital, Zhengzhou Children's Hospital, Zhengzhou, China

In recent years, considerable achievements have been made in pediatric oncology with the innovation and development of antitumor drugs. However, compared to adults, children as a special group have not yet matured fully in terms of liver and kidney function. Moreover, pediatric patients are prone to more adverse drug reactions (ADRs) from the accumulation of antineoplastic drugs due to their smaller body size and larger body surface area. Chemotherapy-related ADRs have become a non-negligible factor that affects cancer remission. To date, studies on ADRs in pediatric cancer patients have emerged internationally, but few systematic summaries are available. Here, we reviewed the various systemic ADRs associated with antitumor drugs in children and adolescent patients, as well as the advances in strategies to cope with ADRs, which consisted of neurotoxicity, hematological toxicity, cardiotoxicity, ADRs of the respiratory system and gastrointestinal system and urinary system, ADRs of the skin and its adnexa, allergic reactions, and other ADRs. For clinicians and researchers, understanding the causes, symptoms, and coping strategies for ADRs caused by anticancer treatments will undoubtedly benefit more children.

KEYWORDS

adverse drug reactions, anticancer drugs, prevention, measures, children

1 Introduction

Malignant tumors are serious diseases that threaten the health and lives of children. It was reported that more than 1.3 million children and adolescents were annually diagnosed with cancer worldwide (YOU et al., 2021). The incidence rate of developing cancer ranged from 130 to 160 cases per million children, and the incidence had been increasing at a rate of about 2.8% per year for the past 10 years (GUPTA et al., 2020a). As a global public health crisis, childhood tumors have become the second leading cause of childhood death, second to accidental deaths (STELIAROVA-FOUCHER et al., 2017). From 2010 to 2020, the incidence rate of childhood tumors was 8.71/100,000 and the mortality rate was 3.63/100,000 in China, according to the data from the National Cancer Center of China (ZHENG et al., 2015). The first global burden of disease (GBD) assessment of childhood and adolescent cancer using disability-adjusted life-years (DALYs) showed that childhood

cancer had become the sixth largest cancer burden in the world (The global burden of childhood, 2019). Thus, it is urgent to focus on the issue of childhood cancers.

With the development of antitumor drugs in recent years, significant achievements have been made in the treatment of childhood cancers. The 5-year survival rate of children under 14 years old with tumors was 84.0% according to U.S. statistics in 2021, with the 5-year survival rate of children with lymphoid leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma (including Burkitt) exceeding 90.0% (SIEGEL et al., 2021). Unfortunately, unlike adults, pediatric patients are more susceptible to ADRs because of the special characteristics of children. Firstly, children have a smaller body size and a larger proportion of body surface area, which makes it easier for drug accumulation to occur in the body. Secondly, the growth and development process of children is a combination of many highly complex organ maturation processes, and these parallel developmental processes follow different temporal developmental trajectories, so that the absorption, distribution, metabolism, excretion and drug responsiveness of children to drugs are different from those of adults. Finally, children's bodies are at a stage of growth and development where the blood-brain-barrier (BBB) is still imperfect, and metabolic organs such as the liver and kidneys are not yet mature, and the distribution and activity of drug-metabolising enzymes/transporters are poorer than those of adults, so their tolerance and responsiveness to drugs are different from adults. The ADRs caused in children are multifaceted, such as hematopoietic suppression, gastrointestinal reactions, and neurotoxicity (BOND et al., 2008; PAWAR et al., 2018). ADRs refer to the harmful and unrelated to the purpose of medication that occur when a normal dose of medication is used for the prevention, diagnosis, treatment of disease or regulation of physiological functions.

Chemotherapy-related ADRs have become an important factor affecting cancer remission. Most ADRs are caused by chemotherapeutic agents, which damage the DNA of tumor cells and disrupt DNA replication in proliferating cells. However, many drugs fail to specifically target tumor tissues, resulting in ADRs causing damage to proliferating cells in healthy tissues. It was shown that the overall incidence of ADRs to medications among adults hospitalized for tumors was 8.37%, with 10.77% of severe ADRs (LAVAN et al., 2019). Among children hospitalized for tumors, the overall incidence of ADRs to medications was 9.53%, with severe ADRs accounting for 12.29% (IMPICCIATORE et al., 2001). In addition, over the course of drug therapy for children with tumors, 39.3% of ADRs that resulted in hospitalization were fatal (IMPICCIATORE et al., 2001). More than 21% of adult oncology patient visits were ADRs-related (LAVAN et al., 2019). Among pediatric cancer patients, 22% of hospitalizations were caused by ADRs and 44.2% of ADRs in general led to hospitalization (PAWAR et al., 2018). In recent years, there have been numerous domestic and international studies on ADRs in pediatric cancer patients, but few systematic summaries have been reported. In this article, we will review the ADRs associated with antitumor drugs in children and adolescent patients and the advances in strategies to cope with ADRs that consist of neurotoxicity, hematological toxicity, cardiotoxicity, ADRs of the respiratory system and gastrointestinal system and urinary system, ADRs of the skin and its adnexa, allergic reactions, and other ADRs (Figure 1). We also summarize countermeasures for managing ADRs in order to guide future research and clinical practices on the harmful adverse effects of anti-cancerous treatments in children.

2 Critical pediatric antitumor drugs

Anti-tumor drugs for children are classified according to their source and pharmacological mechanism, which include cytotoxic drugs, hormonal drugs, biological response modifiers, monoclonal antibodies, adjuvants, and other drugs. Based on their effects on the cell cycle, these drugs can also be categorized into cell cycle-specific and cell cycle-nonspecific drugs (Table 1 for details). The ADRs of antitumor drugs in children vary due to their wide variety and the different pharmacological effects of each drug. Different systems and organs in the body are affected in different ways, resulting in different clinical manifestations. Alkylating agents such as cyclophosphamide are more potent in killing M and G1-phase cells, but are less selective and also strongly toxic to normal cells (ABULFADL et al., 2023). Antimetabolites such as antifolates, antipurines, antipyrimidines, and cytarabine (Ara-C) are sensitive to S-phase cells and also function on G1-and G2-phase cells (AMARO-HOSEY et al., 2021; LI et al., 2022). Antitumor antibiotics such as zorubicin and doxorubicin (adriamycin) (ADM) form complexes with DNA and RNA and inhibit cell division (SKINNER et al., 1993). Anti-tumor phytoconstituents such as vincristine (VCR), vinblastine, and etoposide (VP-16) inhibit the formation of the spindle during cell division, causing mitosis to terminate at mid-cycle (GUTIéRREZ-GUTIéRREZ et al., 2010; SAŁAT, 2020a; MODY et al., 2020; LI et al., 2023). In addition to traditional chemotherapeutic drugs, some emerging therapeutic drugs such as targeted drugs (including anti-angiogenesis targeted drugs), immune checkpoint inhibitors (ICIs), monoclonal antibodies and adoptive cell therapy (ACT) (including chimeric antigen receptor (CAR) T cell (CAR-T) therapy and CAR natural killer cell (CAR-NK) therapy) have also expanded the range of cancer treatments (TURGAY et al., 2020).

3 Antitumor therapy and ADRs in the nervous systems

Chemotherapy-induced neuropathy (CIN) by oncology therapeutic agents in children is one of the most common ADRs. CIN can affect the central nervous system or peripheral nervous system, with chemotherapy-induced peripheral neuropathy (CIPN) accounting for a predominant percentage of cases (SAŁAT, 2020b).

Common chemotherapeutic agents that induce neurotoxicity are platinum-based, such as L-OHP and DDP, PTX, and VLB (GUTIéRREZ-GUTIéRREZ et al., 2010; SAŁAT, 2020a). DDP and CBP may cause neurotoxicity by affecting dorsal root ganglion neurons and peripheral nerves through the accumulation of DNA complexes and inhibition of DNA repair processes. It is characterized by nerve ending impairment, optic nerve papillae edema and retrobulbar optic neuritis, and damage to the auditory nerve, which in severe cases can lead to irreversible high-frequency hearing loss (JIAO et al., 2021). Of the

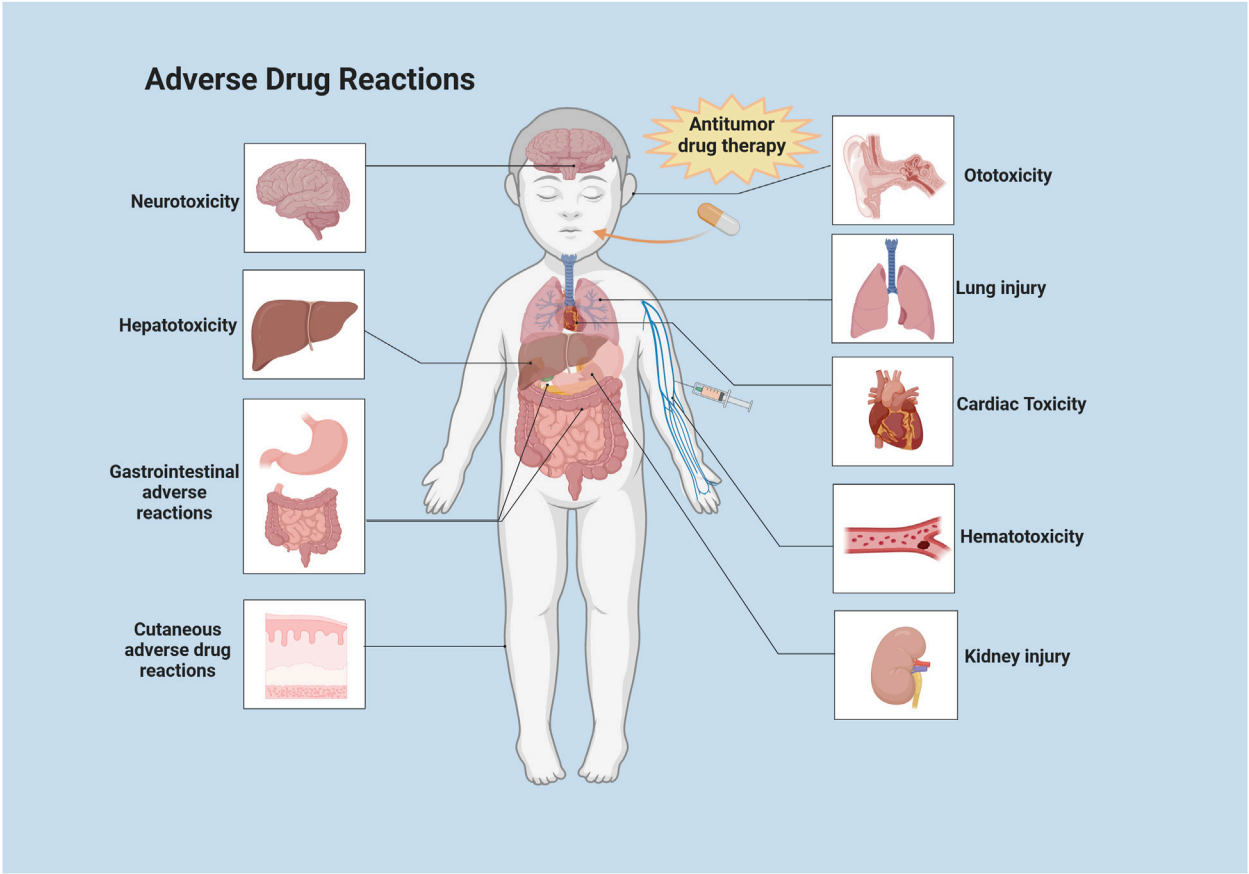


FIGURE 1
Systemic distribution of common ADRs to antitumor drugs in children. This illustration was created with BioRender (agreement number: XF2675PHGR).

platinum-based chemotherapeutic agents, L-OHP has the most pronounced neurotoxicity, including acute and cumulative neurotoxicity. The acute manifestation is mainly characterized by abnormal and delayed sensation in the hands, feet and perioral area. The accumulation is mainly characterized by impaired walking due to delayed fine motor skills and/or impaired organoleptic sensation (SAŁAT, 2020a). Taxanes provoke neurotoxicity by acting on neuronal microtubules, causing destruction and demyelination of nerve axons (IŻYCKI et al., 2016). CIPN is characterized by peripheral bilateral sensory abnormalities, whereas chemotherapy-induced central neuropathy is characterized by developmental cognitive deficits and encephalopathy. VDS causes neurotoxicity mainly by affecting microtubules, which leads to defective axonal transport (FU et al., 2018). Neurotoxicity mainly causes autonomic and peripheral sensory-motor neuropathy, which manifests as numbness or a tingling sensation starting from the tips of the fingers (toes) that progresses centrally, accompanied by weakening or loss of deep tendon reflexes. In severe conditions, it can lead to muscle weakness, especially in the distal hand and foot (DUAN et al., 2018).

Targeted antitumor drugs mainly target tumor cells with little effect on normal cells, leading to fewer reports of neurotoxicity caused by targeted therapy for pediatric tumors. However, vascular endothelial growth factor (VEGF) prevents new blood vessel formation and also plays an important role in the central nervous system. Anti-angiogenic drugs achieve their antitumor effects by inhibiting vascular endothelial growth factor. Therefore, the use of anti-angiogenic drugs may interrupt vascular endothelial growth factors in the central nervous system, leading to cognitive impairment (NG et al., 2014). Cytokines and hormone level changes induced by anticancer drugs can also cause neurotoxicity by altering the hypothalamus-pituitary-adrenal (HPA). The potential pathways by which chemotherapy can cause neurotoxicity in children are shown in Figure 2. Targeted drugs that commonly cause neurotoxicity include thalidomide, pazopanib, C225, and bortezomib. ICIs have been widely applied in the treatment of various pediatric malignant tumors. ICIs have been found to affect different organs and tissues by disrupting the normal immune system and immune tolerance, leading to a variety of immune-related adverse events (irAEs) (MICHOT et al., 2020). These irAEs can also include neurologic immune-related adverse events, which are relatively infrequent (moderate to severe incidence of about 1%), but are extremely serious (MANCONE et al., 2018). Besides, ACT has been found to trigger neurotoxicity in children (ClinicalTrials.gov number: NCT01593696). The CD19/CD28ζ CAR-T cell-based therapies have caused neurotoxicity (e.g., confusion and aphasia) in some individuals during the treatment of children and adolescents with B-cell malignancies. This is closely

TABLE 1 Classification of the main pediatric antitumor drugs.

Classification	Categories	Mechanism of action	Pharmaceuticals
Classification by source and pharmacological mechanism	Cytotoxic drugs	Effects on the chemical structure of DNA	Alkylating agents: Nitrogen mustard (HN2), Cyclophosphamide (CTX), Isocyclophosphamid (IFO), Thiotepa (TSPA), Nitrosoureas and methanesulfonates (Busulfan,BUS/BSF) (ABULFADL et al., 2023)
			Platinum compounds: Cisplatin (DDP), Carboplatin (CBP), Oxaliplatin (L-OHP) (JIN et al., 2021)
			Mitomycin (MMC) (BURZYNSKI, 2006)
			ADM, Epirubicine (EPI), Pirarubincin (THP-adriamycin) (SKINNER et al., 1993)
		Influence on nucleic acid synthesis	Dihydrofolate reductase inhibitor: Methotrexate (MTX), Pemetrexed (PEM) (LOPEZ-LOPEZ et al., 2020)
			Thymidine synthase inhibitor: Fluorouracil (5-Fu), Capecitabine (CAP) (HUANG et al., 2018)
			Purine nucleoside synthase inhibitor: Mercaptopurine (6-MP), Thioguanine (6-TG) (AMARO-HOSEY et al., 2021)
			Nucleotide reductase inhibitor: Hydroxyurea (HU) (PAWAR et al., 2018)
			DNA polymerase inhibitors: Ara-C, Gemcitabine (GEM) (AMARO-HOSEY et al., 2021)
		Effects on Nucleic Acid Transcription	Actinomycin D (ACD), Aclarubicin (aclacinomycin) (ACLA), Plicamycin (mithramycin) (MTH) (PAWAR et al., 2018)
		Topoisomerase inhibitors	Irinotecan (CPT-11), Topotecan (TPT), Hydroxycamptothecin (HCPT), VP-16, Teniposide (VM-26) (MODY et al., 2020)
	Hormones	Predominantly acts in mitotic M phase and interferes with microtubule protein synthesis	Paclitaxel (Taxol) (TAX, PTX), Vinblastine (VLB), Homoharringtonine (HH) (FLAHERTY et al., 2014)
		Other cytotoxic drugs	L-Asparaginase (L-ASP) (HONG et al., 2019)
		Antiestrogen	Tamoxifen (TAM), Toremifene (TOR), Exemestane (EXE) (PAWAR et al., 2018)
		Aromatase inhibitors	Aminoglutethimide (AG), Formestane (FMT), Letrozole (LTZ/LET), Anastrozole (ANA) (PAWAR et al., 2018)
		Progesterone	Medroxyprogesterone (MPA), Megestrol (Megace) (MA) (ZHANG et al., 2020)
		Sex hormone	Androgen: Methyltestosterone, Testosterone Propionate (TP)
			Oestrogen: Diethylstilbestrol (IMAN et al., 2017)
		Antiandrogen	Flutamide (TODD and LIPPARD, 2009)
		Luteinizing hormone-releasing hormone agonist/antagonist	Goserelin (Loanword), Leuprolide acetate (IMAN et al., 2017)
	Biological Response Modifier (BRC)		Interferon (IFN)、Interleukin-2(IL-2), Thymopeptides (FLAHERTY et al., 2014)
	Monoclonal Antibody		Rituximab (Mab Thera) (RTX), Cetuximab (C225), Trastuzumab Emtansine (T-DM1),

(Continued on following page)

TABLE 1 (*Continued*) Classification of the main pediatric antitumor drugs.

Classification	Categories	Mechanism of action	Pharmaceuticals
			Bevacizumab (BEV), PD-1, PD-L1 (TURGAY et al., 2020)
	Other	Cell differentiation/apoptosis inducer	Tretinoin (ATRA), Arsenous acids (PAWAR et al., 2018)
		Neoangiogenesis inhibitors	Rh-Endostatin (YH-16) (NG et al., 2014)
		Epidermal growth factor receptor inhibitor	Gefitinib, Erlotinib (FU et al., 2018)
	Adjuvant	Hematotropic drugs	Granulocyte Colony-Stimulating Factor (GCSF), Granulocyte-Macrophage Colony-Stimulating Factor (GMCSF), Interleukin-11(IL-11), Recombinant human erythropoietin (EPO) (MARTINO et al., 2018)
		Anti-nausea drug	Endansetron, Granisetron hydrochloride (PHILLIPS et al., 2016)
		Analgesic	Aspirin (APC), Paracetamol, Codeine, Tramadol, Morphine, Fentanyl Transdermal (IŻYCKI et al., 2016)
		Osteoclast inhibiting drugs	Bisphosphonate, Pamidronate (ZHU et al., 2020)
Classification by effect on the cell cycle	Cell cycle-specific drugs	M-phase	Vindesine (VDS), VCR, VLB, Vinorelbine (NVB/VRN), HCPT, Docetaxel (TXT, DTX), PTX (GUTIéRREZ-GUTIéRREZ et al., 2010; SAŁAT, 2020a)
		G1-phase	ASP, Adrenocorticotropic Hormone (ADH) (HONG et al., 2019)
		G2-phase	Bleomycin (BLM), Pingyangmycin (PYM) (YU et al., 2016)
		S-phase	Ara-C, GEM, 5-Fu, Ftorafur (FT-207), 6-MP、MTX, HU (AMARO-HOSEY et al., 2021)
	Cell cycle non-specific drugs	Alkylating agents	BUS, HN2, DDP, CTX (ABULFADL et al., 2023)
		Nitrosoureas	Carmustine (BCNU), Lomustine (CCNU), Streptozotocin (STZ) (PAWAR et al., 2018)
		Antimicrobials	Actinomycin D (ACTD), Daunorubicin (DNR), ADM, MMC (PAWAR et al., 2018)
		Other	Procarbazine (PCZ/PCB), Dacarbazine (DTIC) (PAWAR et al., 2018)

related to cytokine release syndrome (CRS) and its severity (SHALABI et al., 2022). In pediatric and young adult patients with relapsed/refractory CD22 malignancies, CAR-T cell therapies targeting CD22 as an alternative to anti-CD19 resulted in CRS in 86.2% of patients, and transient mild neurotoxic symptoms in majority of patients (ClinicalTrials.gov number: NCT02315612) (SHAH et al., 2020).

4 Antitumor therapy and ADRs in the hematologic system

The hematologic system is the most common organ/system involved in ADRs in children treated with antineoplastic drugs. The main clinical manifestation is myelosuppression, which is a universal dose-limiting toxicity of antineoplastic agents. Leukopenia or/and neutropenia, anemia, and thrombocytopenia are the main clinical features of ADRs caused by antineoplastic agents (PAWAR et al., 2018). Among adverse effects, leukopenia, especially neutropenia, is the main cause of death from chemotherapy.

The vast majority of antineoplastic drugs possess a toxic effect on the hematopoietic system to varying degrees. The sensitivity of various blood cells in the bone marrow to chemotherapeutic agents depends on the length of their half-life. The half-life of white blood cells is only 6 h, the half-life of platelets is 5–7 days, and the half-life of red blood cells reaches up to 115 days (FRANCO, 2012). Drugs that damage DNA exhibit strong myelosuppressive effects, followed by those that inhibit RNA synthesis, whereas drugs that affect protein synthesis have the least effect. Representative drugs for myelosuppressive toxicity are Ara-C, MTX, CTX, anthracyclines, HN2, MMC, VM-26, VCR, TPT, TXT, DTX, PTX, GEM, DDP,

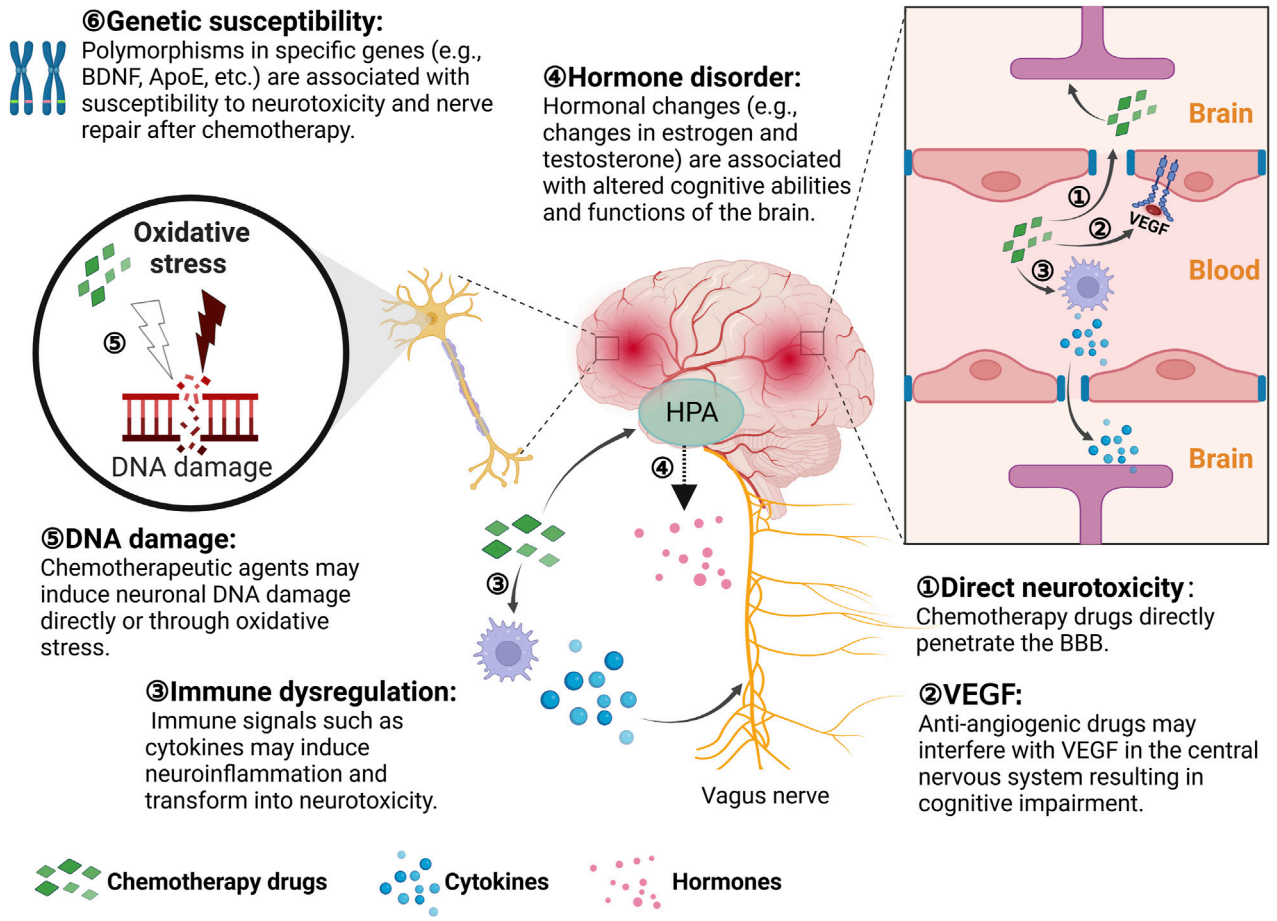


FIGURE 2
Potential neurotoxic pathways of chemotherapy in children. HPA: Hypothalamus-Pituitary-Adrenal; BBB: Blood-Brain-Barrier; VEGF: Vascular Endothelial Growth Factor. This illustration was created with BioRender (agreement number: YP26CY8TOS).

CBP, IFO, VCR, CPT-11, and others. Ara-C is an antimetabolic drug that targets the proliferative phase of cells and is known to interrupt cell proliferation by arresting DNA synthesis. It is clinically utilized to treat acute leukemia, having the best efficacy for acute granulocytic leukemia, and its main ADR consists of myelosuppression (AMARO-HOSEY et al., 2021). MTX is an antifolate drug that hinders tumor growth by inhibiting dihydrofolate reductase. Clinically, it is mostly used for treating acute leukemia, head and neck tumors, bone tumors in children, and its main ADRs consists of gastrointestinal reactions and bone marrow suppression (ClinicalTrials.gov number: NCT00137111) (LOPEZ-LOPEZ et al., 2020). Bone marrow suppression and incidence of gastrointestinal disorders are more frequent due to the heavier use of Ara-C and MTX, as leukemia accounts for the highest proportion of childhood tumors. Therefore, hematopoietic function should be monitored during the application of Ara-C and MTX to avoid serious ADRs.

Aside from myelosuppression, ADRs of antineoplastic drugs on the hematologic system includes leukopenia due to infections (ZHU et al., 2020). In order to minimize post-chemotherapy infections, clinical attention to prevention is more important than treatment when granulocytopenia is present. The defense mechanisms that preserve the patient include reducing the invasion of new pathogens in the environment, reducing traumatic damage to defense mechanisms, and suppressing or killing pathogenic bacteria already present in the body. The series of hematologic ADRs introduced by ACT found in clinical studies should not be underestimated as well. CRS is the most common toxicity associated with CAR-T-related therapies, and even in rare cases it develops into the life-threatening fulminant HLH, which is characterized by anaemia, thrombocytopenia, leukopenia and neutropenia (NEELAPU et al., 2018). And CD22-targeting CAR-T cell therapy also resulted in HLH-like manifestations in 32.8% of children and young adults with relapsed/refractory malignancies (ClinicalTrials.gov number: NCT02315612) (SHAH et al., 2020).

5 Antitumor therapy and ADRs in the cardiac system

Many pediatric antineoplastic drugs produce toxic effects on the myocardium within the course of treatment, mainly manifested by changes in cardiac rhythm, altered blood pressure, ischemia, abnormalities in cardiac systolic or diastolic function, and delayed progressive cardiomyopathy in a minority of children. These ADRs are either temporary episodes or persistently

present. Myocardial ADRs may be subclinical manifestations, but when severe they can be life-threatening and should be emphasized in clinical management. There are a number of chemotherapeutic drugs that cause cardiotoxicity including anthracyclines, PTX, CTX, 5-Fu, MTX, Ara-C, IFN, and monoclonal antibodies.

Cardiomyopathy is one of the earliest reported manifestations of cardiovascular toxicity caused by anthracycline chemotherapeutic agents, a drug commonly utilized in the treatment of leukemia (DE BAAT et al., 2022). Anthracycline-induced cardiovascular toxicity is of type I. One of the possible mechanisms of toxicity is attributed to the inhibition of topoisomerase II activity (TRIPAYDONIS et al., 2019). Topoisomerases are biological enzymes that are essential for biological activities and functions during DNA transcription, replication and recombination (TRIPAYDONIS et al., 2019). Anthracycline-induced cardiovascular toxicity is categorized according to the acuteness of its effects. Acute cardiovascular toxicity is rare, occurring in less than 1% of children at the time of administration or within 1 week after administration, and is characterized by a transient decline in myocardial contractility. Conversely, chronic cardiovascular toxicity occurs more commonly and is further categorized at early onset (within 1 year of dosing) versus late onset (more than 1 year after the end of dosing) (HU et al., 2018). Patients receiving anthracycline-based chemotherapy in childhood are prone to delayed cardiotoxicity when exposed to stressful situations, surgical procedures, or pregnancy during the formative years. The likely mechanism by which PTX causes cardiovascular toxicity is the mediation of massive histamine release. In animal experiments, researchers have found that stimulation of histamine receptors in cardiac tissue resulted in conduction disturbances and arrhythmias. In addition, PTX also affects cellular organelles, thereby causing myocardial injury (SCHIMMEL et al., 2004).

High doses of CTX have been reported to cause cardiovascular toxicity with clinical manifestations consisting of pericardial effusion, pericarditis, reversible decrease in cardiac contractility, and heart failure. Upon activation, CTX forms alkylated molecules that are able to bind to DNA, which triggers intra- and interstrand DNA breaks, leading to inhibition of DNA replication and enhanced apoptosis (ABULFADL et al., 2023). MTX occasionally causes syncope, myocardial infection, and arrhythmia and the most common ADRs related to Ara-C are pericarditis, pericardial effusion, and cardiac tamponade (STRICKLAND and VEY, 2022). GEM is an alternative option applied in recent years for the treatment of refractory or recurrent pediatric solid tumors. Cardiotoxicity, including ventricular arrhythmias and reduced left ventricular ejection fraction, occasionally leading to atrial fibrillation, has been observed in some patients (BENDER et al., 2023). ADRs of IFNs and ILs on the cardiovascular system include ischemia and infarction, arrhythmias, and cardiomyopathy (SONNENBLICK and ROSIN, 1991). Long-term IFN use carries a high risk of reduced left ventricular ejection fraction and congestive heart failure (SONNENBLICK and ROSIN, 1991). High doses of IL-2 are associated with unfavorable cardiovascular and hemodynamic effects, similar to infectious shock and cardiotoxic reactions (JOHN-PAUL and BARTELS, 2017). As a new generation of therapy that has emerged in recent years, monoclonal antibodies are commonly used in the treatment of lymphoma and certain hematological tumors in children. However, these drugs tend to cause massive cytokine release, leading to hypertension, fever, dyspnea, hypoxia and even death (HONG and DIOUN, 2014).

6 Antitumor therapy and ADRs in the respiratory

Although the incidence of respiratory adverse events when using antitumor drugs in clinical practice is relatively low, the consequences are often serious and even fatal. Anticancer drugs that frequently cause pulmonary toxicity include BLM, MTX, Ara-C, CTX, BCNU, and VCR. Pulmonary adverse reactions are clinically divided into two categories: allergic and pulmonary fibrosis (BALDO et al., 2015). The former mainly consists of allergic pneumonitis, mostly comprising of acute attacks. The clinical manifestations of pulmonary fibrosis are generally late, usually appearing weeks to months or even years after halting drug use. The main symptoms include dyspnea, chest tightness, dry cough, fatigue and discomfort. At the onset of drug administration, the lung tissue undergoes a series of complex changes progressively at the subcellular molecular level and exhibits different clinical signs ranging from asymptomatic to lethal pulmonary fibrosis. The molecular basis of this is related to pathological changes in the cellular matrix, which includes collagen, plasma fiber-binding proteins and elastin in the lung tissue, in response to antitumor drugs. The large deposition of extracellular matrix components is caused by the expansion of fibroblasts and the transfer of cells capable of matrix production from other sites to the lungs due to the chemotactic effect of peptides, as well as the elevated level of matrix synthesis in lung cell populations (BENNETT et al., 2007). Antineoplastic drug-induced pulmonary fibrosis was strongly associated with the number of doses, dosages, combinations, and even the timing and rate of drug use.

Pulmonary injury is the most serious and common adverse reaction of BLM, ranging from non-specific pneumonia to fatal pulmonary fibrosis, with a mortality rate as high as 50% (YU et al., 2016). There is evidence that combination with other cytotoxic drugs further increases the pulmonary toxicity of BLM (GALM et al., 2011). The potential mechanisms of pulmonary toxicity caused by BLM include: i) Production of reactive oxygen metabolites that directly damage lung tissue. ii) Massive infiltration of leukocytes and increased release of proteases. iii) Proliferation of fibroblasts, which increases collagen synthesis (YU et al., 2016). In addition to causing hypersensitivity pneumonitis, MTX also has a strong direct toxic effect on lung tissue and can easily cause lung damage, but rarely pulmonary fibrosis (GALM et al., 2011). The pulmonary damage of Ara-C manifests as pulmonary edema and is related to the frequency of administration. When high doses were clinically applied to treat acute leukemia, 22% of children developed subacute pulmonary failure, with the first signs of toxicity occurring at an average of 6 d (2–21 d) after initiation of treatment (YANG et al., 2023). CTX and IFO may injure lung tissue through the production of reactive oxygen metabolites. The incidence of CTX-induced lung injury is less than 1%, in a non-dose-dependent manner, with subacute episodes ranging from 3 weeks to 8 years after drug administration (CAMPAGNE et al., 2020). BCNU can cause acute and even delayed pulmonary fibrosis (BURZYNSKI, 2006).

TABLE 2 Emetogenic risk classification of different chemotherapeutic agents[a].

High >90%	Moderate 30%–90%	Low 10%–30%	Minimal <10%
Anthracycline/CTX >1,500 mg/m^2	Anthracycline/CTX ≤1,500 mg/m^2	PTX	C225
	IFO/DDP <50 mg/m^2	TXT, DTX (IV&Oral)	T-DM1
	CBP/L-OHP >75 mg/m^2	Albumin-bound PTX	BEV
DDP ≥50 mg/m^2	CPT-11	GEM, 5-Fu	Gefitinib
		ADM liposomal	Sorafenib
		PEM, VP-16	CAP

[a]According to the National Comprehensive Cancer Network (NCCN) Antiemetic Guidelines: For nausea and vomiting caused by a combination of multiple medications, the regimen should be based on the medication with the highest risk of causing vomiting.

Vincristine analogs (VLB, VDS, VCR) have been shown to cause adverse pulmonary effects, but the mechanism of injury is unclear. Most reports state that their combination with MMC or CTX and ADM frequently triggers subacute pulmonary toxic effects with symptoms of respiratory distress (ClinicalTrials.gov number: NCT00006237) (FLAHERTY et al., 2014).

7 Antitumor therapy and ADRs in the digestive system

Digestive system ADRs are the most common adverse reactions during chemotherapy for malignant tumors, mainly manifesting as loss of appetite, nausea, vomiting, acute gastritis, mucositis, abdominal pain, diarrhea, and constipation. These ADRs not only affect the quality of life of the child directly, but also tend to impede the smooth implementation of chemotherapy and drug dosage, and even become life-threatening in severe cases. Common highly emetogenic agents include DDP, CTX, and BCNU. The emetogenic risk classification of different chemotherapeutic agents is shown in Table 2.

Nausea and vomiting are the most frequent toxic side effects of chemotherapy drugs on the digestive system (KARPMAN and KURZROCK, 2004). Chemotherapeutic drugs cause nausea and vomiting through two main pathways: Injuries to the GI mucosa leads to the release of substances from enterochromaffin cells, such as 5-hydroxytryptamine (5-HT), which stimulates 5-HT$_3$ receptors on afferent vagus nerves in the intestinal wall and excites the vomiting center in the medulla oblongata. Alternatively, chemicals cause vomiting by acting on the emetic chemoreceptor zone (CTZ) in the fourth ventricle of the brain (JIN et al., 2021). DDP is one of the most emetogenic chemotherapeutic agents to date, and the types of nausea and vomiting caused by the drug are usually categorized into five types based on the time of onset: acute, delayed, anticipatory, eruptive, and refractory (JIN et al., 2021). Chemotherapeutic agents cause acute or persistent diarrhea in approximately 10% of children, with diarrhea rates ranging from 50% to 80%, especially with 5-Fu and CPT-11 containing regimens (CASANOVA et al., 2016). Among them, CPT-11 causes delayed diarrhea and L-OHP causes neurogenic diarrhea. Diarrhea occurs mainly as a result of an imbalance in the secretion and absorption functions of the small intestine caused by acute damage to the intestinal mucosa from chemotherapeutic drugs. Severe diarrhea predisposes to fatal dehydration, acute renal insufficiency and electrolyte disturbances. Mucositis with neutropenia can be further aggravated by secondary intestinal and systemic infections (MODY et al., 2020).

Oral mucositis and ulcers are another common GI reaction to chemotherapy (HONG et al., 2019). Chemotherapeutic agents that predispose to mucositis are predominantly antimetabolites including MTX, Ara-C, 5-Fu, CAP, and VP-16. Mucositis is one of the dose-limiting toxicities of 5-Fu and MTX. The mechanism by which chemotherapeutic agents evoke oral mucositis is twofold: direct damage to the mucosa and secondary localized infection (MAUNEY et al., 2022). Bone marrow transplantation and high-dose chemotherapy with graft-versus-host disease (GVHD) and some cytokines such as IL-1 and TNF-α are also involved in the mucosal damage process. The reduction of neutrophils after chemotherapy tends to exacerbate secondary localized infections of ulcers with anaerobic, aerobic bacteria and even mycobacteria (HONG et al., 2019). Oral mucositis tends to appear within 2–4 days after chemotherapy, which intensifies over the next week and then gradually moves into a healing phase. Chemotherapeutic agents that tend to cause abdominal pain are usually found in vincristine analogs, deoxyfluorouracil, VM-26, DNR, Ara-C, RTX, T-DM1, etc., Medications that are prone to constipation mainly include VLB, PTX, VP-16, DDP, etc., In addition, loss of appetite is also a common adverse reaction of most chemotherapy drugs. Hepatotoxicity and liver injury are also common and unwanted adverse reactions occurring in patients due to chemotherapeutic agents such as MTX, BUS/BSF, PTX, CTX, PTX, 5-Fu, and MMC (KARPMAN and KURZROCK, 2004). Toxic reactions in the liver are mainly hepatocellular dysfunction, veno-occlusive liver disease and chronic liver fibrosis. ASP, which is routinely applied in childhood leukemia, is susceptible to hepatic abnormalities and acute pancreatitis (MAUNEY et al., 2022).

8 Antitumor therapy and ADRs in the urinary system

Damage to the urinary system from antineoplastic agents occurs mainly as a result of renal parenchymal injury and urinary tract irritation reactions (CRONA et al., 2017). Renal damage includes abnormal renal function, elevated serum creatinine or proteinuria, oliguria or anuria, and acute renal failure. Medications that lead to renal parenchymal injury include MTX, DDP, MMC, and BUS/BSF, among which DDP in particular is the most nephrotoxic and

dose-limiting. DDP has been found to be predisposed to renal tubular epithelial necrosis, and in severe cases, acute renal failure (JIN et al., 2021). MTX readily forms crystals in normal acidic urine, which contributes to urinary tract obstruction and tubular damage. The clinical features of cytotoxicity are cystitis, including urinary frequency, urgency, dysuria and hematuria, and bladder fibrosis (SKINNER et al., 1993). IFO, CTX, and HCPT have been shown to lead to urinary tract irritation and hemorrhagic cystitis, which manifests as difficulty in urination, frequent and painful urination, and in severe cases produces hematuria. These symptoms appear over a period of hours or weeks and eventually subside within a few days of withdrawal.

9 Antitumor therapy and ADRs in the skin and its appendages

Dermal toxicity mainly refers to local skin damage, rash, alopecia, and other direct or indirect damage to the skin and its appendages caused by antitumor drugs (STRUMIA et al., 2022). Antitumor drugs will damage the skin tissue locally to different degrees upon extravasation from the blood vessels to the surrounding tissues (STRUMIA et al., 2022). In mild cases, it can trigger localized pain and phlebitis, whereas in severe cases, it can lead to localized skin blisters, ulcers, tissue detachment, and even lead to dysfunction. For example, anthracyclines, MMC, and VCR induces severe skin necrosis; BLM, platinum, 5-FU, TXL, and MTZ induce moderate damage; and L-ASP, BCNU, DTIC, MEL, TSPA, and MTX can cause mild skin irritation. The management of dermal reactions to toxicity caused by drug extravasation lies in careful infusion, close observation, and prompt detection and treatment of leakages. Most antitumor drugs can cause skin rashes to varying degrees (NG et al., 2018). The most common ADR, of targeted drugs such as gefitinib and C225, is skin rash. These rashes are mainly located on the face and upper trunk, are non-pruritic, and may resolve spontaneously.

The ADR that CAP predisposes to is hand-foot syndrome, which is manifested by warmth, pain, and redness of the fingers (toes), and in severe cases, may progress to desquamation, ulceration, and severe pain (WRIGHT et al., 2015). Although alopecia is also a common ADR of antineoplastic drugs, most of them are reversible. Hair regeneration usually occurs within 1 month–2 months after drug withdrawal, and no additional treatment is required. If necessary, a scalp tourniquet or ice cap cooling can be used to reduce the amount of medication that reaches hair follicles, thereby reducing hair loss (NG et al., 2018). In addition, certain drugs can cause nail deformities, such as CTX, BLM, TXT, DTX, ADM, 5-Fu, and paxillin (STRUMIA et al., 2022).

10 Antitumor therapy and allergic reactions and other ADRs

The incidence of allergic reactions to antineoplastic drugs in children is 5%–15% (GIAVINA-BIANCHI et al., 2017). Clinical manifestations include rash, angioneurotic edema, dyspnea, hypotension, anaphylactic shock, etc., (TURGAY et al., 2020). Common drugs that cause allergic reactions include L-ASP, PYM, BLM, PTX, anthracyclines, platinum drugs, etc., among which allergic reactions caused by L-ASP and TXL are more frequent. For chemotherapeutic drugs that have a high incidence and severity of allergic reactions, antiallergic pretreatment must be performed regardless of the dose and duration of titration. In the case of allergic manifestations, administration of the drug should be stopped immediately, and a combination of H_1 and H_2 receptor antagonists should be used for symptomatic relief. Supplementation with glucocorticoids, antihypertensive agents or bronchodilators may also be appropriate (GIAVINA-BIANCHI et al., 2017). RTX, T-DM1, and BEV are also susceptible to immediate hypersensitivity (BALDO and PHAM, 2013). In addition, pain and skin redness may occur at the venous sites where antitumor agents are injected, and long-term use of the drugs will lead to skin pigmentation, striated hardening of the veins and venous embolism (LYLE et al., 2015). Chemotherapeutic drugs that tend to cause venous damage includes HN, 5-FU, NVB, anthracyclines, etc.

In addition to the common ADRs of antineoplastic drugs in children as outlined above, hearing loss, dysgenitalism, gynecomastia and early menarche or amenorrhea in girls may occur. Long-term toxic effects including reproductive dysfunction, carcinogenesis and teratogenesis may also occur. Studies have shown that 22%–74% of pediatric oncology patients developed permanent hearing damage after DDP treatment (FREYER et al., 2020). DDP ototoxicity severely reduces the quality of life of children, especially affecting early language development and social cognitive ability. Numerous studies have confirmed that DDP leads to caspase-3-activated apoptosis in auditory hair cells by inducing elevated reactive oxygen species (RAMKUMAR et al., 2021). Mammalian auditory hair cells, once damaged, are permanently inactive with no capacity for spontaneous regeneration. A large number of animal experiments have confirmed that platinum drugs can cause a series of irreversible health damage, such as reproductive system damage, DNA damage, and chromosomal aberrations (TODD and LIPPARD, 2009; ZHANG et al., 2020; IBRAHIM et al., 2021). Toxic effects of DDP on the uterus and ovaries and irreversible genotoxicity have been demonstrated in animals (ZHANG et al., 2020; IBRAHIM et al., 2021).

11 Similarities and differences in ADRs to antineoplastic drugs in adults and children

Antitumor drugs may cause ADRs in children such as growth inhibition and infertility. The ADRs for antineoplastic drugs in adults and children involve more similar systems but differ in their specific manifestations. For example, when treated with RTX, rare but serious events—described primarily in adults—include progressive multifocal encephalopathy, prolonged neutropenia, and fatal viral reactivation (MCATEE et al., 2021). Children were susceptible to infusion reactions with an incidence of 50%–90% and adults had an incidence of 4%–15% (SALLES et al., 2017). The incidence of infection in children was 40%–50%, which was higher than that in adults (26%–35%) (FLEURY et al., 2016). Children were also more likely to be immunosuppressed compared to adults (about 50% incidence in children compared to 20%–30% in adults)

(HIRANO et al., 2014). ASP was an effective drug for acute lymphoblastic leukemia (ALL) in children, and in recent years it had been increasingly used for adults over 22 years of age. The main risk factors for hepatotoxicity due to ASP involved older age and weight gain, and thus adults were more prone to hepatotoxicity than children during treatment (ALDOSS et al., 2022). The incidence of pancreatitis was higher in adults (about 10%) than in children (about 5%) (Stock et al., 2019). However, children were more prone to allergic reactions (GUPTA et al., 2020b). CRS occurred in both adults and children during treatment with immunotherapy, but occurred more frequently in children (about 77%) than in adults (about 50%) (RAGOONANAN et al., 2021). Children were also more prone to neurologic adverse effects, with a higher incidence of electroencephalogram (EEG) changed (about 83.3%) than adults (about 76%) (GUST et al., 2019). Given the differences in response to antitumor drugs between children and adults, child-specific standards and criteria should be established in clinical practice to enhance safety monitoring and effectiveness evaluation.

12 Measures to address ADRs to antitumor drugs

To mitigate the unfavorable impact of ADRs on the treatment and quality of life of children, a range of preventive and responsive measures have been implemented clinically. To prevent local tissue necrosis caused by extravasation of chemotherapeutic drugs, the vascular condition of the child should be assessed before intravenous injection, and intravenous access should be established with saline. Drugs should be diluted to a certain concentration, the drip rate should be controlled when titrating, and the stimulating drugs need to be preferentially infused in the case of multidrug combination therapy (GOOLSBY and LOMBARDO, 2006). Children should be instructed to protect the blood vessels, and localized pressure should be applied for 5–7 min after needle removal. In cold weather, the limb on the side of the puncture is immersed in warm water before performing venipuncture to dilate the blood vessels and facilitate puncture (LV et al., 2021). In case of extravasation, infusion must be stopped immediately, followed by limitation of limb movement, retraction of extravasated drug, needle removal, and the application of antagonistic drugs or local closure measures in severe cases (GOOLSBY and LOMBARDO, 2006). Cold or hot compresses should also be applied when appropriate.

Little benefit is currently available for the treatment of drug-mediated neurotoxicity. In symptomatic individuals, the duration of intravenous infusion may be extended. Potentially effective drugs include gabapentin, duloxetine, and VB_6 tablets (IŻYCKI et al., 2016). Peripheral neurotoxicity is reversible, and in severe cases, chemotherapy needs to be stopped first. Intermittent supplementation of large amounts of B vitamins is beneficial to alleviate peripheral neuritis (FU et al., 2018). To tackle hematologic toxicity led by antitumor drugs, prevention should be emphasized to reduce the risk of infection. Protective isolation measures can be taken to maintain the sterility of the ward room utilizing air purification equipment. When broad-spectrum antibiotics are administered, the medication needs to be adjusted based on the drug sensitivity results. Granulocyte colony-stimulating factor can also be administered to alleviate hematologic toxicity, and discontinuation is indicated by leukocytes over 10×10^9/L (MARTINO et al., 2018). Thrombopoietin and IL-11 need to be administered in cases of low platelet counts, and monoclonalized platelets should be transfused in cases of severe platelet drop (ZHU et al., 2020).

For the prevention and treatment of cardiotoxicity, the main concern is to be vigilant against anthracyclines. Dexpropylenimine is the only agent that is available to prevent anthracycline cardiotoxicity (DE BAAT et al., 2022). For co-administration, anthracyclines are given first followed by PTX to minimize cardiotoxicity from their interaction (SCHIMMEL et al., 2004). Concomitant treatment with anthracyclines and T-DM1 should be avoided (HU et al., 2018). For the management of respiratory ADRs, the total dose of the drug needs to be controlled, with the total dose of BLM not exceeding 400 mg (YU et al., 2016). Immediate discontinuation of medication and symptomatic management is the first action in response to pulmonary toxicity. Oxygen intake is not allowed at high levels when treating with hormones and antibiotics. Antiemetic drugs are prescribed when nausea and vomiting occur with chemotherapy. Currently, commonly available antiemetic drugs include: dopamine receptor blockers, such as metoclopramide and domperidone; phenothiazines, such as isoprinosine, chlorpromazine, and phenazopyridine; adrenocorticotropic hormones, such as dexamethasone; antihistamines, such as phenylephrine; $5\text{-}HT_3$ receptor antagonists, such as paroxetine, granisetine, and tolstanesetron; NK-1 receptor antagonists, such as aripipipramine; and benzodiazepines, such as diazepam (PHILLIPS et al., 2016). It is also necessary to prevent water and electrolyte imbalance. Octreotide represents one of the preferable drugs available for alleviating diarrhea caused by oncological chemotherapy (WU et al., 2008). It improves electrolyte absorption by reducing intestinal motility and digestive fluid secretion, thus reducing stool volume. Receiving folic acid and vitamin B_{12} supplementation in conjunction with PEM therapy is effective in preventing or reducing treatment-related hematologic or gastrointestinal reactions (ClinicalTrials.gov identifier: NCT00520936) (WARWICK et al., 2013). In order to prevent or minimize nephrotoxicity caused by antitumor drugs, patients should drink adequate amounts of water to accelerate drug elimination, and have a light diet to avoid the formation of uric acid aggravated by heavy meats. Hydration and alkalinization of the urine are required when administering highly nephrotoxic drugs such as DDP and MTX (JIN et al., 2021). When taking high doses of MTX, calcium folinate is available to alleviate ADRs (SKINNER et al., 1993). Systemic administration of sodium thiosulfate is expected to reduce toxicity and improve efficacy when high-dose DDP is given intracavitally for the treatment of malignant pleural and ascites (CRONA et al., 2017). Moreover, amphotericin has been shown to prevent or minimize the nephrotoxicity of DDP (CRONA et al., 2017). Mescaline sodium should be supplemented concurrently to prevent cystitis that may result from high-dose IFO and CTX therapy (SKINNER et al., 1993). To mitigate hand-foot syndrome due to CAP treatment, the duration of the drip can be shortened or switched to oral administration (HUANG et al., 2018). Furthermore, dermatitis can be controlled with anti-allergic drugs or hormones (LUPO et al., 2014). Targeted delivery of antitumor drugs via nanomaterials has also been reported to alleviate ADRs (CHOU

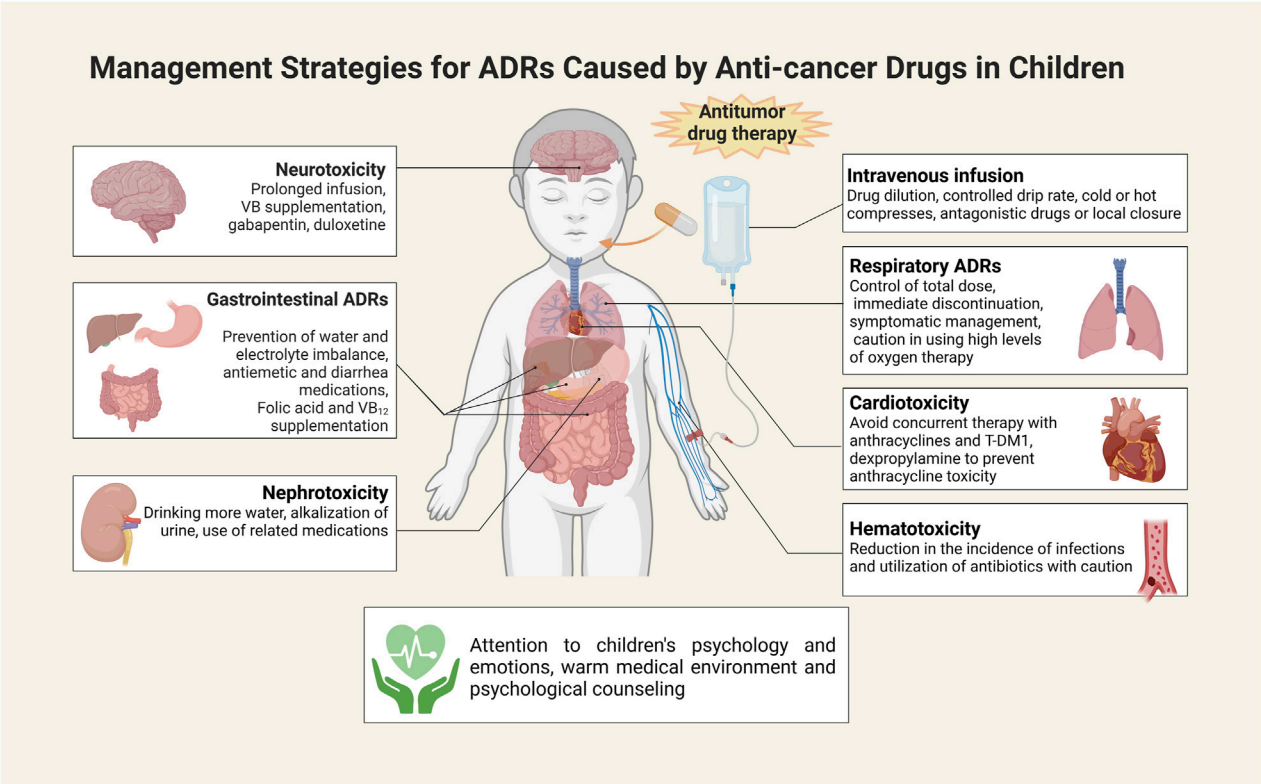


FIGURE 3
Measures to address ADRs to antitumor drugs in children. This illustration was created with BioRender (agreement number: IK26CU3ATC).

et al., 2020; JINDAL et al., 2020; KURZĄTKOWSKA et al., 2021), but additional studies are needed for confirmation.

Efforts to address ADRs associated with ACT also continue to evolve. The production of CAR-T cells is time-consuming and hence fails to meet the therapeutic needs of rapidly progressing cancers. To shorten infusion time, the FasT CAR-T next-day manufacturing platform was developed (YANG et al., 2022). The novel anti-CD19 CAR-T cells based on this production platform are more proliferative and provide better anti-tumor efficacy and less cellular depletion in refractory/relapsed B-cell acute lymphoblastic leukemia (B-ALL) compared to conventional CAR-T therapy. However, in addition to multi-system ADRs, CAR-T cell therapies still face obstacles such as long production periods and the scarcity of patients' own T-cells available for mass production applications. NK cells, as a class of natural tumor-killing lymphocytes, have attracted much attention owing to their advantages over T cells, such as unrestricted allogeneic graft-versus-host disease (GVHD), short production periods, and non-antigen-dependent natural tumor-killing effects (XIE et al., 2020; LIU et al., 2021). Clinical trials (ClinicalTrials.gov number: NCT03056339) of CAR-NK therapies for hematologic malignancies have been conducted and no major toxicities including CRS, neurotoxicity and GVHD have been reported to date, suggesting that CAR-NK might be an alternative therapy to CAR-T (ZHANG et al., 2022). Although CAR-T and CAR-NK therapies, as a new generation of therapeutic methods to regulate immune cells as an entry point to fight against tumors, have achieved a good outcome in hematological tumors, their application in solid tumors is still greatly hindered by the lack of cancer-specific antigens, the inefficiency of immune cells transported to the tumor site, and the immunosuppressive microenvironment (PAN et al., 2022). More recently, CAR macrophages are being explored in an attempt to overcome the shortcomings of other cell therapies in the treatment of solid tumors as a new approach towards cell therapy (KLICHINSKY et al., 2020; PAN et al., 2022; CHEN et al., 2023).

In addition to the above countermeasures, it is also critical for healthcare professionals and parents to pay close attention to the psychology and emotions of the children during treatment. Favorable psychological care measures are helpful for children to adapt to the new medical environment by influencing their state of mind and perceptions. On the other hand, psychological counseling helps create an optimal psychological state that is beneficial to the treatment and recovery process, and can help mitigate ADRs associated with chemotherapeutic drugs (Figure 3).

13 Conclusion and outlook

In summary, ADRs caused by antineoplastic drugs in children may involve multiple organs or systems. The top 3 common ADRs occur in the gastrointestinal system, the hematologic system, and the skin. As leukemia accounts for the highest proportion of pediatric tumors, Ara-C and MTX are highly utilized. Therefore, among all antineoplastic drugs, ADRs from these two drugs are the most frequent, followed by CTX and platinum compounds. The type and

severity of ADRs to antineoplastic drugs varies depending on the drug and the individual, and the treatment varies as well. The general principle of management is prevention and symptomatic treatment. Reasonable dosages and treatment regimens according to the specific conditions of the children should be developed to avoid overuse and abuse when using these drugs. Meanwhile, the emergence of ADRs must be monitored closely and treatment programs should be promptly adjusted. Early prevention, close monitoring, and timely management are critical approaches to improving drug efficacy, reducing ADRs, and alleviating pain in children. Based on previous studies, we systematically summarized common ADRs of antineoplastic drugs in children and the measures to prevent or minimize ADRs. This review thus provides an informative basis for future studies and clinical applications.

Nevertheless, there are certain scientific problems and challenges that need to be addressed with regard to ADRs that are common in pediatric and adolescent oncology patients. Firstly, conducting clinical trials of drugs for children is very challenging due to their special physiological characteristics and ethical issues. How to design reasonable clinical trial protocols to ensure the accuracy and reliability of trial results is an urgent issue to be solved. Secondly, the construction of vigilance and risk management system for ADRs in children is not yet perfect, how to improve the level of pharmacovigilance, detection and treatment of ADRs in a timely manner is an important challenge at present. Finally, the individualized drug therapy for pediatric oncology patients is in high demand, and how to individualized drug therapy to reduce the risk of adverse effects according to children's genes, age, weight and other factors is an important focus of future research.

Author contributions

HY: Conceptualization, Formal Analysis, Methodology, Visualization, Writing–original draft, Writing–review and editing. PW: Data curation, Formal Analysis, Visualization, Writing–original draft. FY: Data curation, Formal Analysis, Investigation, Visualization, Writing–original draft. WC: Supervision, Writing–review and editing. CC: Data curation, Formal Analysis, Investigation, Writing–original draft. BZ: Funding acquisition, Visualization, Writing–review and editing, Writing–original draft. YZ: Conceptualization, Funding acquisition, Project administration, Resources, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by National Natural Science Foundation of China (NSFC) (82203398), China Postdoctoral Science Foundation (CPSF) (2023M733241), Henan Province Key R&D and Promotion Project (Science and Technology Research) (222102310026 and 232102310036).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

GBD 2017 Childhood Cancer Collaborators (2019). The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol.* 20 (9), 1211–1225. doi:10.1016/S1470-2045(19)30339-0

Abulfadl, Y. S., El Ela, Y. A., Al Khaiyat, A. M., Elkhodary, K. I., and Badran, M. (2023). Cyclophosphamide enfeebles myocardial isometric contraction force via RIP1/RIP3/MLKL/TRPM7-mediated necroptosis. *Biomed. Pharmacother. = Biomedecine Pharmacother.* 163, 114819. doi:10.1016/j.biopha.2023.114819

Aldoss, I., Pourhassan, H., and Douer, D. (2022). SOHO state of the art updates and next questions | asparaginase-understanding and overcoming toxicities in adults with ALL. *myeloma & leukemia* 22 (11), 787–794. doi:10.1016/j.clml.2022.08.009

Amaro-Hosey, K., DanéS, I., and Agustí, A. (2021). Adverse drug reactions in pediatric oncohematology: a systematic review. *Front. Pharmacol.* 12, 777498. doi:10.3389/fphar.2021.777498

Baldo, B. A., and Pham, N. H. (2013). Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. *Cancer metastasis Rev.* 32 (3-4), 723–761. doi:10.1007/s10555-013-9447-3

Baldo, P., Fornasier, G., Francescon, S., Ferrarin, E., Truccolo, I., and De Paoli, P. (2015). Toxicities and adverse drug reactions experienced during anticancer treatment: it is desirable to consider the problem within the international system of pharmacovigilance. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 33 (25), 2824–2825. doi:10.1200/JCO.2015.61.7613

Bender, J. D., Rubinstein, J. D., Mizukawa, B., Perentesis, J. P., and Pommert, L. (2023). Use of gemcitabine, oxaliplatin, and anti-CD20 therapy in children and adolescents with non-Hodgkin lymphoma unfit for intensive therapy. *Pediatr. blood cancer* 70 (4), e30214. doi:10.1002/pbc.30214

Bennett, C. L., Tigue, C. C., Angelotta, C., Mckoy, J. M., and Edwards, B. J. (2007). Adverse effects of drugs used to treat hematologic malignancies: surveillance efforts from the research on adverse drug events and reports project. *Seminars thrombosis hemostasis* 33 (4), 365–372. doi:10.1055/s-2007-976172

Bond, M., Bernstein, M. L., Pappo, A., Schultz, K. R., Krailo, M., Blaney, S. M., et al. (2008). A phase II study of imatinib mesylate in children with refractory or relapsed solid tumors: a Children's Oncology Group study. *Pediatr. blood cancer* 50 (2), 254–258. doi:10.1002/pbc.21132

Burzynski, S. R. (2006). Treatments for astrocytic tumors in children: current and emerging strategies. *Paediatr. drugs* 8 (3), 167–178. doi:10.2165/00148581-200608030-00003

Campagne, O., Zhong, B., Nair, S., Lin, T., Huang, J., Onar-Thomas, A., et al. (2020). Exposure-toxicity association of cyclophosphamide and its metabolites in infants and young children with primary brain tumors: implications for dosing. *Clin. cancer Res. official J. Am. Assoc. Cancer Res.* 26 (7), 1563–1573. doi:10.1158/1078-0432.CCR-19-2685

Casanova, M., Özyar, E., Patte, C., Orbach, D., Ferrari, A., Veyrat-Follet, C., et al. (2016). International randomized phase 2 study on the addition of docetaxel to the combination of cisplatin and 5-fluorouracil in the induction treatment for nasopharyngeal carcinoma in children and adolescents. *Cancer Chemother. Pharmacol.* 77 (2), 289–298. doi:10.1007/s00280-015-2933-2

Chen, C., Huang, R., Wang, N., Zheng, Y., Zhou, J., Yang, B., et al. (2023). Fu-Zheng-Yi-Liu formula inhibits the stem cells and metastasis of prostate cancer via tumor-

associated macrophages/C-C motif chemokine ligand 5 pathway in tumor microenvironment. *Chin. J. Nat. Med.* 21, 1–14. doi:10.1016/S1875-5364(23)60514-X

Chou, P. L., Huang, Y. P., Cheng, M. H., Rau, K. M., and Fang, Y. P. (2020). Improvement of paclitaxel-associated adverse reactions (ADRs) via the use of nano-based drug delivery systems: a systematic review and Network meta-analysis. *Int. J. nanomedicine* 15, 1731–1743. doi:10.2147/IJN.S231407

Crona, D. J., Faso, A., Nishijima, T. F., Mcgraw, K. A., Galsky, M. D., and Milowsky, M. I. (2017). A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. *Oncol.* 22 (5), 609–619. doi:10.1634/theoncologist.2016-0319

De Baat, E. C., Van Dalen, E. C., Mulder, R. L., Hudson, M. M., Ehrhardt, M. J., Engels, F. K., et al. (2022). Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Child Adolesc. health* 6 (12), 885–894. doi:10.1016/S2352-4642(22)00239-5

Duan, S., Yu, Y., Lai, C., Wang, D., Wang, Y., Xue, D., et al. (2018). Vincristine-loaded and sgc8-modified liposome as a potential targeted drug delivery system for treating acute lymphoblastic leukemia. *J. Biomed. Nanotechnol.* 14 (5), 910–921. doi:10.1166/jbn.2018.2530

Flaherty, L. E., Othus, M., Atkins, M. B., Tuthill, R. J., Thompson, J. A., Vetto, J. T., et al. (2014). Southwest Oncology Group S0008: a phase III trial of high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 32 (33), 3771–3778. doi:10.1200/JCO.2013.53.1590

Fleury, I., Chevret, S., Pfreundschuh, M., Salles, G., Coiffier, B., Van Oers, M. H., et al. (2016). Rituximab and risk of second primary malignancies in patients with non-Hodgkin lymphoma: a systematic review and meta-analysis. *Ann. Oncol. official J. Eur. Soc. Med. Oncol.* 27 (3), 390–397. doi:10.1093/annonc/mdv616

Franco, R. S. (2012). Measurement of red cell lifespan and aging. *Transfus. Med. hemotherapy offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie* 39 (5), 302–307. doi:10.1159/000342232

Freyer, D. R., Brock, P. R., Chang, K. W., Dupuis, L. L., Epelman, S., Knight, K., et al. (2020). Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. *Lancet Child Adolesc. health* 4 (2), 141–150. doi:10.1016/S2352-4642(19)30336-0

Fu, B., Wang, N., Tan, H. Y., Li, S., Cheung, F., and Feng, Y. (2018). Multi-component herbal products in the prevention and treatment of chemotherapy-associated toxicity and side effects: a review on experimental and clinical evidences. *Front. Pharmacol.* 9, 1394. doi:10.3389/fphar.2018.01394

Galm, U., Wendt-Pienkowski, E., Wang, L., Huang, S. X., Unsin, C., Tao, M., et al. (2011). Comparative analysis of the biosynthetic gene clusters and pathways for three structurally related antitumor antibiotics: bleomycin, tallysomycin, and zorbamycin. *J. Nat. Prod.* 74 (3), 526–536. doi:10.1021/np1008152

Giavina-Bianchi, P., Patil, S. U., and Banerji, A. (2017). Immediate hypersensitivity reaction to chemotherapeutic agents. *J. allergy Clin. Immunol. Pract.* 5 (3), 593–599. doi:10.1016/j.jaip.2017.03.015

Goolsby, T. V., and Lombardo, F. A. (2006). Extravasation of chemotherapeutic agents: prevention and treatment. *Seminars Oncol.* 33 (1), 139–143. doi:10.1053/j.seminoncol.2005.11.007

Gupta, S., Harper, A., Ruan, Y., Barr, R., Frazier, A. L., Ferlay, J., et al. (2020a). International trends in the incidence of cancer among adolescents and young adults. *J. Natl. Cancer Inst.* 112 (11), 1105–1117. doi:10.1093/jnci/djaa007

Gupta, S., Wang, C., Raetz, E. A., Schore, R., Salzer, W. L., Larsen, E. C., et al. (2020b). Impact of asparaginase discontinuation on outcome in childhood acute lymphoblastic leukemia: a report from the children's oncology group. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 38 (17), 1897–1905. doi:10.1200/JCO.19.03024

Gust, J., Finney, O. C., Li, D., Brakke, H. M., Hicks, R. M., Futrell, R. B., et al. (2019). Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy. *Ann. neurology* 86 (1), 42–54. doi:10.1002/ana.25502

GutiéRREZ-GutiéRREZ, G., Sereno, M., Miralles, A., Casado-SáENZ, E., and GutiéRREZ-Rivas, E. (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clin. Transl. Oncol. official Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mexico* 12 (2), 81–91. doi:10.1007/S12094-010-0474-z

Hirano, K., Tada, M., Sasahira, N., Isayama, H., Mizuno, S., Takagi, K., et al. (2014). Incidence of malignancies in patients with IgG4-related disease. *Intern. Med.* 53 (3), 171–176. doi:10.2169/internalmedicine.53.1342

Hong, B. Y., Sobue, T., Choquette, L., Dupuy, A. K., Thompson, A., Burleson, J. A., et al. (2019). Chemotherapy-induced oral mucositis is associated with detrimental bacterial dysbiosis. *Microbiome* 7 (1), 66. doi:10.1186/s40168-019-0679-5

Hong, D. I., and Dioun, A. F. (2014). Indications, protocols, and outcomes of drug desensitizations for chemotherapy and monoclonal antibodies in adults and children. *J. allergy Clin. Immunol. Pract.* 2 (1), 13–19. ; quiz 20. doi:10.1016/j.jaip.2013.11.007

Hu, H. M., Zhang, X. L., Zhang, W. L., Huang, D. S., and Du, Z. D. (2018). Detection of subclinical anthracyclines' cardiotoxicity in children with solid tumor. *Chin. Med. J.* 131 (12), 1450–1456. doi:10.4103/0366-6999.233950

Huang, X. Z., Chen, Y., Chen, W. J., Zhang, X., Wu, C. C., Wang, Z. N., et al. (2018). Clinical evidence of prevention strategies for capecitabine-induced hand-foot syndrome. *Int. J. cancer* 142 (12), 2567–2577. doi:10.1002/ijc.31269

Ibrahim, M. A., Albahlol, I. A., Wani, F. A., Abd-Eltawab Tammam, A., Kelleni, M. T., Sayeed, M. U., et al. (2021). Resveratrol protects against cisplatin-induced ovarian and uterine toxicity in female rats by attenuating oxidative stress, inflammation and apoptosis. *Chemico-biological Interact.* 338, 109402. doi:10.1016/j.cbi.2021.109402

Iman, M., Araghi, M., Heidari, T., and Mohammadi, V. (2017). Melissa of cinalis and vitamin E as the potential therapeutic candidates for reproductive toxicity caused by anti-cancer drug, cisplatin, in male rats. *Recent Pat. anti-cancer drug Discov.* 12 (1), 73–80. doi:10.2174/1574892811666161026111721

Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C., and Bonati, M. (2001). Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br. J. Clin. Pharmacol.* 52 (1), 77–83. doi:10.1046/j.0306-5251.2001.01407.x

Iżycki, D., Niezgoda, A. A., Kaźmierczak, M., Piorunek, T., Iżycka, N., Karaszewska, B., et al. (2016). Chemotherapy-induced peripheral neuropathy - diagnosis, evolution and treatment. *Ginekol. Pol.* 87 (7), 516–521. doi:10.5603/GP.2016.0036

Jiao, Z., Feng, Z., Yan, Z., Zhang, J., Li, G., Wang, G., et al. (2021). Suspected adverse drug reactions in pediatric cancer patients in China: an analysis of henan Province spontaneous reporting system database. *Front. Oncol.* 11. 807171. doi:10.3389/fonc.2021.807171

Jin, Y. N., Yao, J. J., You, Y. F., Cao, H. J., Li, Z. Z., Dai, D. L., et al. (2021). Optimal cumulative cisplatin dose during concurrent chemoradiotherapy among children and adolescents with locoregionally advanced nasopharyngeal carcinoma: a real-world data study. *J. Eur. Soc. Ther. Radiology Oncol.* 161, 83–91. doi:10.1016/j.radonc.2021.06.003

Jindal, M., Nagpal, M., Singh, M., Aggarwal, G., and Dhingra, G. A. (2020). Gold nanoparticles- boon in cancer theranostics. *Curr. Pharm. Des.* 26 (40), 5134–5151. doi:10.2174/1381612826666200701151403

John-Paul, K., and Bartels, U. (2017). Intracystic interferon-alpha in pediatric craniopharyngioma patients-reply. *Neuro-oncology* 19 (10), 1420–1421. doi:10.1093/neuonc/nox147

Karpman, E., and Kurzrock, E. A. (2004). Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J. urology* 172 (2), 448–453. doi:10.1097/01.ju.0000130653.74548.d6

Klichinsky, M., Ruella, M., Shestova, O., Lu, X. M., Best, A., Zeeman, M., et al. (2020). Human chimeric antigen receptor macrophages for cancer immunotherapy. *Nat. Biotechnol.* 38 (8), 947–953. doi:10.1038/s41587-020-0462-y

Kurzątkowska, K., Pazosnd, M. A., Herschkowitz, J. I., and Hepel, M. (2021). Cancer-targeted controlled delivery of chemotherapeutic anthracycline derivatives using apoferritin nanocage carriers. *Int. J. Mol. Sci.* 22 (3), 1362. doi:10.3390/ijms22031362

Lavan, A. H., O'Mahony, D., Buckley, M., O'Mahony, D., and Gallagher, P. (2019). Adverse drug reactions in an oncological population: prevalence, predictability, and preventability. *Oncol.* 24 (9), e968–e977. doi:10.1634/theoncologist.2018-0476

Li, K., Li, Z., Men, L., Li, W., and Gong, X. (2022). Potential of ginsenoside Rh_2 and its derivatives as anti-cancer agents. *Chin. J. Nat. Med.* 20 (12), 881–901. doi:10.1016/S1875-5364(22)60193-6

Liu, S., Galat, V., Galat, Y., Lee, Y. K. A., Wainwright, D., and Wu, J. (2021). NK cell-based cancer immunotherapy: from basic biology to clinical development. *J. Hematol. Oncol.* 14 (1), 7. doi:10.1186/s13045-020-01014-w

Li, W., Gao, M., Xue, W., Li, X., Chang, Y., Zhang, K., et al. (2023). Palmitic acid reduces the methylation of the FOXO1 promoter to suppress the development of diffuse large B-cell lymphoma via modulating the miR-429/DNMT3A axis. *Chin. J. Nat. Med.* 21, 1–15. doi:10.1016/S1875-5364(23)60502-3

Lopez-Lopez, E., Autry, R. J., Smith, C., Yang, W., Paugh, S. W., Panetta, J. C., et al. (2020). Pharmacogenomics of intracellular methotrexate polyglutamates in patients' leukemia cells *in vivo*. *J. Clin. investigation* 130 (12), 6600–6615. doi:10.1172/JCI140797

Lupo, P. J., Zhou, R., Skapek, S. X., Hawkins, D. S., Spector, L. G., Scheurer, M. E., et al. (2014). Allergies, atopy, immune-related factors and childhood rhabdomyosarcoma: a report from the Children's Oncology Group. *Int. J. cancer* 134 (2), 431–436. doi:10.1002/ijc.28363

Lv, D. N., Xu, H. Z., Zheng, L. L., Chen, L. L., Ling, Y., and Ye, A. Q. (2021). Extravasation of chemotherapeutic drug from an implantable intravenous infusion port in a child: a case report. *World J. Clin. cases* 9 (26), 7840–7844. doi:10.12998/wjcc.v9.i26.7840

Lyle, C. A., Sidonio, R. F., and Goldenberg, N. A. (2015). New developments in pediatric venous thromboembolism and anticoagulation, including the target-specific oral anticoagulants. *Curr. Opin. Pediatr.* 27 (1), 18–25. doi:10.1097/MOP.0000000000000173

Mancone, S., Lycan, T., Ahmed, T., Topaloglu, U., Dothard, A., Petty, W. J., et al. (2018). Severe neurologic complications of immune checkpoint inhibitors: a single-center review. *J. neurology* 265 (7), 1636–1642. doi:10.1007/s00415-018-8890-z

Martino, E., Casamassima, G., Castiglione, S., Cellupica, E., Pantalone, S., Papagni, F., et al. (2018). Vinca alkaloids and analogues as anti-cancer agents: looking back, peering ahead. *Bioorg. Med. Chem. Lett.* 28 (17), 2816–2826. doi:10.1016/j.bmcl.2018.06.044

Mauney, E. E., Power-Hays, A., Flamand, Y., Vrooman, L., Silverman, L. B., and Grover, A. S. (2022). Clinical characteristics and short-term outcomes of children with asparaginase-associated pancreatitis. *J. Pediatr. gastroenterology Nutr.* 74 (3), 402–407. doi:10.1097/MPG.0000000000003334

Mcatee, C. L., Lubega, J., Underbrink, K., Curry, K., Msaouel, P., Barrow, M., et al. (2021). Association of rituximab use with adverse events in children, adolescents, and young adults. *JAMA Netw. open* 4 (2), e2036321. doi:10.1001/jamanetworkopen.2020.36321

Michot, J. M., Lappara, A., Le Pavec, J., Simonaggio, A., Collins, M., De Martin, E., et al. (2020). The 2016-2019 ImmunoTOX assessment board report of collaborative management of immune-related adverse events, an observational clinical study. *Eur. J. cancer (Oxford, Engl. 1990)* 130, 39–50. doi:10.1016/j.ejca.2020.02.010

Mody, R., Yu, A. L., Naranjo, A., Zhang, F. F., London, W. B., Shulkin, B. L., et al. (2020). Irinotecan, temozolomide, and dinutuximab with GM-CSF in children with refractory or relapsed neuroblastoma: a report from the children's oncology group. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 38 (19), 2160–2169. doi:10.1200/JCO.20.00203

Neelapu, S. S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F. L., et al. (2018). Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat. Rev. Clin. Oncol.* 15 (1), 47–62. doi:10.1038/nrclinonc.2017.148

Ng, C. Y., Chen, C. B., Wu, M. Y., Wu, J., Yang, C. H., Hui, R. C., et al. (2018). Anticancer drugs induced severe adverse cutaneous drug reactions: an updated review on the risks associated with anticancer targeted therapy or immunotherapies. *J. Immunol. Res.* 2018, 5376476. doi:10.1155/2018/5376476

Ng, T., Cheung, Y. T., Ng, Q. S., Ho, H. K., and Chan, A. (2014). Vascular endothelial growth factor inhibitors and cognitive impairment: evidence and controversies. *Expert Opin. drug Saf.* 13 (1), 83–92. doi:10.1517/14740338.2013.828034

Pan, K., Farrukh, H., Chittepu, V., Xu, H., Pan, C. X., and Zhu, Z. (2022). CAR race to cancer immunotherapy: from CAR T, CAR NK to CAR macrophage therapy. *J. Exp. Clin. cancer Res. CR* 41 (1), 119. doi:10.1186/s13046-022-02327-z

Pawar, S., Anand, A., Khaparde, M., and Pawar, S. (2018). Chemotherapy-induced adverse drug reactions in pediatric oncology. *J. Young Pharm.* 10, 340–343. doi:10.5530/jyp.2018.10.75

Phillips, R. S., Friend, A. J., Gibson, F., Houghton, E., Gopaul, S., Craig, J. V., et al. (2016). Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane database Syst. Rev.* 2 (2), Cd007786. doi:10.1002/14651858.CD007786.pub2

Ragoonanan, D., Khazal, S. J., Abdel-Azim, H., Mccall, D., Cuglievan, B., Tambaro, F. P., et al. (2021). Diagnosis, grading and management of toxicities from immunotherapies in children, adolescents and young adults with cancer. *Nat. Rev. Clin. Oncol.* 18 (7), 435–453. doi:10.1038/s41571-021-00474-4

Ramkumar, V., Mukherjea, D., Dhukhwa, A., and Rybak, L. P. (2021). Oxidative stress and inflammation caused by cisplatin ototoxicity. *Antioxidants Basel, Switz.* 10 (12), 1919. doi:10.3390/antiox10121919

Sałat, K. (2020a). Chemotherapy-induced peripheral neuropathy: part 1-current state of knowledge and perspectives for pharmacotherapy. *Pharmacol. Rep. P. R.* 72 (3), 486–507. doi:10.1007/s43440-020-00109-y

Sałat, K. (2020b). Chemotherapy-induced peripheral neuropathy-part 2: focus on the prevention of oxaliplatin-induced neurotoxicity. *Pharmacol. Rep. P. R.* 72 (3), 508–527. doi:10.1007/s43440-020-00106-1

Salles, G., Barrett, M., Foà, R., Maurer, J., O'Brien, S., Valente, N., et al. (2017). Rituximab in B-cell hematologic malignancies: a review of 20 Years of clinical experience. *Adv. Ther.* 34 (10), 2232–2273. doi:10.1007/s12325-017-0612-x

Schimmel, K. J., Richel, D. J., Van Den Brink, R. B., and Guchelaar, H. J. (2004). Cardiotoxicity of cytotoxic drugs. *Cancer Treat. Rev.* 30 (2), 181–191. doi:10.1016/j.ctrv.2003.07.003

Shah, N. N., Highfill, S. L., Shalabi, H., Yates, B., Jin, J., Wolters, P. L., et al. (2020). CD4/CD8 T-Cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: updated results from a phase I anti-CD22 CAR T-cell trial. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 38 (17), 1938–1950. doi:10.1200/JCO.19.03279

Shalabi, H., Martin, S., Yates, B., Wolters, P. L., Kaplan, C., Smith, H., et al. (2022). Neurotoxicity following CD19/CD28ζ CAR T-cells in children and young adults with B-cell malignancies. *Neuro-oncology* 24 (9), 1584–1597. doi:10.1093/neuonc/noac034

Siegel, R. L., Miller, K. D., Fuchs, H. E., and Jemal, A. (2021). Cancer statistics. *CA a cancer J. Clin.* 71(1): 7–33. doi:10.3322/caac.21654

Skinner, R., Sharkey, I. M., Pearson, A. D., and Craft, A. W. (1993). Ifosfamide, mesna, and nephrotoxicity in children. *J. Clin. Oncol. official J. Am. Soc. Clin. Oncol.* 11 (1), 173–190. doi:10.1200/JCO.1993.11.1.173

Sonnenblick, M., and Rosin, A. (1991). Cardiotoxicity of interferon. A review of 44 cases. *Chest* 99 (3), 557–561. doi:10.1378/chest.99.3.557

Steliarova-Foucher, E., Colombet, M., Ries, L. A. G., Moreno, F., Dolya, A., Bray, F., et al. (2017). International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol.* 18 (6), 719–731. doi:10.1016/S1470-2045(17)30186-9

Stock, W., Luger, S. M., Advani, A. S., Yin, J., Harvey, R. C., Mullighan, C. G., et al. (2019). A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood.* 133(14):1548–1559. doi:10.1182/blood-2018-10-881961

Strickland, S. A., and Vey, N. (2022). Diagnosis and treatment of therapy-related acute myeloid leukemia. *Crit. Rev. oncology/hematology* 171, 103607. doi:10.1016/j.critrevonc.2022.103607

Strumia, M., Perrin, M. L., Patras De Compaigno, E., Conte, C., Montastruc, F., Lapeyre-Mestre, M., et al. (2022). Dermatological adverse drug reactions of anticancer drugs: international data of pharmacovigilance: VigiBase®. *Therapie* 77 (2), 219–227. doi:10.1016/j.therap.2021.12.006

Todd, R. C., and Lippard, S. J. (2009). Inhibition of transcription by platinum antitumor compounds. *Metallomics Integr. biometal Sci.* 1 (4), 280–291. doi:10.1039/b907567d

Tripaydonis, A., Conyers, R., and Elliott, D. A. (2019). Pediatric anthracycline-induced cardiotoxicity: mechanisms, pharmacogenomics, and pluripotent stem-cell modeling. *Clin. Pharmacol. Ther.* 105 (3), 614–624. doi:10.1002/cpt.1311

Turgay, YAGMUR I., Guzelkucuk, Z., Yarali, N., Ozyoruk, D., Toyran, M., Civelek, E., et al. (2020). Evaluation of hypersensitivity reactions to cancer chemotherapeutic agents in pediatric patients. *Ann. allergy, asthma & Immunol. official Publ. Am. Coll. Allergy, Asthma, & Immunol.* 124 (4), 350–356. doi:10.1016/j.anai.2020.01.010

Warwick, A. B., Malempati, S., Krailo, M., Melemed, A., Gorlick, R., Ames, M. M., et al. (2013). Phase 2 trial of pemetrexed in children and adolescents with refractory solid tumors: a Children's Oncology Group study. *Pediatr. blood cancer* 60 (2), 237–241. doi:10.1002/pbc.24244

Wright, K. D., Daryani, V. M., Turner, D. C., Onar-Thomas, A., Boulos, N., Orr, B. A., et al. (2015). Phase I study of 5-fluorouracil in children and young adults with recurrent ependymoma. *Neuro-oncology* 17 (12), 1620–1627. doi:10.1093/neuonc/nov181

Wu, S. F., Chen, A. C., Peng, C. T., and Wu, K. H. (2008). Octreotide therapy in asparaginase-associated pancreatitis in childhood acute lymphoblastic leukemia. *Pediatr. blood cancer* 51 (6), 824–825. doi:10.1002/pbc.21721

Xie, G., Dong, H., Liang, Y., Ham, J. D., Rizwan, R., and Chen, J. (2020). CAR-NK cells: a promising cellular immunotherapy for cancer. *EBioMedicine* 59, 102975. doi:10.1016/j.ebiom.2020.102975

Yang, J., He, J., Zhang, X., Li, J., Wang, Z., Zhang, Y., et al. (2022). Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia: first-in-human clinical study. *Blood cancer J.* 12 (7), 104. doi:10.1038/s41408-022-00694-6

Yang, Y., Wang, C., Chen, Y., Wang, X., Jiao, Z., and Wang, Z. (2023). External evaluation and systematic review of population pharmacokinetic models for high-dose methotrexate in cancer patients. *Eur. J. Pharm. Sci. official J. Eur. Fed. Pharm. Sci.* 186, 106416. doi:10.1016/j.ejps.2023.106416

You, L., Lv, Z., Li, C., Ye, W., Zhou, Y., Jin, J., et al. (2021). Worldwide cancer statistics of adolescents and young adults in 2019: a systematic analysis of the Global Burden of Disease Study 2019. *ESMO open* 6 (5), 100255. doi:10.1016/j.esmoop.2021.100255

Yu, Z., Yan, B., Gao, L., Dong, C., Zhong, J., Nguyen, B., et al. (2016). Targeted delivery of bleomycin: a comprehensive anticancer review. *Curr. cancer drug targets* 16 (6), 509–521. doi:10.2174/1568009616666151130213910

Zhang, K., Weng, H., Yang, J., and Wu, C. (2020). Protective effect of Liuwei Dihuang Pill on cisplatin-induced reproductive toxicity and genotoxicity in male mice. *J. Ethnopharmacol.* 247, 112269. doi:10.1016/j.jep.2019.112269

Zhang, L., Meng, Y., Feng, X., and Han, Z. (2022). CAR-NK cells for cancer immunotherapy: from bench to bedside. *Biomark. Res.* 10 (1), 12. doi:10.1186/s40364-022-00364-6

Zheng, R., Peng, X., Zeng, H., Zhang, S., Chen, T., Wang, H., et al. (2015). Incidence, mortality and survival of childhood cancer in China during 2000-2010 period: a population-based study. *Cancer Lett.* 363 (2), 176–180. doi:10.1016/j.canlet.2015.04.021

Zhu, Y., Yang, R., Cai, J., Yu, J., Tang, Y., Chen, Y., et al. (2020). Septicemia after chemotherapy for childhood acute lymphoblastic leukemia in China: a multicenter study CCCG-ALL-2015. *Cancer Med.* 9 (6), 2113–2121. doi:10.1002/cam4.2889

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 16 February 2024
DOI 10.3389/fphar.2024.1338902

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Pedro Dorado,
University of Extremadura, Spain
Vera Battini,
University of Milan, Italy

*CORRESPONDENCE
Yuanbo Lan,
lybivy@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 November 2023
ACCEPTED 31 January 2024
PUBLISHED 16 February 2024

CITATION
Zou F, Cui Z, Lou S, Ou Y, Zhu C, Shu C, Chen J, Zhao R, Wu Z, Wang L, Chen Z, Chen H and Lan Y (2024), Adverse drug events associated with linezolid administration: a real-world pharmacovigilance study from 2004 to 2023 using the FAERS database.
Front. Pharmacol. 15:1338902.
doi: 10.3389/fphar.2024.1338902

Adverse drug events associated with linezolid administration: a real-world pharmacovigilance study from 2004 to 2023 using the FAERS database

Fan Zou[1†], Zhiwei Cui[2†], Siyu Lou[1†], Yingyong Ou[1], Chengyu Zhu[1], Chengjie Shu[1], Junyou Chen[1], Ruizhen Zhao[1], Zhu Wu[3], Li Wang[3], Zhenyong Chen[1], Huayu Chen[3] and Yuanbo Lan[1]*

[1]Department of Tuberculosis, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China, [2]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3]Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China

Introduction: Linezolid is an oxazolidinone antibiotic that is active against drug-resistant Gram-positive bacteria and multidrug-resistant *Mycobacterium tuberculosis*. Real-world studies on the safety of linezolid in large populations are lacking. This study aimed to determine the adverse events associated with linezolid in real-world settings by analyzing data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Methods: We retrospectively extracted reports on adverse drug events (ADEs) from the FAERS database from the first quarter of 2004 to that of 2023. By using disproportionality analysis including reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), along with the multi-item gamma Poisson shrinker (MGPS), we evaluated whether there was a significant association between linezolid and ADE. The time to onset of ADE was further analyzed in the general population and within each age, weight, reporting population, and weight subgroups.

Results: A total of 11,176 reports of linezolid as the "primary suspected" drug and 263 significant adverse events of linezolid were identified, including some common adverse events such as thrombocytopenia (n = 1,139, ROR 21.98), anaemia (n = 704, ROR 7.39), and unexpected signals that were not listed on the drug label such as rhabdomyolysis (n = 90, ROR 4.33), and electrocardiogram QT prolonged (n = 73, ROR 4.07). Linezolid-induced adverse reactions involved 27 System Organ Class (SOC). Gender differences existed in ADE signals related to linezolid. The median onset time of all ADEs was 6 days, and most ADEs (n = 3,778) occurred within the first month of linezolid use but some may continue to occur even after a year of treatment (n = 46).

Conclusion: This study reports the time to onset of adverse effects in detail at the levels of SOC and specific preferred term (PT). The results of our study provide valuable insights for optimizing the use of linezolid and reducing potential side effects, expected to facilitate the safe use of linezolid in clinical settings.

KEYWORDS

linezolid, adverse drug event, FAERS, disproportionality analysis, pharmacovigilance, real-world analysis

1 Introduction

Linezolid, an oxazolidinone antibiotic, is effective against drug-resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and multidrug-resistant *Mycobacterium tuberculosis* (Sotgiu et al., 2012; Hashemian et al., 2018; Crass et al., 2019). It targets the bacterial ribosomes and inhibits protein synthesis, thereby preventing the formation of the initiation complex (Ippolito et al., 2008; Wilson et al., 2008; Long et al., 2010; Long and Vester, 2012). Linezolid reduces toxin production by Gram-positive pathogens (Ippolito et al., 2008). Owing to its high bioavailability, it can be administered intravenously or orally without dosage adjustment (Welshman et al., 2001). Linezolid is considered a first-line antibiotic for methicillin-resistant *S. aureus* pneumonia and is more cost-effective and reduces mortality significantly compared to vancomycin in the treatment of methicillin-resistant *S. aureus* (MRSA) infections (Liu et al., 2011; Niederman et al., 2014; Collins and Schwemm, 2015; von Dach et al., 2017). Linezolid has been approved for the treatment of hospital-acquired pneumonia caused by *S. aureus*, vancomycin-resistant *Enterococcus faecalis* (VREF) infections, complicated skin and skin structure infections (SSSIs), uncomplicated SSSIs caused by meticillin-sensitive S.aureus (MSSA) or *Streptococcus* pyogenes, community-acquired pneumonia, and pneumococcal meningitis caused by penicillin-resistant *Streptococcus* pneumoniae. Linezolid is associated with lower mortality rates compared to daptomycin in the treatment of vancomycin-resistant *Enterococcus* (VRE) bacteremia, with lower infection-related and hospitalization mortality rates. Moreover, linezolid is effective in treating multidrug-resistant tuberculosis (TB) (Cox and Ford, 2012; Brown et al., 2015; Hughes et al., 2015; Tang et al., 2015). Overall, linezolid exerts promising therapeutic effects and has been approved by the U.S. FDA for treating various infections.

In Phase III and IV clinical studies and randomized controlled trials, the most common adverse drug reactions (ADRs) of linezolid use included gastrointestinal reactions, including diarrhea, nausea and vomiting, bone marrow suppression, peripheral neuropathy, and headache (Rubinstein et al., 2001; Prokocimer et al., 2013; O'Riordan et al., 2019; Esmail et al., 2022; Kotsaki et al., 2023). Fortunately, most ADRs did not result in serious adverse outcomes and given the strict diagnostic criteria, selection criteria, relatively small sample size, and limited follow-up time, ADRs targeted single or limited number of systems. Linezolid has been approved for extensively drug-resistant TB and multidrug-resistant TB, which may result in the development of some ADR exacerbations or previously unidentified safety concerns. Data on the combined safety profile of linezolid from large samples and in the real world are lacking. With the expansion of indications for linezolid, it is now being widely used in clinical settings. Therefore, post-marketing evaluation of linezolid using data mining is necessary.

The FDA Adverse Event Reporting System (FAERS) database is a valuable resource for post-marketing surveillance and early detection of drug safety issues (Cirmi et al., 2020; Feng et al., 2022). It contains real adverse event reports from various sources, including those documented by healthcare professionals, consumers, and manufacturers. The database is regularly updated and publicly available for download on the FDA website (Sakaeda et al., 2013). Considering the lack of evidence of adverse events of linezolid at the real-world level, we conducted a post-marketing surveillance to assess adverse events associated with linezolid use in FAERS from the first quarter of 2004 to that of 2023. We comprehensively analyzed system-specific side effects of linezolid and their time of onset as well as gender-based differences. The results of this study can guide physicians and health policymakers in monitoring adverse drug reactions and providing recommendations for the safe clinical use of linezolid.

2 Materials and methods

2.1 Data sources and preprocessing

We conducted this retrospective pharmacovigilance analysis using the FAERS database. FAERS is a compilation of adverse drug event (ADE) reports and allows researchers to perform signal detection and quantify the associations between drug dosing and ADEs (Sakaeda et al., 2013). The FAERS database is updated quarterly and comprises seven datasets on demographic and administrative information (DEMO), drug information (DRUG), adverse drug reaction information (REAC), patient outcomes information (OUCT), reported sources (RPSR), drug therapy start dates and end dates (THER), and indications for drug administration (INDI). There are unavoidable cases of duplicate reporting in FAERS due to the characteristics of data updating. Therefore, we set the retrieval timeframe from 1 January 2004, to 31 March 2023, and removed duplicates to enhance the reliability of the findings based on the following criteria recommended by the FDA (Shu et al., 2022; Wang et al., 2023): if CASEIDs were the same, the most recent FDA_DT was chosen; if CASEIDs and FDA_DTs were the same, the higher PRIMARYID was chosen (Cui et al., 2023). After data preprocessing, we obtained 16,529,987 DEMO reports, 60,498,943 DRUG cases, and 49,568,379 REAC records (Figure 1).

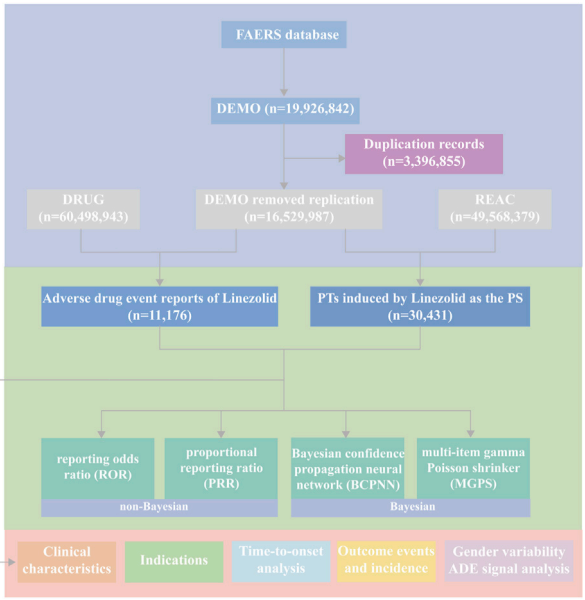


FIGURE 1
A flowchart of the whole study.

2.2 Study design (drug selection and signal detection)

Because FAERS does not utilize a uniform drug coding system, both generic (LINEZOLID) and brand (ZYVOXID) names were used to identify ADEs associated with linezolid (see Supplementary Table S1 for the detailed list of drug names used for search). Drugs reported in FAERS were categorized into four patterns, namely PS (primary suspect), SS (second suspect), C (concomitant), and I (interacting). To improve accuracy, only drugs with linezolid as the PS was retained in the role codes for ADEs, resulting in 11,176 ADE reports (linezolid-related ADEs) screened for linezolid administration (Ji et al., 2022a). Medical Dictionary for Regulatory Activities (MedDRA) is a standardized medical terminology that globally facilitates the recording and reporting of ADE data (Brown, 2004; Singh, 2015). Its hierarchical structure encompasses multiple levels, ranging from lower terminology to system organ class (SOC) (Brown, 2003). SOC is the highest level of terminology in MedDRA used for classifying and reporting adverse events in the Drug Safety Monitoring and Reporting System. To summarize and analyze ADE features in a structured way, all ADEs in our collection were coded using the preferred term (PT) and then mapped to their corresponding highest SOC level in MedDRA (version 26.0) (Wang et al., 2014; Zhou et al., 2023). In total, 30,431 PTs induced by linezolid as the PS (linezolid-related PTs) were identified.

In pharmacovigilance studies, disproportionality analysis is an instrumental method for identifying and detecting drug-related adverse reaction signals (van Puijenbroek et al., 2002). To improve the results' reliability, we employed different methods of disproportionality analysis, including two non-Bayesian methods(the reporting odds ratio [ROR] and the proportional reporting ratio [PRR]) and two Bayesian methods, including the Bayesian Confidence Propagation Neural Network (BCPNN), along with the multi-item gamma Poisson shrinker (MGPS) (Trippe et al., 2017). Non-Bayesian methods such as ROR may exhibit better efficacy for early signal detection, while the Bayesian approach has a strong detection power for unique signals even when there are few ADEs reported for the drug (Chen et al., 2008; Nomura et al., 2015). The two-by-two contingency table and detailed formulas for these methods of disproportionality analysis and the positive signal thresholds are provided in Table 1. Beyond the threshold, a larger value indicates a stronger signal value. We indicated signals not listed in the drug label as "unexpected signals." To enhance the reliability of the findings, separate disproportionality analyses were performed based on patient age, gender, weight, and reporting sources.

Additionally, to discern the disproportional signals between male and female following linezolid administration, we employed the formula of ROR method. The ROR used here does not strictly adhere to the pharmacoepidemiological definition of ROR, as elucidated in the caption of Supplementary Table S4. According to the 2 by 2 contingency table, we calculated the *p*-value based on the chi-square ($\chi 2$) test. We generated a volcano plot displaying the log2-transformed ROR values on the horizontal axis and the -log10-transformed corrected *p*-values (*P*.adj, adjusted by FDR) on the vertical axis, utilizing the R package "ggplot2" (version 3.3.6) (Li et al., 2023). When the ROR is greater than 1 and the *P*.adj is greater than 0.05, it suggests that female patients are more likely than male patients to report a specific ADE. Conversely, when the ROR is less than 1 and the *P*.adj is less than 0.05, it suggests that male patients are more likely than female patients to report a specific ADE.

2.3 Time to onset (TTO) analysis

The TTO of linezolid-related ADEs is defined as the time interval between the ADE onset date in the DEMO file

TABLE 1 A two-by-two contingency table and detailed formulas for disproportionality analysis.

	Target adverse drug event	Other adverse drug events	Sums
Linezolid	a	b	a+b
Other drugs	c	d	c+d
Sums	a+c	b+d	a+b+c+d

Algorithms	Equation	Criteria
R	ROR = ad/bc	lower limit of 95% CI>1, N≥3
	95%CI = $e^{\ln(ROR) \pm 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}}$	
PRR	PRR = [a(c + d)]/[c(a + b)]	PRR≥2, χ2≥4, N≥3
BCPNN	$\chi 2 = [(ad - bc)^2](a + b + c + d)/[(a + b)(c + d)(a + c)(b + d)]$ IC = log 2a(a + b + c + d)/[(a + c)(a + b)]	IC025>0
	95%CI = $E(IC) \pm 2\sqrt{[V(IC)]}$	
MGPS	EBGM = a(a + b + c + d)/[(a + c)(a + b)]	EBGM05>2
	95%CI = $e^{\ln(EBGM) \pm 1.96\sqrt{(1/a + 1/b + 1/c + 1/d)}}$	

The formulas to calculate the signal strength are as follows: a, number of reports containing both the target drug and the target adverse drug event; b, number of reports containing other adverse drug events of the target drug; c, number of reports containing the target adverse drug event of other drugs; d, number of reports containing other drugs and other adverse drug events. Abbreviations: 95% CI, 95% confidence interval; N, the number of reports; χ2, chi-squared; ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, Bayesian confidence propagation neutral network; MGPS, multi-item gamma Poisson shrinker; IC, information component; IC025, the lower limit of the 95% CI of the IC; E (IC), the IC expectations; V (IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM.

10.3389/fphar.2024.1338902

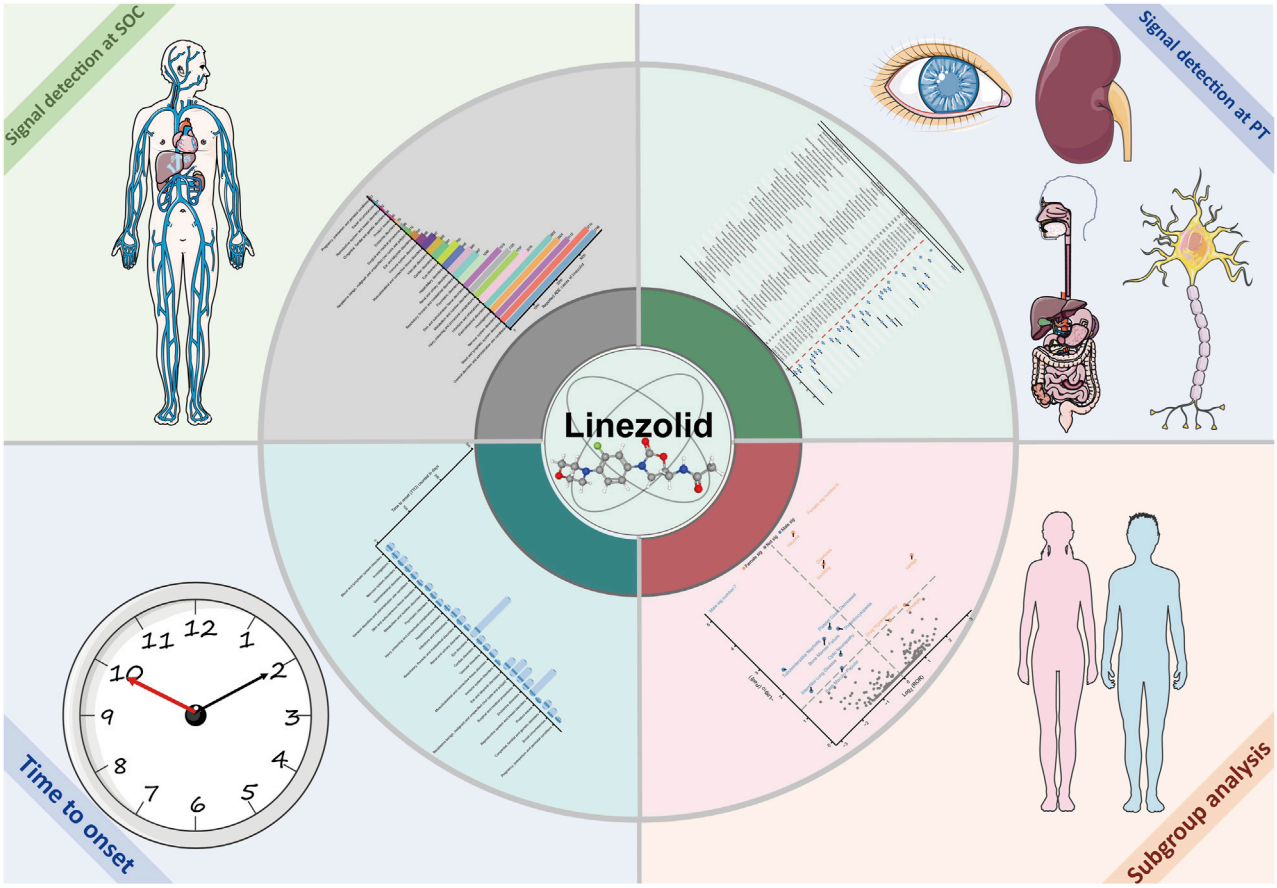


FIGURE 2
The main findings of this study. After data cleaning, we detected the signal strength of ADEs at the SOC and PT levels. Moreover, we performed gender-based subgroup analysis and conducted detailed calculations and comparisons of TTO. ADEs, adverse drug events; SOC, System Organ Class; PT, preferred term; TTO, time to onset.

(EVENT_DT) and the date of medication initiation in the THER file (START_DT). Inaccurate or missing dates, and cases with ADE onset dates earlier than the start date of linezolid medication were excluded. The frequency of adverse events post-therapy initiation is contingent upon the drug's mechanism of action and may fluctuate over time. In contrast, adverse events unrelated to drug therapy transpire at a consistent rate (Cornelius et al., 2012). The Weibull distribution test determines the proportional change in the adverse event rate, indicating the risk of increase or decrease over time. Consequently, we conducted a comprehensive TTO assessment based on median, quartile, extremes, and the Weibull distribution test (Kinoshita et al., 2020). The Weibull distribution curve is defined by two primary parameters: the scale parameter (α) and the shape parameter (β). For the purposes of this study, only parameter β is considered and discussed. If the shape parameter β <1 and its 95% confidence interval (CI) <1, the risk of adverse reactions is considered to decrease over time (early failure type curve); if the shape parameter β is approximately equal to or close to 1 and its 95% CI contains the value of 1, it is estimated that the risk occurs constantly over time (random failure type curve); and if the shape parameter β >1 and its 95% CI excludes the value of 1, the hazard is considered to increase over time (wear failure type curve) (Sauzet et al., 2013; Mazhar et al., 2021). In order to enhance the reliability of the analyses, Weibull distribution test was performed in the overall and subgroups respectively.

2.4 Statistical analysis

Differences in values among multiple groups were assessed using the Kruskal–Wallis test and Dunn's test. SAS 9.4 and Microsoft EXCEL 2019 were used to process the data. The R (version 4.2.1) language was used for data visualization and statistical calculations. The 3D structure of linezolid was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Kim et al., 2023). The image source in Figure 2 is Servier Medical Art (https://smart.servier.com/), provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

3 Results

3.1 Descriptive characteristics

In this study, 16,529,987 reported cases were collected from the FAERS database during the study period (Q1 2004–Q1 2023), and

TABLE 2 Demographic characteristics of ADEs reported in the FAERS database (January 2004-March 2023) with linezolid as the primary suspect drug.

Characteristics	Case number	Case proportion, %
Gender, n (%)		
F	4,028	36.04%
M	5,222	46.73%
Unknown	1,926	17.23%
Age		
<18	19	0.17%
18–64	162	1.45%
>64	138	1.23%
Unknown	10,857	97.15%
Weight		
<80	2,258	20.20%
80–100	701	6.27%
>100	413	3.70%
Unknown	7,804	69.83%
Reported Countries (top five)		
US	2,683	24.01%
FR	1,204	10.77%
JP	1,089	9.74%
GB	985	8.81%
CN	645	5.77%
Reported person		
Health professionals	9,472	84.76%
Consumer	1,261	11.28%
Unknown	443	3.96%
Outcome		
HO	3,595	27.92%
LT	934	7.26%
DS	268	2.09%
RI	98	0.76%
DE	1,440	11.20%
OT	6,441	50.07%
Unknown	90	0.70%
Indication (top five)		
Staphylococcal infection	1,081	9.67%
Tuberculosis	673	6.02%
Infection	552	4.94%
Pneumonia	396	3.54%
Enterococcal infection	355	3.18%

F, female; M, male; US, United States; FR, France; JP, Japan; GB, Great Britain; CN, China; HO, hospitalization; LT, life-threatening; DS, disability; RI, required intervention; DE, death; OT, other serious outcomes; ADEs, adverse drug events.

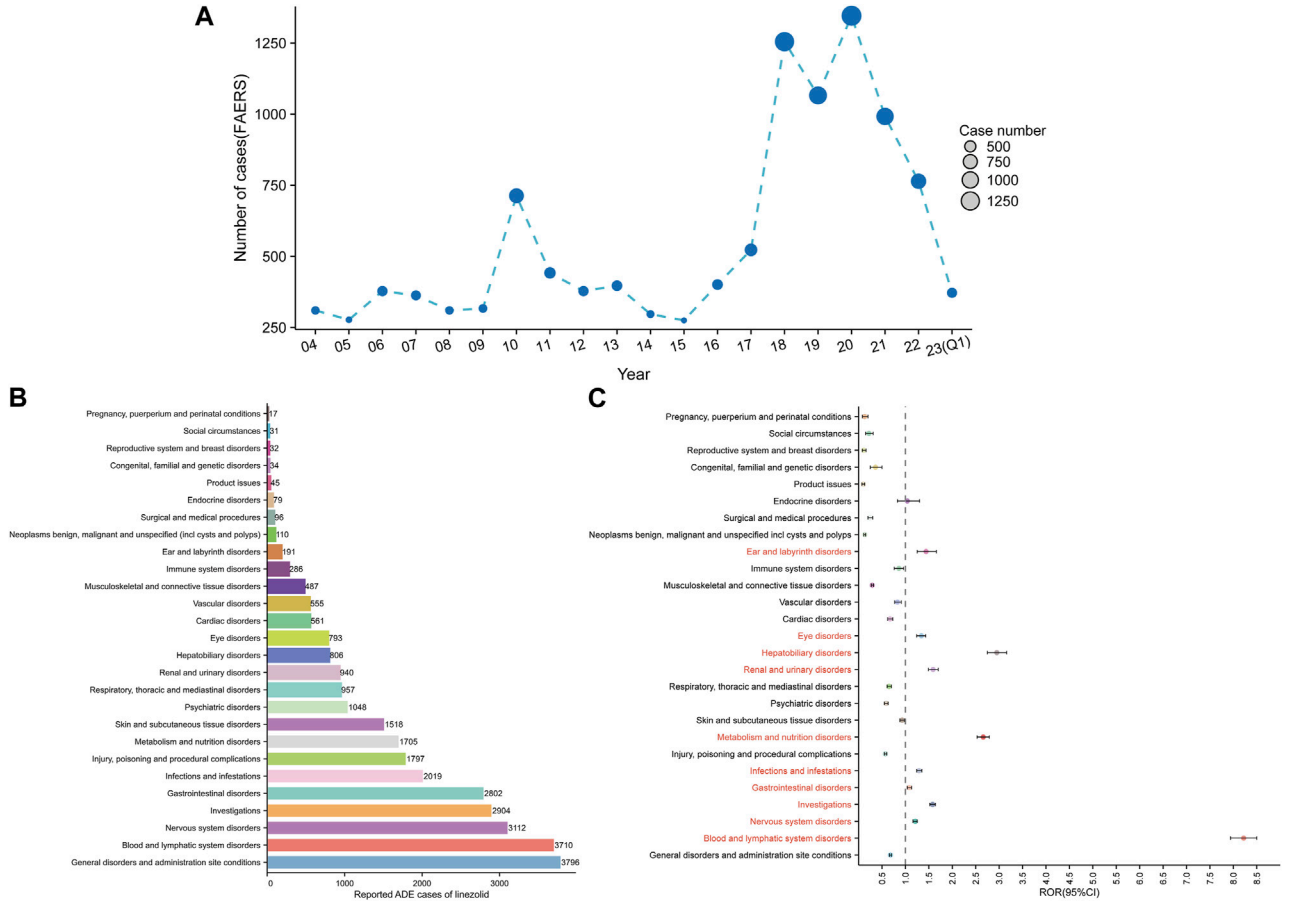


FIGURE 3
Signals detection at the SOC level. **(A)** Distribution of ADEs of linezolid from 2004 to the first quarter of 2023 (2023 Q1). **(B)** The bar chart displays the reported cases of ADEs at each SOC level. **(C)** Signals detection at the SOC level. The ROR values and their 95% confidence intervals (95% CI) are visualized. We label the SOCs with positive signal values to make a distinction. FAERS, Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS); ADEs, adverse drug events; SOC, System Organ Class; ROR, reporting odds ratio.

11,176 linezolid-related ADEs and 30,431 linezolid-related PTs were finally obtained after removing duplicates. The demographic characteristics of linezolid-associated ADEs are described in Table 2. The number of reports identifying the gender of the submitters was 9,250, of which 5,222 were submitted by male (46.73%) and 4,028 by female (36.04%). The number of reports containing age-specific information was 319, with 19 (0.17%), 162 (1.45%), and 138 (1.23%) reports for <18, 18–64, and >64 years of age, respectively. Weight data were available for 3,372 patients, with the group<80 kg accounting for the largest proportion (20.20%).

The country with the most documented information was United States (24.10%), followed by France (10.77%), Japan (9.74%), Great Britain (8.81%), and China (5.77%). The majority of reports submitted were by health professionals (n = 9,472, 84.76%), which greatly increased the reliability of the ADE information. Nearly half of the outcomes were other serious outcomes (50.07%), followed by hospitalization, death, and life-threatening events, which occurred in 3,595 (27.92%), 1,440 (11.20%), and 934 (7.26%) cases, respectively.

Staphylococcal infections were the most commonly reported indication (n = 1,081, 9.67%), followed by TB (n = 673, 6.02%), infections (n = 552, 4.94%), pneumonia (n = 396, 3.54%), and Enterococcal infection (n = 355, 3.18%).

Figure 3A shows the annual distribution of linezolid-related ADE reports. The lowest and highest number of reports were documented in 2015 (275 reports) and in 2020 (1346 reports), respectively. The number of ADE reports increased from 2015 to 2020 and remained high in 2020–2022.

3.2 Signal detects at the SOC level

Signal strengths and reports of linezolid at the SOC level are described in Supplementary Table S2. Linezolid-associated ADEs occurred in 27 organ systems. The number of case reports for linezolid-associated SOCs are shown in Figure 3B. The top five SOCs were general disorders and administration site conditions (n = 3,796, 12.47%), blood and lymphatic system disorders (n = 3,710, 12.19%), nervous system disorders (n = 3,112, 10.23%), investigations (n = 2,904, 9.54%), and gastrointestinal disorders (n = 2,802, 9.21%). Significant SOCs for which at least one of the four methods of disproportionality analysis met the criteria were blood

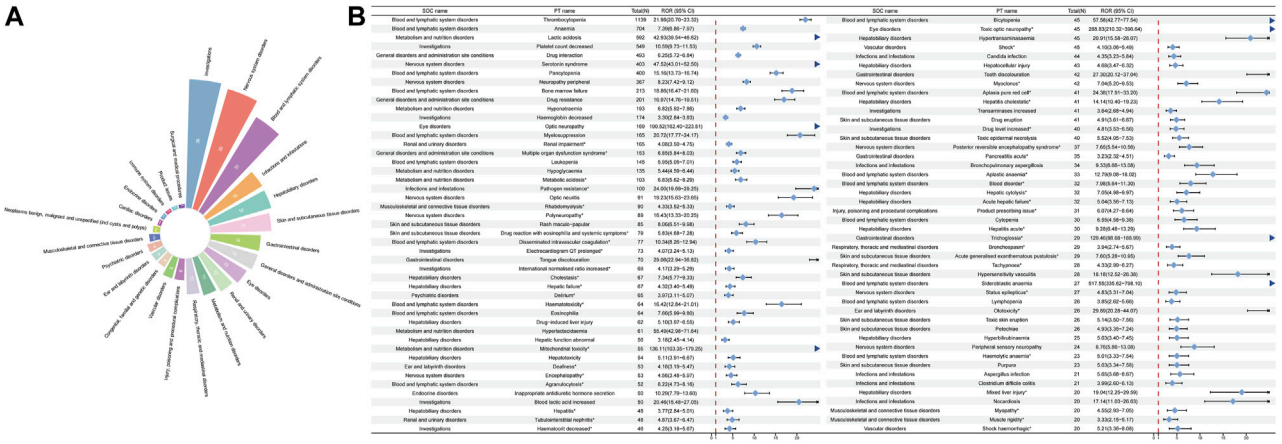


FIGURE 4
Signals detection at the PT level. **(A)** SOC attribution and number of 263 PTs that simultaneously satisfy the 4 methods of disproportionality analysis with positive signal values. **(B)** We selected PTs with a minimum of 20 cases and displayed the ROR and corresponding 95% CI using a forest plot. The blue arrows signify that the lower limit of the 95% confidence interval of the ROR exceeds 25.PTs, preferred terms; SOC, System Organ Class; PTs, preferred terms; CI, confidence interval; ROR, reporting odds ratio.

and lymphatic system disorders (SOC code: 10005329, *n* = 3,710), nervous system disorders (SOC code: 10029205, *n* = 3,112), investigations (SOC code: 10022891, n = 2,904), gastrointestinal disorders (SOC code: 10017947, n = 2,802), infections and infestations (SOC code: 10021881, *n* = 2019), metabolism and nutrition disorders (SOC code: 10027433, *n* = 1705), renal and urinary disorders (SOC code: 10038359, *n* = 940), hepatobiliary disorders (SOC code: 10019805, *n* = 806), eye disorders (SOC code: 10015919, *n* = 793), and ear and labyrinth disorders (SOC code: 10013993, *n* = 191). Notably, disorders of the blood and lymphatic system were the SOCs that met all four criteria simultaneously (Supplementary Table S2). Figure 3C shows the ROR and its 95% confidence interval for linezolid-associated SOC signal strength.

3.3 Disproportionality analysis for ADEs associated with linezolid use

After excluding PT as a possible indication for linezolid medication, the 263 significantly disproportionate PTs corresponding to all four methods of disproportionality analysis simultaneously and ordered by the number of cases are displayed in Supplementary Table S3. Furthermore, we have ranked the SOCs in descending order according to the SOCs corresponding to these 263 PTs, as shown in Figure 4A. Next, we categorized PTs with more than 20 ADE cases and selected 93 ADEs that met this screening criterion, including 18 corresponding SOCs. To improve visualization, we present the PT signals in a forest plot format, arranged in descending order of case number (Figure 4B). Additionally, these data were grouped by SOC and the whole results are presented in Table 3. We identified that PT entries with more than 100 cases included thrombocytopenia (*n* = 1,139), anaemia (*n* = 704), lactic acidosis (*n* = 592), platelet count decreased (*n* = 549), drug interaction (*n* = 493), serotonin syndrome (*n* = 403), pancytopenia (*n* = 400), neuropathy peripheral (*n* = 367), bone marrow failure (*n* = 213), drug resistance (*n* = 201), hyponatraemia (*n* = 193), haemoglobin decreased (*n* = 174), optic neuropathy (*n* = 169), myelosuppression (*n* = 165), leukopenia (*n* = 145), and hypoglycaemia (*n* = 135), consistent with the medication warnings in the drug label. Interestingly, unexpected significant ADEs were identified, and PTs with more than 50 reports included renal impairment (*n* = 165), multiple organ dysfunction syndrome (*n* = 153), metabolic acidosis (*n* = 103), pathogen resistance (*n* = 100), rhabdomyolysis (*n* = 90), polyneuropathy (*n* = 89), drug reaction with eosinophilia and systemic symptoms (*n* = 79), disseminated intravascular coagulation (*n* = 77), electrocardiogram QT prolonged (*n* = 73), international normalised ratio increased (*n* = 69), hepatic failure (*n* = 67), delirium (*n* = 65), haematotoxicity (*n* = 64), mitochondrial toxicity (*n* = 55), deafness (*n* = 53), encephalopathy (*n* = 53), and agranulocytosis (*n* = 52). We also considered the IC025 value due to the increased stability of calculated results offered by the Bayesian approach in instances of low numbers of adverse events (Kubota et al., 2004). High IC025 values were found for unexpected signals such as toxic optic neuropathy (*n* = 45, IC025 [6.26]) and trichoglossia (*n* = 29, IC025 [5.23]), despite the low number of cases, indicating a strong association with linezolid administration. Digestive events, such as nausea, vomiting, and diarrhea were common in patients treated with linezolid. However, these events did not meet any of the four criteria set in our analysis.

Additionally, given the potential confounding effect of baseline information on the results of the disproportionality analyses (de Vries et al., 2020), sensitivity analyses incorporating weight (<80 kg, 80–100 kg, >100 kg), age (18–64 years, >64 years, subgroups <18 years were under-reported and excluded), gender (male, female), and reported population (consumers and health professionals) were performed to bolster result confidence (Liang et al., 2023). Notably, serotonin syndrome (*n* = 18, ROR 46.07, 95% CI 28.93–73.37) exhibited the highest signal strength in the group >100 kg; however, it was absent from the first 15 adverse drug event signals in the two groups ≤100 kg. Moreover, other

TABLE 3 Signal strength of ADE reports for linezolid at the preferred term (PT) level in the FAERS database.

SOC name	PT name	Frequency	Case number	ROR (95% CI)	PRR	χ2	EBGM (EBGM05)	IC (IC025)
Blood and lymphatic system disorders	Sideroblastic anaemia	0.09%	27	517.55 (335.62–798.10)	517.09	10554.82	392.68 (273.30)	8.62 (6.93)
Blood and lymphatic system disorders	Bicytopenia	0.15%	45	57.58 (42.77–77.54)	57.5	2413.1	55.57 (43.33)	5.80 (4.13)
Blood and lymphatic system disorders	Aplasia pure red cell*	0.13%	41	24.38 (17.91–33.20)	24.35	904.55	24.01 (18.54)	4.59 (2.92)
Blood and lymphatic system disorders	Thrombocytopenia	3.74%	1139	21.98 (20.70–23.32)	21.19	21668.44	20.93 (19.91)	4.39 (2.72)
Blood and lymphatic system disorders	Myelosuppression	0.54%	165	20.72(17.77–24.17)	20.62	3041.86	20.37 (17.91)	4.35 (2.68)
Blood and lymphatic system disorders	Bone marrow failure	0.70%	213	18.86(16.47–21.60)	18.74	3537.31	18.54 (16.55)	4.21 (2.55)
Blood and lymphatic system disorders	Haematotoxicity*	0.21%	64	16.42 (12.84–21.01)	16.39	915.86	16.24 (13.21)	4.02 (2.35)
Blood and lymphatic system disorders	Pancytopenia	1.31%	400	15.16 (13.73–16.74)	14.97	5173.54	14.85 (13.67)	3.89 (2.23)
Blood and lymphatic system disorders	Aplastic anaemia*	0.11%	33	12.79 (9.08–18.02)	12.78	355.51	12.69 (9.52)	3.67 (2.00)
Blood and lymphatic system disorders	Disseminated intravascular coagulation*	0.25%	77	10.34 (8.26–12.94)	10.32	644.05	10.26 (8.50)	3.36 (1.69)
Blood and lymphatic system disorders	Blood disorder*	0.11%	32	7.98 (5.64–11.30)	7.97	194.25	7.94 (5.94)	2.99 (1.32)
Blood and lymphatic system disorders	Eosinophilia	0.21%	64	7.66 (5.99–9.80)	7.65	368.23	7.62 (6.20)	2.93 (1.26)
Blood and lymphatic system disorders	Anaemia	2.31%	704	7.39 (6.86–7.97)	7.25	3785.64	7.22 (6.78)	2.85 (1.19)
Blood and lymphatic system disorders	Cytopenia	0.10%	30	6.55 (4.58–9.38)	6.55	140.46	6.53 (4.83)	2.71 (1.04)
Blood and lymphatic system disorders	Agranulocytosis*	0.17%	52	6.22 (4.73–8.16)	6.21	226.31	6.19 (4.93)	2.63 (0.96)
Blood and lymphatic system disorders	Leukopenia	0.48%	145	5.95 (5.05–7.01)	5.93	592.45	5.91 (5.16)	2.56 (0.90)
Blood and lymphatic system disorders	Haemolytic anaemia*	0.08%	23	5.01 (3.33–7.54)	5.01	73.54	4.99 (3.55)	2.32 (0.65)
Blood and lymphatic system disorders	Lymphopenia	0.09%	26	3.85 (2.62–5.66)	3.85	54.74	3.84 (2.78)	1.94 (0.28)
Ear and labyrinth disorders	Ototoxicity*	0.09%	26	29.89(20.28–44.07)	29.87	712.42	29.35 (21.21)	4.88 (3.21)
Ear and labyrinth disorders	Deafness*	0.17%	53	4.18(3.19–5.47)	4.17	127.53	4.16 (3.32)	2.06 (0.39)
Endocrine disorders	Inappropriate antidiuretic hormone secretion	0.16%	50	10.29 (7.79–13.60)	10.28	416.22	10.22 (8.10)	3.35 (1.69)
Eye disorders	Toxic optic neuropathy*	0.15%	45	288.83 (210.32–396.64)	288.4	10948.67	245.15 (188.00)	7.94 (6.26)
Eye disorders	Optic neuropathy	0.56%	169	190.52 (162.40–223.51)	189.47	28381.15	169.82 (148.58)	7.41 (5.74)
Gastrointestinal disorders	Trichoglossia*	0.10%	29	129.46 (88.68–188.99)	129.34	3421.24	119.89 (87.36)	6.91 (5.23)

(Continued on following page)

TABLE 3 (*Continued*) Signal strength of ADE reports for linezolid at the preferred term (PT) level in the FAERS database.

SOC name	PT name	Frequency	Case number	ROR (95% CI)	PRR	χ2	EBGM (EBGM05)	IC (IC025)
Gastrointestinal disorders	Tongue discolouration	0.23%	70	29.06 (22.94–36.82)	29	1859.12	28.51 (23.39)	4.83 (3.17)
Gastrointestinal disorders	Tooth discolouration	0.14%	42	27.30 (20.12–37.04)	27.26	1045.06	26.83 (20.78)	4.75 (3.08)
Gastrointestinal disorders	Pancreatitis acute*	0.12%	35	3.23 (2.32–4.51)	3.23	53.87	3.23 (2.45)	1.69 (0.02)
General disorders and administration site conditions	Drug resistance	0.66%	201	16.97 (14.76–19.51)	16.86	2970.08	16.70 (14.86)	4.06 (2.40)
General disorders and administration site conditions	Multiple organ dysfunction syndrome*	0.50%	153	6.85 (5.84–8.03)	6.82	757.72	6.80 (5.95)	2.77 (1.10)
General disorders and administration site conditions	Drug interaction	1.62%	493	6.25 (5.72–6.84)	6.17	2132.63	6.15 (5.71)	2.62 (0.95)
Hepatobiliary disorders	Hypertransaminasaemia	0.15%	45	20.91 (15.58–28.07)	20.88	841.12	20.63 (16.13)	4.37 (2.70)
Hepatobiliary disorders	Mixed liver injury*	0.07%	20	19.04 (12.25–29.59)	19.03	337.68	18.82 (13.01)	4.23 (2.57)
Hepatobiliary disorders	Hepatitis cholestatic*	0.13%	41	14.14 (10.40–19.23)	14.12	495.67	14.01 (10.83)	3.81 (2.14)
Hepatobiliary disorders	Hepatitis acute*	0.10%	30	9.28 (6.48–13.29)	9.27	220.12	9.22 (6.83)	3.21 (1.54)
Hepatobiliary disorders	Cholestasis*	0.22%	67	7.34 (5.77–9.33)	7.33	364.48	7.30 (5.97)	2.87 (1.20)
Hepatobiliary disorders	Hepatic cytolysis*	0.11%	32	7.05 (4.98–9.97)	7.04	165.15	7.01 (5.24)	2.81 (1.14)
Hepatobiliary disorders	Hepatotoxicity	0.18%	54	5.11 (3.91–6.67)	5.1	177.42	5.09 (4.07)	2.35 (0.68)
Hepatobiliary disorders	Drug-induced liver injury	0.20%	62	5.10 (3.97–6.55)	5.09	203.39	5.08 (4.12)	2.34 (0.68)
Hepatobiliary disorders	Acute hepatic failure*	0.11%	32	5.04 (3.56–7.13)	5.04	103.19	5.02 (3.76)	2.33 (0.66)
Hepatobiliary disorders	Hyperbilirubinaemia	0.08%	25	5.03 (3.40–7.45)	5.03	80.38	5.01 (3.61)	2.33 (0.66)
Hepatobiliary disorders	Hepatocellular injury	0.14%	43	4.68 (3.47–6.32)	4.68	124.02	4.67 (3.63)	2.22 (0.56)
Hepatobiliary disorders	Hepatic failure*	0.22%	67	4.32 (3.40–5.49)	4.31	169.94	4.30 (3.52)	2.10 (0.44)
Hepatobiliary disorders	Hepatitis*	0.16%	48	3.77 (2.84–5.01)	3.77	97.5	3.76 (2.97)	1.91 (0.25)
Hepatobiliary disorders	Hepatic function abnormal	0.18%	56	3.18 (2.45–4.14)	3.18	83.59	3.18 (2.55)	1.67 (0.00)
Infections and infestations	Pathogen resistance*	0.33%	100	24.00 (19.69–29.25)	23.93	2165.19	23.59 (20.00)	4.56 (2.89)
Infections and infestations	Nocardiosis	0.07%	20	17.14 (11.03–26.63)	17.13	300.55	16.96 (11.73)	4.08 (2.42)
Infections and infestations	Bronchopulmonary aspergillosis	0.11%	34	9.33 (6.66–13.08)	9.32	251.2	9.28 (6.99)	3.21 (1.55)
Infections and infestations	Aspergillus infection	0.07%	21	5.65 (3.68–8.67)	5.64	79.96	5.63 (3.93)	2.49 (0.83)
Infections and infestations	Candida infection	0.14%	44	4.35 (3.23–5.84)	4.34	112.9	4.33 (3.38)	2.12 (0.45)
Infections and infestations	Clostridium difficile colitis	0.07%	21	3.99 (2.60–6.13)	3.99	46.95	3.98 (2.78)	1.99 (0.33)
Injury, poisoning and procedural complications	Product prescribing issue*	0.10%	31	6.07 (4.27–8.64)	6.07	130.78	6.05 (4.50)	2.60 (0.93)
Investigations	Blood lactic acid increased	0.16%	50	20.46 (15.48–27.05)	20.43	912.58	20.19 (15.98)	4.34 (2.67)
Investigations	Platelet count decreased	1.80%	549	10.59 (9.73–11.53)	10.42	4652.28	10.36 (9.65)	3.37 (1.71)

(Continued on following page)

TABLE 3 (*Continued*) Signal strength of ADE reports for linezolid at the preferred term (PT) level in the FAERS database.

SOC name	PT name	Frequency	Case number	ROR (95% CI)	PRR	χ2	EBGM (EBGM05)	IC (IC025)
Investigations	Drug level increased*	0.13%	40	4.81 (3.53–6.56)	4.81	120.26	4.80 (3.70)	2.26 (0.60)
Investigations	Haematocrit decreased*	0.15%	46	4.25 (3.18–5.67)	4.24	113.77	4.23 (3.32)	2.08 (0.42)
Investigations	International normalised ratio increased*	0.23%	69	4.17 (3.29–5.29)	4.17	165.67	4.16 (3.41)	2.06 (0.39)
Investigations	Electrocardiogram QT prolonged*	0.24%	73	4.07 (3.24–5.13)	4.07	168.51	4.06 (3.35)	2.02 (0.36)
Investigations	Transaminases increased	0.13%	41	3.64 (2.68–4.94)	3.64	78.19	3.63 (2.81)	1.86 (0.19)
Investigations	Haemoglobin decreased	0.57%	174	3.30 (2.84–3.83)	3.29	276.72	3.28 (2.90)	1.71 (0.05)
Metabolism and nutrition disorders	Mitochondrial toxicity*	0.18%	55	136.11 (103.35–179.25)	135.86	6795.77	125.47 (99.66)	6.97 (5.30)
Metabolism and nutrition disorders	Hyperlactacidaemia	0.20%	61	55.49 (42.98–71.64)	55.38	3150.37	53.59(43.28)	5.74 (4.08)
Metabolism and nutrition disorders	Lactic acidosis	1.95%	592	42.93 (39.54–46.62)	42.12	23174.56	41.08 (38.34)	5.36 (3.69)
Metabolism and nutrition disorders	Metabolic acidosis*	0.34%	103	6.83 (5.62–8.29)	6.81	508.53	6.78 (5.77)	2.76 (1.10)
Metabolism and nutrition disorders	Hyponatraemia	0.63%	193	6.82 (5.92–7.86)	6.78	948.73	6.76 (6.00)	2.76 (1.09)
Metabolism and nutrition disorders	Hypoglycaemia	0.44%	135	5.44 (4.59–6.44)	5.42	485.44	5.41 (4.69)	2.43 (0.77)
Musculoskeletal and connective tissue disorders	Myopathy*	0.07%	20	4.55 (2.93–7.05)	4.54	55.15	4.53 (3.14)	2.18 (0.51)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis*	0.30%	90	4.33 (3.52–5.33)	4.32	229.37	4.31 (3.63)	2.11 (0.44)
Musculoskeletal and connective tissue disorders	Muscle rigidity*	0.07%	20	3.33 (2.15–5.17)	3.33	32.53	3.32 (2.30)	1.73 (0.07)
Nervous system disorders	Serotonin syndrome	1.32%	403	47.52 (43.01–52.50)	46.9	17601.38	45.61 (41.96)	5.51 (3.85)
Nervous system disorders	Optic neuritis	0.30%	91	19.23 (15.63–23.65)	19.17	1549.56	18.96 (15.95)	4.25 (2.58)
Nervous system disorders	Polyneuropathy*	0.29%	89	16.43 (13.33–20.25)	16.39	1273.16	16.23 (13.63)	4.02 (2.35)
Nervous system disorders	Peripheral sensory neuropathy	0.08%	24	8.76(5.86–13.08)	8.75	163.88	8.71 (6.22)	3.12 (1.46)
Nervous system disorders	Neuropathy peripheral	1.21%	367	8.23 (7.42–9.12)	8.14	2291.29	8.11 (7.44)	3.02 (1.35)
Nervous system disorders	Posterior reversible encephalopathy syndrome*	0.12%	37	7.65 (5.54–10.56)	7.64	212.51	7.61 (5.81)	2.93 (1.26)
Nervous system disorders	Myoclonus*	0.14%	42	7.04 (5.20–9.53)	7.03	216.27	7.00 (5.43)	2.81 (1.14)
Nervous system disorders	Status epilepticus*	0.09%	27	4.83 (3.31–7.04)	4.82	81.59	4.81 (3.51)	2.27 (0.60)
Nervous system disorders	Encephalopathy*	0.17%	53	4.56 (3.48–5.97)	4.55	146.65	4.54 (3.63)	2.18 (0.52)
Psychiatric disorders	Delirium*	0.21%	65	3.97 (3.11–5.07)	3.96	143.79	3.96 (3.23)	1.98 (0.32)

(Continued on following page)

TABLE 3 (*Continued*) Signal strength of ADE reports for linezolid at the preferred term (PT) level in the FAERS database.

SOC name	PT name	Frequency	Case number	ROR (95% CI)	PRR	χ2	EBGM (EBGM05)	IC (IC025)
Renal and urinary disorders	Tubulointerstitial nephritis*	0.16%	48	4.87 (3.67–6.47)	4.87	147.08	4.86 (3.83)	2.28 (0.61)
Renal and urinary disorders	Renal impairment*	0.54%	165	4.08 (3.50–4.75)	4.06	380.3	4.05 (3.57)	2.02 (0.35)
Respiratory, thoracic and mediastinal disorders	Tachypnoea*	0.09%	28	4.33 (2.99–6.27)	4.33	71.43	4.32 (3.17)	2.11 (0.44)
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	0.10%	29	3.94 (2.74–5.67)	3.94	63.43	3.93 (2.90)	1.97 (0.31)
Skin and subcutaneous tissue disorders	Hypersensitivity vasculitis	0.09%	28	18.18 (12.52–26.38)	18.16	449.02	17.97 (13.16)	4.17 (2.50)
Skin and subcutaneous tissue disorders	Rash maculo-papular	0.28%	85	8.06 (6.51–9.98)	8.04	521.86	8.01 (6.70)	3.00 (1.34)
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis*	0.10%	29	7.60 (5.28–10.95)	7.59	165.31	7.56 (5.57)	2.92 (1.25)
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms*	0.26%	79	5.83 (4.68–7.28)	5.82	314.54	5.81 (4.82)	2.54 (0.87)
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis	0.13%	40	5.52 (4.05–7.53)	5.51	147.35	5.50 (4.24)	2.46 (0.79)
Skin and subcutaneous tissue disorders	Toxic skin eruption	0.09%	26	5.14 (3.50–7.56)	5.14	86.35	5.12 (3.71)	2.36 (0.69)
Skin and subcutaneous tissue disorders	Purpura	0.08%	23	5.03 (3.34–7.58)	5.03	74.08	5.02 (3.56)	2.33 (0.66)
Skin and subcutaneous tissue disorders	Petechiae	0.09%	26	4.93 (3.35–7.24)	4.92	81.03	4.91 (3.56)	2.30 (0.63)
Skin and subcutaneous tissue disorders	Drug eruption	0.13%	41	4.91 (3.61–6.67)	4.9	127.08	4.89 (3.78)	2.29 (0.62)
Vascular disorders	Shock haemorrhagic*	0.07%	20	5.21 (3.36–8.08)	5.2	67.72	5.19 (3.59)	2.38 (0.71)
Vascular disorders	Shock*	0.15%	45	4.10 (3.06–5.49)	4.09	104.99	4.09 (3.20)	2.03 (0.36)

The table demonstrates the 93 PT entries that satisfy all 4 methods of disproportionality analysis with positive signal values and a number of cases not less than 20. PT entries are categorized by SOC. Asterisks (*) indicate unexpected signals that are not indicated in the drug label. ADE, adverse drug event.

signals exclusive to the group >100 kg comprised asthenia (n = 20, ROR 2.39), sepsis (n = 15, ROR 6.00), product use issue (n = 11, ROR 2.81), and paraesthesia (n = 11, ROR 3.01) (Supplementary Figure S1). Similar sensitivity analyses were conducted to assess the impact of age (Supplementary Figure S2), gender (Supplementary Figure S3), and reported person (Supplementary Figure S4) on the signals within distinct subgroups. This critical assessment provides essential insights into refining clinical management strategies, enabling clinical decision-makers to customize treatments based on the specific characteristics of these subgroups.

3.4 Gender-based difference in risk signals for linezolid

The distribution of linezolid volume is slightly lower in females than in males, and plasma concentrations of the drug are higher in females than in males(Sisson et al., 2002). However, a significant increase in drug exposure in females above known, well-tolerated levels is unexpected. To analyze whether gender influences linezolid adverse effects, we used the ROR method to identify 40 PTs with disproportionate ADE incidence between males and females, categorized by SOC. The results are presented in Figure 5A. The results of all data are presented in Supplementary Table S4. Some ADEs such as thrombocytopenia, bone marrow failure, optic neuropathy, drug interaction, drug resistance, treatment failure, off-label use, decrease in platelet count, state of confusion, acute kidney injury, renal impairment, drug reaction with eosinophilia and systemic symptoms, and rash maculo-papular were more common in males. High-risk ADEs in females included neutropenia, vertigo, vision blurred, nausea, vomiting, diarrhea, abdominal pain, pancreatitis, swollen tongue, asthenia, malaise, fatigue, feeling abnormal, hepatotoxicity, drug hypersensitivity, blood pressure decreased, lactic acidosis, arthralgia, dizziness, paresthesia, headache, cough, pruritus, hyperhidrosis, and hypotension.

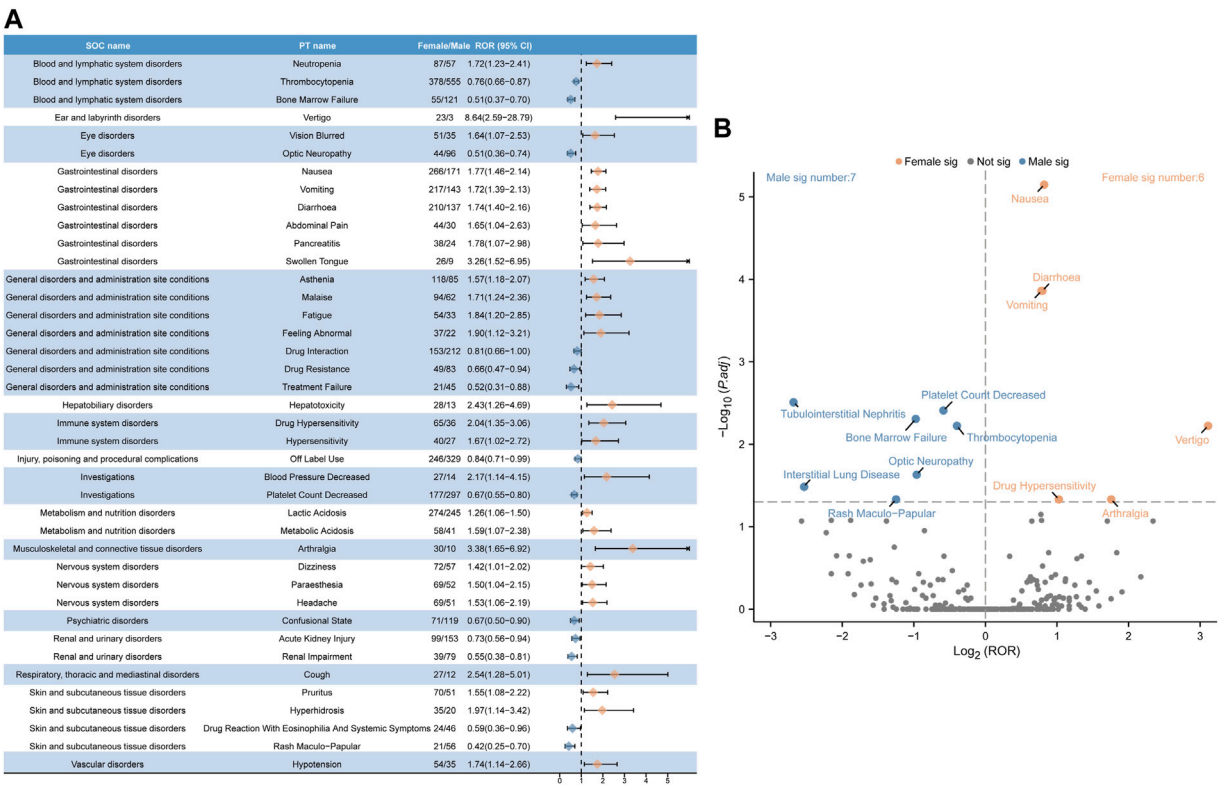


FIGURE 5
Analysis of gender-differentiated risk signals in linezolid. **(A)** Reporting odds ratios (ROR) with 95% CI for all positive gender-related ADEs. **(B)** Gender-differentiated risk signal volcano plot for linezolid. The horizontal coordinate shows the log2 ROR value and the vertical coordinate indicates the adjusted *p*-value after -log10 conversion. Significant signals are highlighted and annotated in prominent colors. The *p*-value is adjusted with false discovery rate (FDR) method.

We plotted a "volcano diagram" to visualize the signals and analyze the results of gender-based differences in ADE signal extraction for linezolid (Figure 5B). Each point in the figure represents a linezolid-associated ADE and we labeled statistically significant ADEs. Seven significant signals were observed in males, including tubulointerstitial nephritis, platelet count decrease, bone marrow failure, thrombocytopenia, optic neuropathy, interstitial lung disease, and rash maculo-papular. Six adverse reactions were observed in females, including nausea, diarrhea, vomiting, vertigo, drug hypersensitivity, and arthralgia.

3.5 TTO analysis of linezolid-related ADEs from overall and subgroup perspectives

After excluding inaccurate, missing, or unknown reports of onset, 4,362 ADEs were collected, and the median TTO was determined as 6 days (interquartile range [IQR] 1–15 days) (Supplementary Table S5).

As shown in Figure 6, most cases occurred within the first month (n = 3,788, 86.84%) of linezolid administration. The number of ADEs decreased over time, with 243 ADEs (5.57%) occurring in the second month and 84 ADEs (1.93%) in the third month. Notably, in 1.05% of cases, adverse drug events could still occur even after 1 year of treatment with linezolid. To examine whether the risk of linezolid-associated ADEs increases or decreases over time, we conducted Weibull distribution tests on both the overall patient population and various subgroups. For overall analysis, the calculated shape parameter (β) was 0.62 and the upper limit of its 95% confidence interval (CI) was 0.64. Both values were below 1, indicating a decline in the prevalence of ADEs over time (Supplementary Table S5). In the subgroup analyses based on age, it is noteworthy that β values were close to 1 for the subgroups <18 years (n = 6, β 2.53, 95% CI 0.51–4.55) and >64 years (n = 70, β 1.06, 95% CI 0.86–1.27). Additionally, their 95% CI encompassed 1, indicating the Weibull curve type as random failure, and implying a continued occurrence of ADEs over time. Additionally, the Weibull distribution test for the remaining subgroups revealed that all curve types were early failure. Comprehensive statistical descriptions for the different subgroups of TTO could be found in Supplementary Table S5.

3.6 TTO analysis of linezolid-related ADEs at the SOC and PT levels

ADEs in clinical trials for linezolid have focused on single or limited number of organ systems. To determine the timing of ADEs in more detail, we analyzed the TTO at the SOC level (Figure 7A). Linezolid-related eye disease, the median longest-onset SOC,

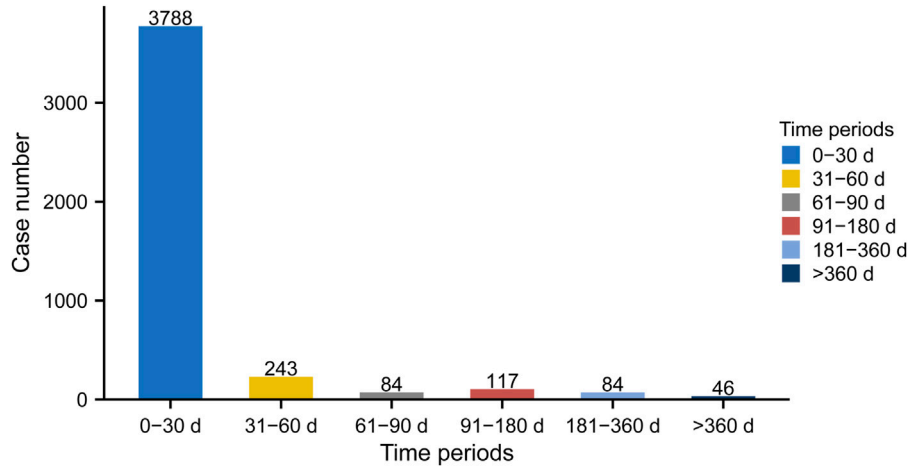


FIGURE 6
Time to onset (TTO) analysis (counted in days) of linezolid-related ADEs at the overall level. The frequency bar chart illustrates the distribution of TTO reports across various time periods.

occurred at a median of 20 days (IQR 2–120 days). In contrast, injury, poisoning, and procedural complications (IQR 0–10 days) and immune system disorders (IQR 0–4 days) had the shortest median disease onset times associated with linezolid, each at 0 days. Other systemic diseases, such as blood and lymphatic system disorders, infections and infestations, ear and labyrinth disorders, neoplasms benign, malignant, and unspecified, surgical and medical procedures, endocrine disorders, and congenital, familial, and genetic disorders, had a median time to onset of 1–2 weeks. The median onset of most adverse events, including the other 19 SOCs, was within 1 week (Supplementary Table S6).

SOCs often contain multiple types of PTs. For clarity on the onset time of individual PTs in the SOC and to identify whether there are differences in the onset time of PTs within the same SOC, we analyzed and compared the detailed onset times of ADEs at the PT level according to the SOC (Figure 7B and Supplementary Table S6). Overall, except for liver disease ($p = 0.37$) and kidney disease ($p = 0.91$), there was a significant difference in TTO between PTs for the remaining six SOCs ($p < 0.05$). The mean (standard deviation [SD]) time for the earliest occurrence of disseminated intravascular coagulation in hematologic and lymphatic disorders was 7.45 days (7.30 days), while the average time for the latest occurrence of bicytopenia was 42.5 days (34.65 days). More detailed and complete results are shown in Figure 7B and Supplementary Table S6. These TTO analyses at the SOC and PT levels provide a more precise guide for detecting adverse events following linezolid administration.

4 Discussion

Our findings show that linezolid-related side effects occur more frequently in males (46.37%) than in females (36.04%). This can be attributed to the main indications of linezolid such as staphylococcal infection, tuberculosis, infection, pneumonia, etc., which are more common in males (Shaweno et al., 2021; Corica et al., 2022; Stensen et al., 2022). Epidemiological characteristics of the population support our results. Unfortunately, most reports (97.15%) do not contain detailed information on the patients' age. Overweight and obese patients have lower linezolid exposure rates and appear to be at higher risk of treatment failure (Bandín-Vilar et al., 2022). Given this background, we conducted a study stratified by population weight (Supplementary Figure S1). We found that unique signals, such as asthenia ($n = 20$, ROR 2.39) and serotonin syndrome ($n = 18$, ROR 46.07), were discovered among the top 15 significant signals in a subgroup of patients weighing >100 kg. Due to the lack of specific dosages of medications used by patients and the lack of body weight data for almost 70% of patients, our results can only be considered indicative, but serious neurological side effects should be of particular concern within this patient subgroup. Nearly, 84.76% of adverse event reports were documented by healthcare professionals. Notably, serious adverse outcomes such as hospitalization, death, and life-threatening conditions accounted for approximately half of linezolid-related outcomes (46.38%). The annual distribution of linezolid-related ADE reports showed an annual increase in linezolid-related ADE reports since 2015 (Figure 3A). These results highlight the widespread clinical use and efficacy of linezolid and emphasize the importance of improving the detection of linezolid-related adverse drug reactions for its association with serious adverse events in clinical settings.

Based on the results of disproportionality analysis, significant signals at the SOC level were indicated for blood and lymphatic system disorders, nervous system disorders, investigations, gastrointestinal disorders, infections and infestations, metabolism and nutrition disorders, renal and urinary disorders, hepatobiliary disorders, eye disorders and ear and labyrinth disorders (Figure 3C). In addition to ear and labyrinth diseases, some SOCs were commonly reported in clinical trials and mentioned in the drug label (Wunderink et al., 2012; Tang et al., 2015; O'Riordan et al., 2019; Wunderink et al., 2021). Several specific adverse reactions mentioned in the drug label such as myelosuppression, peripheral and optic neuropathy, serotonin syndrome, increased blood pressure, lactic acidosis, hypoglycemia, and drug resistance were

10.3389/fphar.2024.1338902

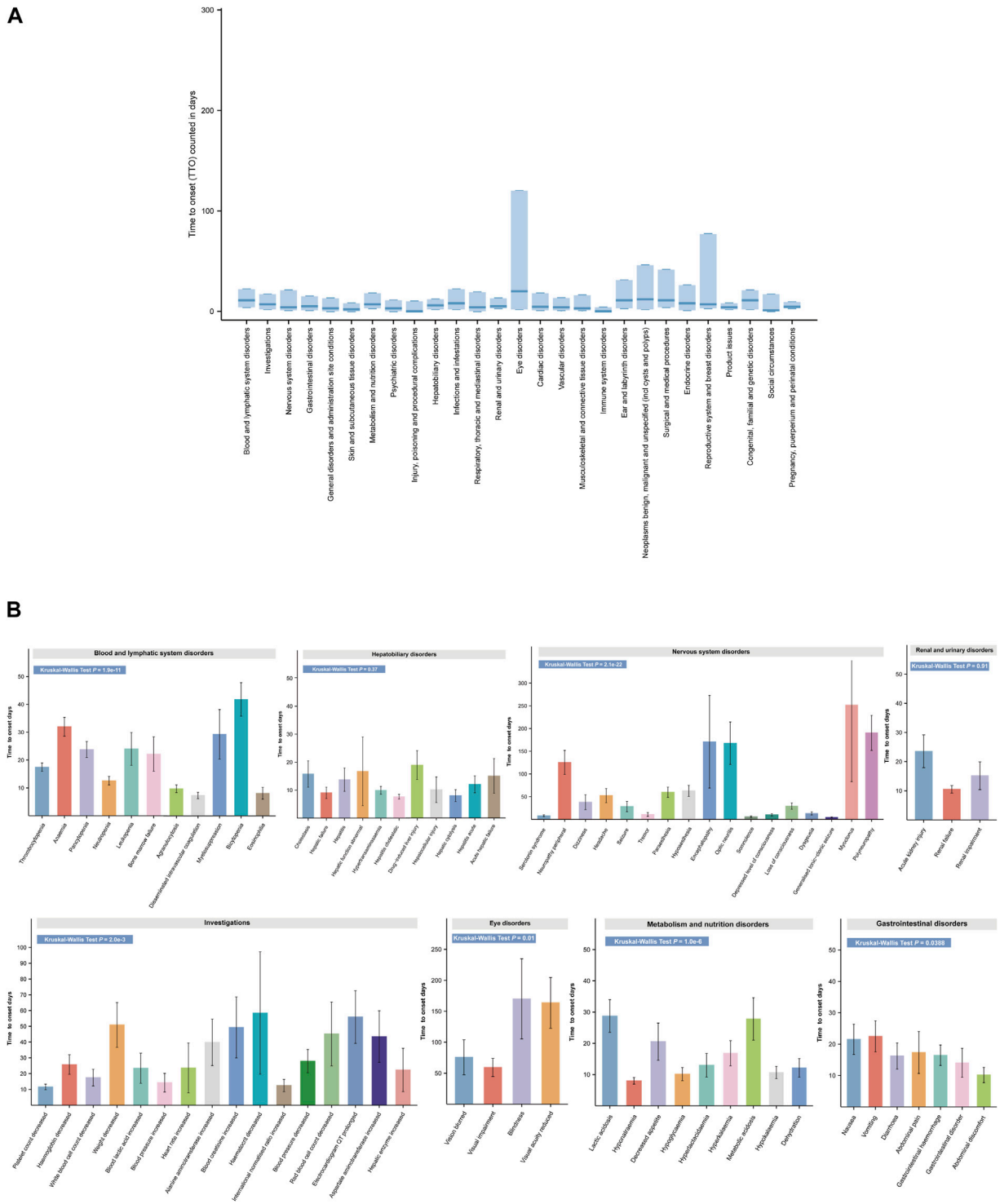


FIGURE 7
Time to onset (TTO) analysis of ADEs at the SOC and PT levels. **(A)** Box plot of the TTO at the SOC level for linezolid. Bold bar within the stick: median TTO; Lower end of the stick: 1/4 quantile of the TTO; Upper end of the stick: 3/4 quantile of the TTO. **(B)** Specific comparison of TTO in PTs at eight different SOC levels. SOC, System Organ Class; PTs, preferred term.

found to be positive signals in the present study, further confirming the reliability of our results.

Of the significant SOC signals, the most common were indicated for blood and lymphatic system disorders, nervous system disorders, investigations, gastrointestinal disorders, metabolism, and nutrition disorders. However, SOCs with a small number of cases also showed significant signals, for example, in diseases of the ear and labyrinth (n = 191).

4.1 ADEs related to the disorders of the blood and lymphatic system

The three most common ADEs in the blood system in terms of report numbers were thrombocytopenia (*n* = 1,139, ROR 21.98 [20.70–23.32]), anemia (*n* = 704, ROR 7.39 [6.86–7.97]), and pancytopenia (*n* = 400, ROR 15.16 [13.73–16.74]). Numerous previous clinical studies have confirmed linezolid's hematological toxicity. In a double-blind, randomized, controlled trial in drug-resistant TB, different doses of linezolid resulted in myelosuppression in approximately 11.6% of patients (Conradie et al., 2022). In the Nix-TB phase 3 trial (NCT02333799), adverse events above grade 1, including thrombocytopenia (6%) and anemia (37%), severely limited the use of linezolid (Conradie et al., 2020). In a randomized, double-blind, phase 3 trial of two-week linezolid for the treatment of hospital- or ventilator-acquired pneumonia, the incidence of treatment-emergent adverse events, thrombocytopenia, and anemia related to linezolid therapy was 0.8% and 1.1%, respectively (Wunderink et al., 2021). A meta-analysis that summarized the results of 11 randomized controlled trials of skin and soft tissue infections showed that patients using linezolid were more likely to develop thrombocytopenia than those on vancomycin (Li and Xu, 2018). However, the mechanism of linezolid-induced hematological toxicity largely remains unknown. One possible molecular mechanism is that linezolid leads to the increased phosphorylation of myosin light chain 2, which further regulates platelet release in MEG-01 cells (Tajima et al., 2016). Furthermore, Wang et al. observed that linezolid-induced thrombocytopenia was associated with reduced antioxidant capacity as well as lipid peroxidation and free radical formation (Wang et al., 2016). Severe thrombocytopenia is immunologically related, and a study found the presence of linezolid-associated platelet antibodies in thrombocytopenic patients (Pascoalinho et al., 2011). Importantly, risk factors for linezolid-associated thrombocytopenia include baseline platelet count, minimum concentration, and renal insufficiency, which must be considered when administering linezolid (Matsumoto et al., 2010; Natsumoto et al., 2014; Tsuji et al., 2017; Crass et al., 2019; Cazavet et al., 2020). Through a real-world analysis of linezolid, we also identified several significant hematologic adverse signals, including bone marrow failure (*n* = 213, ROR 18.86 [16.47–21.60]), myelosuppression (*n* = 165, ROR 20.72 [17.77–24.17), leukopenia (*n* = 145, ROR 5.95 [5.05–7.01]), eosinophilia (*n* = 64, ROR 7.66 [5.99–9.80]), and bicytopenia (*n* = 45, ROR 57.58 [42.77–77.54]), consistent with previous clinical studies and drug label. We also identified new and unexpected signals, such as disseminated intravascular coagulation (DIC) (*n* = 77, ROR 10.34 [8.26–12.94]), aplasia pure red cell (*n* = 41, ROR 24.38 [17.91–33.20]) and aplastic anaemia (*n* = 33, ROR 12.79 [9.08–18.02]). DIC is associated with disease progression and portends poor outcomes. This could be related to the other side effects of linezolid found in our data, such as thrombocytopenia, a hypocoagulable state, and low fibrinogen levels. Cases of aplasia pure red cell caused by linezolid have been reported (Monson et al., 2002; Waki et al., 2012; Yang et al., 2022), which is consistent with our results. In summary, in addition to hemoglobin and platelet count, coagulation and reticulocyte count must also be considered. When using anticoagulants and antiplatelet agents in patients, linezolid should be used with caution.

4.2 ADEs related to nervous system disorders

Peripheral neuropathy and optic neuropathy are common neurological adverse reactions underlying the main reason for the discontinuation of linezolid (Rubinstein et al., 2001; Koh et al., 2012; Tang et al., 2015; O'Riordan et al., 2019). However, our real-world data showed that the most frequent case report of neurological adverse effects was serotonin syndrome (*n* = 403, ROR 47.52 [43.0–52.50]). This may be due to the different identities of the reporters, leading to different descriptions of peripheral neuropathy and optic neuropathy in general. However, relative to the total number of cases, peripheral neuropathy and optic neuropathy remain the most common, which is consistent with clinical observational studies. Serotonin syndrome is a rare but potentially fatal adverse drug reaction (Boyer and Shannon, 2005; Woytowish and Maynor, 2013). The mechanism by which linezolid causes serotonin syndrome may be that it does not selectively inhibit the enzyme monoamine oxidase, resulting in serotonin overload in the central nervous system (Francescangeli et al., 2019). Therefore, linezolid may interact with other medications and increase the risk of serotonin syndrome (Gatti et al., 2021b). According to recent studies, including a cohort study (Bai et al., 2022), a cross-sectional study (Traver et al., 2022), and a retrospective cohort study (Kufel et al., 2023), serotonin syndrome is a rare linezolid-induced ADE, whereas it was reported in larger numbers in our study. This result suggests that vigilance should be exercised toward linezolid-induced serotonin syndrome and further studies are required to assess the risk. Several clinical trials have shown that the long-term use of linezolid predisposes patients to peripheral neuropathy. In ZeNix's study, grade 3 or lower peripheral neuropathy was reported in 45 of 181 participants (25%) across all groups (Conradie et al., 2022). Investigator-reported peripheral neuropathy (≥ Grade 1) was reported in 80 (77%) participants (Imperial et al., 2022). Eighty-eight (81%) participants developed peripheral neuropathy at the time of treatment, typically with mild to moderate symptoms (Conradie et al., 2022). Side effects of optic neuritis were also reported in the clinical studies mentioned above. We identified some PTs with positive signal values but relatively small numbers, such as myoclonus (*n* = 42, ROR 7.04 [5.20–9.53]), posterior reversible encephalopathy syndrome (n = 37, ROR 7.65 [5.54–10.56]), status epilepticus (*n* = 27, ROR 4.83 [3.31–7.04]); these were not highlighted in the drug label. Although peripheral neuropathies are mentioned in the drug label, our data provide a detailed list of case numbers and signal values of linezolid-associated neurological adverse effects. These provide clues for the doctors to promptly recognize this side effect.

Adverse drug reactions associated with ocular lesions complicate long-term treatment with linezolid. As shown in Table 3, optic neuropathy shows both a high number of reported cases (*n* = 169) as well as a higher signal value (ROR 190.52, PRR 189.47, EBGM05 148.58, IC025 5.74). Optic neuropathy associated with linezolid has been reported in many clinical trials. A French clinical trial for multidrug-resistant tuberculosis reported a high incidence of confirmed optic neuropathy (25% of the cohort) (Jaspard et al., 2020). Two meta-analyses on the safety of linezolid use in drug-resistant TB reached similar conclusions (Sotgiu et al., 2012; Lifan et al., 2019). The above findings support our results. However, a

synthesis of the results from the two prospective studies found no optic neuropathy in children with multidrug-resistant TB taking linezolid (Garcia-Prats et al., 2019). The inconsistency in these findings may be related to the different baseline characteristics of the included populations and the short follow-up period. Toxic optic neuropathy (n = 45, ROR 288.83 [210.32–396.64]) is also a specific manifestation of optic neuropathy. Some case reports suggest that this ADE may develop rapidly (Lee et al., 2003; Joshi et al., 2009). Taken together, patients administered linezolid need a regular, periodic eye exam to detect possible optic neuropathy in the early stage.

4.3 ADEs related to gastrointestinal disorders

Among the ADEs of the gastrointestinal system, some PTs that were not indicated in the drug label were found. Trichoglossia (n = 29, ROR 129.46 [88.68–188.99]), or black hairy tongue (BHT), is characterized by pigmentation, whereby the dorsal tongue appears black, green, or yellow; it is a self-limiting benign disease. Linezolid-associated trichoglossia has primarily been documented in case reports (Jover-Diaz et al., 2010; Lee et al., 2021; Tomita et al., 2023). A literature report of three patients who developed black hairy tongue after treatment with linezolid all demonstrated severe dysbiosis in their oral bacterial communities, with Proteobacteria being the most common phylum, suggesting that linezolid may cause disruption of the oral flora (Shangguan et al., 2022). Acute pancreatitis (n = 35, ROR 3.23 [2.32–4.51]) is an unexpected adverse effect. In several cases it has been reported that linezolid can cause acute pancreatitis (Fortún et al., 2005; Rose et al., 2012; Kim et al., 2023). However, the exact mechanism of occurrence is unknown. This may be due to mitochondrial dysfunction resulting in damage to the pancreatic acinar cells, but this requires further validation. Our data also reported adverse reactions consistent with those specified on the drug label, such as tongue discoloration (n = 70, ROR 29.06 [22.94–36.82]) and tooth discoloration (n = 42, ROR 27.30 [20.12–37.04]). A high incidence of vomiting and diarrhea has been reported in several previous studies (Li and Xu, 2018; Shi et al., 2023), but no positive signals were found after our disproportionality analysis. This may be because these adverse reactions are common with the adverse reaction reports for other drugs in the FAERS database, which in turn influences the signal value. Disproportionality requires a higher (or lower) frequency of ADE reporting for certain drugs. The absence of a signal does not mean that there are no relative adverse events but simply indicates that these side effects are not disproportionately common.

4.4 ADEs at other SOC levels

The results of our disproportionality analysis suggested that ADEs associated with linezolid medications may also affect other organs or tissues. Renal diseases associated with linezolid dosing observed in our study included renal impairment (n = 165, ROR 4.08 [3.50–4.75]) and tubulointerstitial nephritis (n = 48, ROR 4.87 [3.67–6.47]), with a greater number of case reports and positive signals. According to the drug label, no dosage adjustments are recommended for patients at any stage of renal impairment, including hemodialysis. The trough concentration of linezolid increases due to renal dysfunction, resulting in an increased incidence of adverse reactions (Bandín-Vilar et al., 2022; Wu et al., 2022). A report described a case of a patient presenting with drug rash with eosinophilia and systemic symptoms indicative of linezolid-associated acute interstitial nephritis (Savard et al., 2009). Although no dose adjustments are recommended in the drug label for patients with renal impairment, we recommend that physicians be aware of these possible side effects and continuously monitor renal function when linezolid is administered.

Moreover, we identified unexpected significant safety signals for rhabdomyolysis (n = 90, ROR 4.33 [3.52–5.33]), electrocardiogram QT prolonged (n = 73, ROR 4.07 [3.24–5.13]) and cholestasis (n = 67, ROR 7.34 [5.77–9.33]). Rhabdomyolysis is a potentially life-threatening disease caused by damage to muscle cells and the subsequent release of cellular components into the bloodstream (Stahl et al., 2020). Four cases of rhabdomyolysis associated with linezolid have been reported (Allison et al., 2009; Carroll et al., 2012; Lechner et al., 2017). Moreover, a FAERS-based study identified an association between linezolid and prolongation of the QT interval along with a higher incidence in TB patients (Shao et al., 2023). The causal relationship between linezolid and rhabdomyolysis and QT interval prolongation is unclear, necessitating further clinical studies to comprehend the pathogenesis of these adverse events. In conclusion, our findings present a comprehensive list of linezolid side effects across various SOCs, which serves as a valuable reference for physician decision-making. Physician awareness of these novel and unexpected signals is crucial. If deemed necessary, the FDA can update the drug label and release appropriate warnings.

4.5 Gender-based differences

As described previously, in the description of the baseline profile, we found proportional differences in the gender distribution of ADEs. In fact, the analysis of gender differences must be considered when assessing drug safety, which facilitates more precise management of ADEs. The study found that males are more prone to develop tubulointerstitial nephritis, platelet count decreased, bone marrow failure, thrombocytopenia, optic neuropathy, interstitial lung disease, and rash maculo-papular, while females are more prone to suffer from nausea, diarrhoea, vomiting, vertigo, drug hypersensitivity, arthralgia. Of note, thrombocytopenia and platelet count decrease are common in both males and females, but males are at higher risk of develop hematologic ADEs, while females exhibited a greater association with gastrointestinal disorders in comparison to males. Gastrointestinal-related symptoms (nausea, vomiting, and diarrhea) were the most common reasons for discontinuation of the drug (Moise et al., 2002; Noel et al., 2012). Nausea (Shorr et al., 2015), gastrointestinal intolerance (Veerman et al., 2023), diarrhea, and vomiting (Shi et al., 2023) were the most common side effects reported in previous studies. A single-center retrospective observational study (Tsutsumi et al., 2022) found that female gender is an independent risk factor for linezolid-induced vomiting, which may be associated with multiple signaling pathways including D2, 5-HT3, and neurokinin-1 receptors

(Navari and Aapro, 2016). However, in addition to gender-related biological factors, gendered social factors are primarily responsible for this gender difference. Males tend to downplay illness (i.e., wait for symptoms to subside without intervening) compared to females, who engage in more active health-promoting behaviors and have frequent contact with healthcare professionals, which may contribute to male's likelihood of more serious illnesses adverse events is higher (Lee et al., 2023). Our results provide these gender-specific side effects. Although these findings require subsequent validation, they offer improved guidance on medication monitoring for both males and females. In addition, we should emphasize gendered social factors in order to better improve the safe use of linezolid.

4.6 TTO analysis

The temporal relationship between administration and time of onset is crucial for assessing drug safety as it identifies specific risk windows and leads to prevention or early diagnosis of adverse reactions (Leroy et al., 2014). Our findings indicated that adverse reactions associated with linezolid mostly occurred in the first 2 months (92.41%), with the highest incidence in the first month (n = 3,788, 86.84%), followed by the second month (n = 243, 5.57%). The main indications for linezolid are infections, including staphylococcal infection, infection, pneumonia and enterococcal infection, in which linezolid is not used for a long period of time, which may result in the vast majority of adverse drug reactions being concentrated in the first month, and in general we tend to associate side effects with the start of treatment with the drug, which can lead to biased results. The Weibull distribution test revealed a decrease in the probability of ADEs over time within the general population and across most subgroups. However, ADEs persisted over time in subgroups comprising individuals younger than 18 years and those older than 64 years. This indicates that continued vigilance for ADEs related to linezolid is especially warranted in both subgroups. Most importantly, we provide a comprehensive study of the specific time of onset following linezolid administration in each organ system. Previous researchers have reported the median time to occurrence of some specific ADEs for linezolid dosing (Matsumoto et al., 2014; Jaspard et al., 2020; Veerman et al., 2023). Although these results may not reflect the actual TTO given the population in the clinical trial, our results are close to the findings and provide a more detailed and concrete list. Abnormal liver function tests are among the side effects listed in the drug label of linezolid. Our data analysis revealed that PT associated with hepatobiliary disease occurred on average within 1–3 weeks. Linezolid can cause many types of neurological side effects, some of which occur on average after more than 4 months, e.g. neuropathy peripheral, encephalopathy, optic neuritis, myoclonus, and polyneuropathy. The effects of linezolid on the urinary system include acute kidney injury, renal failure, and renal dysfunction, which occur on average within 1 month. Eye disorders are serious side effects of linezolid use, and can cause blurred vision, visual impairment, blindness, and even vision loss, with the first two typically occurring earlier than the latter two, at about 2 months, and the latter two on average more than 5 months later. Severe gastrointestinal symptoms are the main reasons for discontinuation of linezolid, and these reactions often occur within 3 weeks or less. The median TTO was less than 2 months for all systems, except neurological and ocular adverse events. Therefore, the requirements for early detection and follow-up of adverse reactions occurring in different systems should be different. Our research makes a valuable contribution in this area by helping to better and promptly reduce patient discomfort and improve the patient's experience with medication outcomes.

Other studies have reported associations between linezolid and specific side effects using centralized data (Lee and Caffrey, 2018; Dai et al., 2020; Gatti et al., 2021a; Battini et al., 2022; Ni et al., 2022; Shao et al., 2023). This study, for the first time, comprehensively documented and evaluated the safety of post-marketing administration of linezolid based on the largest sample of real-world data to date. However, some limitations remain. Firstly, the FAERS is inherently limited by underreporting, incomplete reporting, and selective reporting (Alatawi and Hansen, 2017; Raschi et al., 2019). Less serious or common adverse events may be underreported, while more serious or rare events may be overreported (Wang et al., 2023). Among the ADE reports we collected, 97% were missing detailed age data, and 85% originated from health professionals. Therefore, potential biases caused by the data should be carefully considered when interpreting the results (Shi et al., 2023). Secondly, the absence of detailed clinical information on patients such as comorbidities, severity of underlying disease, and concomitant medications, further hinders the control for confounding variables (Zhang et al., 2023). Thirdly, disproportionality analyses are limited to assessing signal strength and establishing statistical associations; they are unable to quantify risk or determine causality (Ji et al., 2022b). Fourth, because the total number of people receiving linezolid administration is unknown, we were unable to quantify the incidence of each ADE (Chedid et al., 2018). Despite these limitations, inherent in the use of the FAERS database for pharmacovigilance studies, a comprehensive characterization of ADEs related to linezolid in this study may provide insightful evidence for safe use and further clinical studies.

5 Conclusion

In conclusion, our comprehensive and systematic pharmacovigilance analysis of the FAERS database identified several common and rare side effects of linezolid use and their associated timing. Careful monitoring of all populations and determination of the risk of these adverse reactions is recommended. Despite offering valuable evidence for the safety of linezolid, our study necessitates meticulous consideration of the inherent limitations of the FAERS database, as well as potential confounders and biases. This calls for a more cautious interpretation of our analysis results. Additionally, future prospective clinical trials and epidemiological studies will provide a more precise evaluation of the safety risks associated with linezolid.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

FZ: Conceptualization, Formal Analysis, Visualization, Writing–original draft, Writing–review and editing. ZwC: Conceptualization, Formal Analysis, Visualization, Writing–original draft, Writing–review and editing. SL: Conceptualization, Formal Analysis, Visualization, Writing–original draft, Writing–review and editing. YO: Writing–original draft, Writing–review and editing. CZ: Writing–original draft, Writing–review and editing. CS: Writing–original draft, Writing–review and editing. JC: Visualization, Writing–original draft, Writing–review and editing. RZ: Writing–original draft, Writing–review and editing. ZW: Visualization, Writing–original draft. LW: Writing–original draft, Writing–review and editing. ZyC: Visualization, Writing–original draft. HC: Visualization, Writing–original draft. YL: Funding acquisition, Supervision, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by the fund of "Guizhou Provincial Scientific and Technological Programme (Qiankehe Foundation-ZK[2023] Key 060)".

Acknowledgments

We would like to thank everyone who participated in this study. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1338902/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The top 15 adverse event signals at the preferred term level, stratified by weight groups. The arrows signify that the lower limit of the 95% confidence interval of the ROR exceeds 25.

SUPPLEMENTARY FIGURE S2
The top 15 adverse event signals at the preferred term level, stratified by age groups.

SUPPLEMENTARY FIGURE S3
The top 15 adverse event signals at the preferred term level, stratified by gender groups.

SUPPLEMENTARY FIGURE S4
The top 15 adverse event signals at the preferred term level, stratified by reported person groups.

SUPPLEMENTARY TABLE S1
All names used in the search of adverse drug event reports related to linezolid in the FAERS database, including generic names, brand names, and nonstandard names.

SUPPLEMENTARY TABLE S2
Signal strength of ADE reports for linezolid at the System Organ Class (SOC) level in the FAERS database. Positive results that surpass the disproportionality analysis thresholds are highlighted in red. ADE, adverse drug event.

SUPPLEMENTARY TABLE S3
The 263 PT entries that simultaneously satisfied the 4 methods of disproportionality analysis with positive signal values. PT entries are displayed in descending order of case number. Asterisks (*) indicate unexpected signals that are not indicated in the drug label.

SUPPLEMENTARY TABLE S4
Gender-based subgroup analysis of linezolid-related ADEs. a, number of reports of target ADE with linezolid in female; b, number of reports of other ADEs with linezolid in female; c, number of reports of target ADE with linezolid in male; d, number of reports of other ADEs with linezolid in male. Therefore, the ROR here is not a strictly defined ROR in pharmacoepidemiological perspective; we just use this method for signal value calculation of gender-based, linezolid-related signal strength differences.

SUPPLEMENTARY TABLE S5
Weibull distribution test for overall and subgroups of TTO analysis. IQR, interquartile range; Min, minimum; Max: maximum.

SUPPLEMENTARY TABLE S6
A more detailed TTO analysis at the SOC and PT levels. Min, minimum; Max: maximum; IQR, interquartile range; q1, 1/4 quantile; q3, 3/4 quantile; SD, standard deviation; SE, standard error.

References

Alatawi, Y. M., and Hansen, R. A. (2017). Empirical estimation of under-reporting in the U.S. Food and drug administration adverse event reporting system (FAERS). *Expert Opin. Drug Saf.* 16 (7), 761–767. doi:10.1080/14740338.2017.1323867

Allison, G. W., Perla, R. J., Belliveau, P. P., and Angelis, S. M. (2009). Elevated creatine phosphokinase levels associated with linezolid therapy. *Am. J. Health Syst. Pharm.* 66 (12), 1097–1100. doi:10.2146/ajhp080228

Bai, A. D., McKenna, S., Wise, H., Loeb, M., and Gill, S. S. (2022). Association of linezolid with risk of serotonin syndrome in patients receiving antidepressants. *JAMA Netw. Open* 5 (12), e2247426. doi:10.1001/jamanetworkopen.2022.47426

Bandín-Vilar, E., García-Quintanilla, L., Castro-Balado, A., Zarra-Ferro, I., González-Barcia, M., Campos-Toimil, M., et al. (2022). A review of population pharmacokinetic analyses of linezolid. *Clin. Pharmacokinet.* 61 (6), 789–817. doi:10.1007/s40262-022-01125-2

Battini, V., Mari, A., Gringeri, M., Casini, F., Bergamaschi, F., Mosini, G., et al. (2022). Antibiotic-induced neutropenia in pediatric patients: new insights from pharmacoepidemiological analyses and a systematic review. *Front. Pharmacol.* 13, 877932. doi:10.3389/fphar.2022.877932

Boyer, E. W., and Shannon, M. (2005). The serotonin syndrome. *N. Engl. J. Med.* 352 (11), 1112–1120. doi:10.1056/NEJMra041867

Brown, A. N., Drusano, G. L., Adams, J. R., Rodriquez, J. L., Jambunathan, K., Baluya, D. L., et al. (2015). Preclinical evaluations to identify optimal linezolid regimens for tuberculosis therapy. *mBio* 6 (6), e01741–e01715. doi:10.1128/mBio.01741-15

Brown, E. G. (2003). Methods and pitfalls in searching drug safety databases utilising the Medical Dictionary for Regulatory Activities (MedDRA). *Drug Saf.* 26 (3), 145–158. doi:10.2165/00002018-200326030-00002

Brown, E. G. (2004). Using MedDRA: implications for risk management. *Drug Saf.* 27 (8), 591–602. doi:10.2165/00002018-200427080-00010

Carroll, M. W., Choi, H., Min, S., Hwang, S., Park, H., Song, T., et al. (2012). Rhabdomyolysis in a patient treated with linezolid for extensively drug-resistant tuberculosis. *Clin. Infect. Dis.* 54 (11), 1624–1627. doi:10.1093/cid/cis293

Cazavet, J., Bounes, F. V., Ruiz, S., Seguin, T., Crognier, L., Rouget, A., et al. (2020). Risk factor analysis for linezolid-associated thrombocytopenia in critically ill patients. *Eur. J. Clin. Microbiol. Infect. Dis.* 39 (3), 527–538. doi:10.1007/s10096-019-03754-1

Chedid, V., Vijayvargiya, P., and Camilleri, M. (2018). Advantages and limitations of the federal adverse events reporting system in assessing adverse event reporting for eluxadoline. *Clin. Gastroenterology Hepatology Official Clin. Pract. J. Am. Gastroenterological Assoc.* 16 (3), 336–338. doi:10.1016/j.cgh.2017.11.025

Chen, Y., Guo, J. J., Steinbuch, M., Lin, X., Buncher, C. R., and Patel, N. C. (2008). Comparison of sensitivity and timing of early signal detection of four frequently used signal detection methods. *Pharm. Med.* 22 (6), 359–365. doi:10.1007/BF03256733

Cirmi, S., El Abd, A., Letinier, L., Navarra, M., and Salvo, F. (2020). Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). *Cancers (Basel)* 12 (4), 826. doi:10.3390/cancers12040826

Collins, C. D., and Schwemm, A. K. (2015). Linezolid versus vancomycin in the empiric treatment of nosocomial pneumonia: a cost-utility analysis incorporating results from the ZEPHyR trial. *Value Health* 18 (5), 614–621. doi:10.1016/j.jval.2015.04.007

Conradie, F., Bagdasaryan, T. R., Borisov, S., Howell, P., Mikiashvili, L., Ngubane, N., et al. (2022). Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N. Engl. J. Med.* 387 (9), 810–823. doi:10.1056/NEJMoa2119430

Conradie, F., Diacon, A. H., Ngubane, N., Howell, P., Everitt, D., Crook, A. M., et al. (2020). Treatment of highly drug-resistant pulmonary tuberculosis. *N. Engl. J. Med.* 382 (10), 893–902. doi:10.1056/NEJMoa1901814

Corica, B., Tartaglia, F., D'Amico, T., Romiti, G. F., and Cangemi, R. (2022). Sex and gender differences in community-acquired pneumonia. *Intern Emerg. Med.* 17 (6), 1575–1588. doi:10.1007/s11739-022-02999-7

Cornelius, V. R., Sauzet, O., and Evans, S. J. W. (2012). A signal detection method to detect adverse drug reactions using a parametric time-to-event model in simulated cohort data. *Drug Saf.* 35 (7), 599–610. doi:10.2165/11599740-000000000-00000

Cox, H., and Ford, N. (2012). Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int. J. Tuberc. Lung Dis.* 16 (4), 447–454. doi:10.5588/ijtld.11.0451

Crass, R. L., Cojutti, P. G., Pai, M. P., and Pea, F. (2019). Reappraisal of linezolid dosing in renal impairment to improve safety. *Antimicrob. Agents Chemother.* 63 (8), e00605-19. doi:10.1128/aac.00605-19

Cui, Z., Cheng, F., Wang, L., Zou, F., Pan, R., Tian, Y., et al. (2023). A pharmacovigilance study of etoposide in the FDA adverse event reporting system (FAERS) database, what does the real world say? *Front. Pharmacol.* 14, 1259908. doi:10.3389/fphar.2023.1259908

Dai, Y., Wang, Y., Zeng, Y., Zhang, C., Zhou, Z., and Shi, D. (2020). Linezolid and the risk of lactic acidosis: data mining and analysis of the FDA adverse event reporting system. *J. Clin. Pharm. Ther.* 45 (6), 1422–1426. doi:10.1111/jcpt.13245

de Vries, S. T., Denig, P., Ekhart, C., Mol, P. G. M., and van Puijenbroek, E. P. (2020). Sex differences in adverse drug reactions of metformin: a longitudinal survey study. *Drug Saf.* 43 (5), 489–495. doi:10.1007/s40264-020-00913-8

Esmail, A., Oelofse, S., Lombard, C., Perumal, R., Mbuthini, L., Goolam Mahomed, A., et al. (2022). An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT study). *Am. J. Respir. Crit. Care Med.* 205 (10), 1214–1227. doi:10.1164/rccm.202107-1779OC

Feng, Z., Li, X., Tong, W. K., He, Q., Zhu, X., Xiang, X., et al. (2022). Real-world safety of PCSK9 inhibitors: a pharmacovigilance study based on spontaneous reports in FAERS. *Front. Pharmacol.* 13, 894685. doi:10.3389/fphar.2022.894685

Fortún, J., Martín-Dávila, P., Navas, E., Pérez-Elías, M. J., Cobo, J., Tato, M., et al. (2005). Linezolid for the treatment of multidrug-resistant tuberculosis. *J. Antimicrob. Chemother.* 56 (1), 180–185. doi:10.1093/jac/dki148

Francescangeli, J., Karamchandani, K., Powell, M., and Bonavia, A. (2019). The serotonin syndrome: from molecular mechanisms to clinical practice. *Int. J. Mol. Sci.* 20 (9), 2288. doi:10.3390/ijms20092288

Garcia-Prats, A. J., Schaaf, H. S., Draper, H. R., Garcia-Cremades, M., Winckler, J., Wiesner, L., et al. (2019). Pharmacokinetics, optimal dosing, and safety of linezolid in children with multidrug-resistant tuberculosis: combined data from two prospective observational studies. *PLoS Med.* 16 (4), e1002789. doi:10.1371/journal.pmed.1002789

Gatti, M., Fusaroli, M., Raschi, E., Moretti, U., Poluzzi, E., and De Ponti, F. (2021a). Serious adverse events with tedizolid and linezolid: pharmacovigilance insights through the FDA adverse event reporting system. *Expert Opin. Drug Saf.* 20 (11), 1421–1431. doi:10.1080/14740338.2021.1956461

Gatti, M., Raschi, E., and De Ponti, F. (2021b). Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. *Eur. J. Clin. Pharmacol.* 77 (2), 233–239. doi:10.1007/s00228-020-02990-1

Hashemian, S. M. R., Farhadi, T., and Ganjparvar, M. (2018). Linezolid: a review of its properties, function, and use in critical care. *Drug Des. Devel Ther.* 12, 1759–1767. doi:10.2147/dddt.S164515

Hughes, J., Isaakidis, P., Andries, A., Mansoor, H., Cox, V., Meintjes, G., et al. (2015). Linezolid in drug-resistant tuberculosis: haste makes waste. *Eur. Respir. J.* 46 (6), 1844–1846. doi:10.1183/13993003.01374-2015

Imperial, M. Z., Nedelman, J. R., Conradie, F., and Savic, R. M. (2022). Proposed linezolid dosing strategies to minimize adverse events for treatment of extensively drug-resistant tuberculosis. *Clin. Infect. Dis.* 74 (10), 1736–1747. doi:10.1093/cid/ciab699

Ippolito, J. A., Kanyo, Z. F., Wang, D., Franceschi, F. J., Moore, P. B., Steitz, T. A., et al. (2008). Crystal structure of the oxazolidinone antibiotic linezolid bound to the 50S ribosomal subunit. *J. Med. Chem.* 51 (12), 3353–3356. doi:10.1021/jm800379d

Jaspard, M., Butel, N., El Helali, N., Marigot-Outtandy, D., Guillot, H., Peytavin, G., et al. (2020). Linezolid-associated neurologic adverse events in patients with multidrug-resistant tuberculosis, France. *Emerg. Infect. Dis.* 26 (8), 1792–1800. doi:10.3201/eid2608.191499

Ji, C., Bai, J., Zhou, J., Zou, Y., and Yu, M. (2022a). Adverse event profiles of PCSK9 inhibitors alirocumab and evolocumab: data mining of the FDA adverse event reporting system. *Br. J. Clin. Pharmacol.* 88 (12), 5317–5325. doi:10.1111/bcp.15460

Ji, C., Bai, J., Zhou, J., Zou, Y., and Yu, M. (2022b). Adverse event profiles of PCSK9 inhibitors alirocumab and evolocumab: data mining of the FDA adverse event reporting system. *Br. J. Clin. Pharmacol.* 88 (12), 5317–5325. doi:10.1111/bcp.15460

Joshi, L., Taylor, S. R., Large, O., Yacoub, S., and Lightman, S. (2009). A case of optic neuropathy after short-term linezolid use in a patient with acute lymphocytic leukemia. *Clin. Infect. Dis.* 48 (7), e73–e74. doi:10.1086/597298

Jover-Diaz, F., Cuadrado-Pastor, J. M., Talents-Bolos, A., and Martin-Gonzalez, C. (2010). Black tongue associated with linezolid. *Am. J. Ther.* 17 (4), e115–e117. doi:10.1097/MJT.0b013e3181a59bcd

Kim, G. E., Ansari, S. M. R., Ali, A. M., Adam, E., and Eltahir, M. (2023a). Linezolid-induced pancreatitis associated with lactic acidosis and relative hypoglycemia: a rare case report. *Eur. J. Case Rep. Intern. Med.* 10 (10), 004041. doi:10.12890/2023_004041

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., et al. (2023b). PubChem 2023 update. *Nucleic Acids Res.* 51 (D1), D1373–d1380. doi:10.1093/nar/gkac956

Kinoshita, S., Hosomi, K., Yokoyama, S., and Takada, M. (2020). Time-to-onset analysis of amiodarone-associated thyroid dysfunction. *J. Clin. Pharm. Ther.* 45 (1), 65–71. doi:10.1111/jcpt.13024

Koh, W.-J., Kang, Y. R., Jeon, K., Kwon, O. J., Lyu, J., Kim, W. S., et al. (2012). Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J. Antimicrob. Chemother.* 67 (6), 1503–1507. doi:10.1093/jac/dks078

Kotsaki, A., Tziolos, N., Kontopoulou, T., Koutelidakis, I. M., Symbardi, S., Reed, V., et al. (2023). Oral minocycline plus rifampicin versus oral linezolid for complicated skin and skin structure infections caused by methicillin-resistant *Staphylococcus aureus*: the AIDA open label, randomized, controlled Phase 4 trial. *EClinicalMedicine* 56, 101790. doi:10.1016/j.eclinm.2022.101790

Kubota, K., Koide, D., and Hirai, T. (2004). Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiol. Drug Saf.* 13 (6), 387–394. doi:10.1002/pds.964

Kufel, W. D., Parsels, K. A., Blaine, B. E., Steele, J. M., Seabury, R. W., and Asiago-Reddy, E. A. (2023). Real-world evaluation of linezolid-associated serotonin toxicity with and without concurrent serotonergic agents. *Int. J. Antimicrob. Agents* 62 (1), 106843. doi:10.1016/j.ijantimicag.2023.106843

Lechner, A. M., Past, E., Porsche, U., Kern, J. M., Hoppe, U., and Pretsch, I. (2017). Two cases of serious rhabdomyolysis during linezolid treatment. *Infection* 45 (4), 563–566. doi:10.1007/s15010-016-0978-8

Lee, E., Burger, S., Shah, J., Melton, C., Mullen, M., Warren, F., et al. (2003). Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin. Infect. Dis.* 37 (10), 1389–1391. doi:10.1086/379012

Lee, E. Y., and Caffrey, A. R. (2018). Thrombocytopenia with tedizolid and linezolid. *Antimicrob. Agents Chemother.* 62 (1), e01453-17. doi:10.1128/aac.01453-17

Lee, J., Chung, H. S., Roh, J., Oh, Y., and Mok, J. (2021). Linezolid-induced black hairy tongue in a patient with multidrug-resistant tuberculosis: a case report. *Sci. Prog.* 104 (3), 368504211042982. doi:10.1177/00368504211042982

Lee, K. M. N., Rushovich, T., Gompers, A., Boulicault, M., Worthington, S., Lockhart, J. W., et al. (2023). A Gender Hypothesis of sex disparities in adverse drug events. *Soc. Sci. Med.* 339, 116385. doi:10.1016/j.socscimed.2023.116385

Leroy, F., Dauxois, J. Y., Théophile, H., Haramburu, F., and Tubert-Bitter, P. (2014). Estimating time-to-onset of adverse drug reactions from spontaneous reporting databases. *BMC Med. Res. Methodol.* 14, 17. doi:10.1186/1471-2288-14-17

Li, Y., and Xu, W. (2018). Efficacy and safety of linezolid compared with other treatments for skin and soft tissue infections: a meta-analysis. *Biosci. Rep.* 38 (1). doi:10.1042/bsr20171125

Li, Z., Zou, W., Yuan, J., Zhong, Y., and Fu, Z. (2023). Gender differences in adverse events related to Osimertinib: a real-world pharmacovigilance analysis of FDA adverse event reporting system. *Expert Opin. Drug Saf.*, 1–8. doi:10.1080/14740338.2023.2243220

Liang, Y., Ma, L., Wang, Y., Zheng, J., Su, L., and Lyu, J. (2023). Adverse events associated with molnupiravir: a real-world disproportionality analysis in food and drug administration adverse event reporting system. *Front. Pharmacol.* 14, 1253799. doi:10.3389/fphar.2023.1253799

Lifan, Z., Sainan, B., Feng, S., Siyan, Z., and Xiaoqing, L. (2019). Linezolid for the treatment of extensively drug-resistant tuberculosis: a systematic review and meta-analysis. *Int. J. Tuberc. Lung Dis.* 23 (12), 1293–1307. doi:10.5588/ijtld.18.0822

Liu, C., Bayer, A., Cosgrove, S. E., Daum, R. S., Fridkin, S. K., Gorwitz, R. J., et al. (2011). Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin. Infect. Dis.* 52 (3), e18–e55. doi:10.1093/cid/ciq146

Long, K. S., Munck, C., Andersen, T. M., Schaub, M. A., Hobbie, S. N., Böttger, E. C., et al. (2010). Mutations in 23S rRNA at the peptidyl transferase center and their relationship to linezolid binding and cross-resistance. *Antimicrob. Agents Chemother.* 54 (11), 4705–4713. doi:10.1128/aac.00644-10

Long, K. S., and Vester, B. (2012). Resistance to linezolid caused by modifications at its binding site on the ribosome. *Antimicrob. Agents Chemother.* 56 (2), 603–612. doi:10.1128/aac.05702-11

Matsumoto, K., Shigemi, A., Takeshita, A., Watanabe, E., Yokoyama, Y., Ikawa, K., et al. (2014). Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentration target and renal function in adult patients. *Int. J. Antimicrob. Agents* 44 (3), 242–247. doi:10.1016/j.ijantimicag.2014.05.010

Matsumoto, K., Takeshita, A., Ikawa, K., Shigemi, A., Yaji, K., Shimodozono, Y., et al. (2010). Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. *Int. J. Antimicrob. Agents* 36 (2), 179–181. doi:10.1016/j.ijantimicag.2010.02.019

Mazhar, F., Battini, V., Gringeri, M., Pozzi, M., Mosini, G., Marran, A. M. N., et al. (2021). The impact of anti-TNFα agents on weight-related changes: new insights from a real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. *Expert Opin. Biol. Ther.* 21 (9), 1281–1290. doi:10.1080/14712598.2021.1948529

Moise, P. A., Forrest, A., Birmingham, M. C., and Schentag, J. J. (2002). The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J. Antimicrob. Chemother.* 50 (6), 1017–1026. doi:10.1093/jac/dkf215

Monson, T., Schichman, S. A., and Zent, C. S. (2002). Linezolid-induced pure red blood cell aplasia. *Clin. Infect. Dis. Official Publ. Infect. Dis. Soc. Am.* 35 (3), E29–E31. doi:10.1086/340982

Natsumoto, B., Yokota, K., Omata, F., and Furukawa, K. (2014). Risk factors for linezolid-associated thrombocytopenia in adult patients. *Infection* 42 (6), 1007–1012. doi:10.1007/s15010-014-0674-5

Navari, R. M., and Aapro, M. (2016). Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 374 (14), 1356–1367. doi:10.1056/NEJMra1515442

Ni, M., Yin, X. D., Hu, W. J., Zeng, N., Zhao, B., and Li, Z. L. (2022). Stevens-johnson syndrome following vancomycin and linezolid: a real-world analysis of post-marketing surveillance data. *Front. Pharmacol.* 13, 872854. doi:10.3389/fphar.2022.872854

Niederman, M. S., Chastre, J., Solem, C. T., Wan, Y., Gao, X., Myers, D. E., et al. (2014). Health economic evaluation of patients treated for nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*: secondary analysis of a multicenter randomized clinical trial of vancomycin and linezolid. *Clin. Ther.* 36 (9), 1233–1243. doi:10.1016/j.clinthera.2014.06.029

Noel, G. J., Draper, M. P., Hait, H., Tanaka, S. K., and Arbeit, R. D. (2012). A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. *Antimicrob. Agents Chemother.* 56 (11), 5650–5654. doi:10.1128/aac.00948-12

Nomura, K., Takahashi, K., Hinomura, Y., Kawaguchi, G., Matsushita, Y., Marui, H., et al. (2015). Effect of database profile variation on drug safety assessment: an analysis of spontaneous adverse event reports of Japanese cases. *Drug Des. Devel Ther.* 9, 3031–3041. doi:10.2147/dddt.S81998

O'Riordan, W., Cardenas, C., Shin, E., Sirbu, A., Garrity-Ryan, L., Das, A. F., et al. (2019). Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial. *Lancet Infect. Dis.* 19 (10), 1080–1090. doi:10.1016/s1473-3099(19)30275-0

Pascoalinho, D., Vilas, M. J., Coelho, L., and Moreira, P. (2011). Linezolid-related immune-mediated severe thrombocytopenia. *Int. J. Antimicrob. Agents* 37 (1), 88–89. doi:10.1016/j.ijantimicag.2010.10.001

Prokocimer, P., De Anda, C., Fang, E., Mehra, P., and Das, A. (2013). Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. *Jama* 309 (6), 559–569. doi:10.1001/jama.2013.241

Raschi, E., Moretti, U., Salvo, F., Pariente, A., Cosimo Antonazzo, I., De Ponti, F., et al. (2019). "Evolving roles of spontaneous reporting systems to assess and monitor drug safety," in *Pharmacovigilance* (London, UK: IntechOpen), 1–28.

Rose, P. C., Hallbauer, U. M., Seddon, J. A., Hesseling, A. C., and Schaaf, H. S. (2012). Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children. *Int. J. Tuberc. Lung Dis. Official J. Int. Union Against Tuberc. Lung Dis.* 16 (12), 1588–1593. doi:10.5588/ijtld.12.0322

Rubinstein, E., Cammarata, S., Oliphant, T., Wunderink, R., and Linezolid Nosocomial Pneumonia Study Group (2001). Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin. Infect. Dis.* 32 (3), 402–412. doi:10.1086/318486

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Sauzet, O., Carvajal, A., Escudero, A., Molokhia, M., and Cornelius, V. R. (2013). Illustration of the weibull shape parameter signal detection tool using electronic healthcare record data. *Drug Saf.* 36 (10), 995–1006. doi:10.1007/s40264-013-0061-7

Savard, S., Desmeules, S., Riopel, J., and Agharazii, M. (2009). Linezolid-associated acute interstitial nephritis and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. *Am. J. Kidney Dis.* 54 (6), e17–e20. doi:10.1053/j.ajkd.2009.07.013

Shangguan, Y., Ji, Z., Guo, W., Hu, W., Li, X., and Xu, K. (2022). Oral bacteria dysbiosis in patients with linezolid-induced black hairy tongue: a case series. *Infect. Drug Resist* 15, 5449–5454. doi:10.2147/idr.S373266

Shao, H., Shi, D., and Dai, Y. (2023). Linezolid and the risk of QT interval prolongation: a pharmacovigilance study of the food and drug administration adverse event reporting system. *Br. J. Clin. Pharmacol.* 89 (4), 1386–1392. doi:10.1111/bcp.15587

Shaweno, D., Horton, K. C., Hayes, R. J., and Dodd, P. J. (2021). Assortative social mixing and sex disparities in tuberculosis burden. *Sci. Rep.* 11 (1), 7530. doi:10.1038/s41598-021-86869-w

Shi, X., Cheng, Q., Zhao, Y. Z., Zou, S. P., and Sun, M. H. (2023a). A real-world pharmacovigilance study of abaloparatide based on the FDA Adverse Event Reporting System (FAERS). *Osteoporos. Int. a J. Established as Result Coop. Between Eur. Found. Osteoporos. Natl. Osteoporos. Found. U. S. A.* 34 (12), 2047–2058. doi:10.1007/s00198-023-06877-6

Shi, Y., Wu, H. L., Wu, Y. H., Li, S., Zhang, L. Y., Xu, S. S., et al. (2023b). Safety and clinical efficacy of linezolid in children: a systematic review and meta-analysis. *World J. Pediatr.* 19 (2), 129–138. doi:10.1007/s12519-022-00650-1

Shorr, A. F., Lodise, T. P., Corey, G. R., De Anda, C., Fang, E., Das, A. F., et al. (2015). Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. *Antimicrob. Agents Chemother.* 59 (2), 864–871. doi:10.1128/aac.03688-14

Shu, Y., He, X., Liu, Y., Wu, P., and Zhang, Q. (2022). A real-world disproportionality analysis of olaparib: data mining of the public version of FDA adverse event reporting system. *Clin. Epidemiol.* 14, 789–802. doi:10.2147/CLEP.S365513

Singh, J. (2015). International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. *J. Pharmacol. Pharmacother.* 6 (3), 185–187. doi:10.4103/0976-500X.162004

Sisson, T. L., Jungbluth, G. L., and Hopkins, N. K. (2002). Age and sex effects on the pharmacokinetics of linezolid. *Eur. J. Clin. Pharmacol.* 57 (11), 793–797. doi:10.1007/s00228-001-0380-y

Sotgiu, G., Centis, R., D'Ambrosio, L., Alffenaar, J. W., Anger, H. A., Caminero, J. A., et al. (2012). Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur. Respir. J.* 40 (6), 1430–1442. doi:10.1183/09031936.00022912

Stahl, K., Rastelli, E., and Schoser, B. (2020). A systematic review on the definition of rhabdomyolysis. *J. Neurol.* 267 (4), 877–882. doi:10.1007/s00415-019-09185-4

Stensen, D. B., Småbrekke, L., Olsen, K., Grimnes, G., Nielsen, C. S., Ericson, J. U., et al. (2022). Circulating sex-steroids and *Staphylococcus aureus* nasal carriage in a general male population. *Epidemiol. Infect.* 150, e93. doi:10.1017/s0950268822000735

Tajima, M., Kato, Y., Matsumoto, J., Hirosawa, I., Suzuki, M., Takashio, Y., et al. (2016). Linezolid-induced thrombocytopenia is caused by suppression of platelet production via phosphorylation of myosin light chain 2. *Biol. Pharm. Bull.* 39 (11), 1846–1851. doi:10.1248/bpb.b16-00427

Tang, S., Yao, L., Hao, X., Zhang, X., Liu, G., Liu, X., et al. (2015). Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur. Respir. J.* 45 (1), 161–170. doi:10.1183/09031936.00035114

Tomita, Y., Kusama, Y., Nishiyama, C., Atsumi, Y., and Kamimura, K. (2023). Linezolid-induced black hairy tongue in a child following osteomyelitis. *Pediatr. Int.* 65 (1), e15417. doi:10.1111/ped.15417

Traver, E. C., Heil, E. L., and Schmalzle, S. A. (2022). A cross-sectional analysis of linezolid in combination with methadone or buprenorphine as a cause of serotonin toxicity. *Open Forum Infect. Dis.* 9 (7), ofac331. doi:10.1093/ofid/ofac331

Trippe, Z. A., Brendani, B., Meier, C., and Lewis, D. (2017). Identification of substandard medicines via disproportionality analysis of individual case safety reports. *Drug Saf.* 40 (4), 293–303. doi:10.1007/s40264-016-0499-5

Tsuji, Y., Holford, N. H. G., Kasai, H., Ogami, C., Heo, Y. A., Higashi, Y., et al. (2017). Population pharmacokinetics and pharmacodynamics of linezolid-induced thrombocytopenia in hospitalized patients. *Br. J. Clin. Pharmacol.* 83 (8), 1758–1772. doi:10.1111/bcp.13262

Tsutsumi, T., Imai, S., Kashiwagi, H., Sato, Y., Sugawara, M., and Takekuma, Y. (2022). Investigation of the risk factors of vomiting during linezolid therapy: a retrospective observational study. *Eur. J. Clin. Pharmacol.* 78 (2), 279–286. doi:10.1007/s00228-021-03221-x

van Puijenbroek, E. P., Bate, A., Leufkens, H. G., Lindquist, M., Orre, R., and Egberts, A. C. (2002). A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 11 (1), 3–10. doi:10.1002/pds.668

Veerman, K., Goosen, J., Spijkers, K., Jager, N., Heesterbeek, P., and Telgt, D. (2023). Prolonged use of linezolid in bone and joint infections: a retrospective analysis of adverse effects. *J. Antimicrob. Chemother.* 78 (11), 2660–2666. doi:10.1093/jac/dkad276

von Dach, E., Morel, C. M., Murthy, A., Pagani, L., Macedo-Vinas, M., Olearo, F., et al. (2017). Comparing the cost-effectiveness of linezolid to trimethoprim/sulfamethoxazole plus rifampicin for the treatment of methicillin-resistant *Staphylococcus aureus* infection: a healthcare system perspective. *Clin. Microbiol. Infect.* 23 (9), 659–666. doi:10.1016/j.cmi.2017.02.011

Waki, F., Ohnishi, H., Shintani, T., Uemura, M., Matsumoto, K., Fukumoto, T., et al. (2012). Linezolid-induced pure red cell aplasia in a patient with Staphylococcus epidermidis infection after allogeneic stem cell transplantation. *Transpl. Infect. Dis. Official J. Transplant. Soc.* 14 (4), E1–E6. doi:10.1111/j.1399-3062.2012.00728.x

Wang, L., Jiang, G., Li, D., and Liu, H. (2014). Standardizing adverse drug event reporting data. *J. Biomed. Semant.* 5, 36. doi:10.1186/2041-1480-5-36

Wang, T. L., Guo, D. H., Bai, Y., Wen, K., Han, W. Y., and Wang, R. (2016). Thrombocytopenia in patients receiving prolonged linezolid may be caused by oxidative stress. *Clin. Drug Investig.* 36 (1), 67–75. doi:10.1007/s40261-015-0352-0

Wang, Y., Zhao, B., Yang, H., and Wan, Z. (2023). A real-world pharmacovigilance study of FDA adverse event reporting system events for sildenafil. *Andrology*. doi:10.1111/andr.13533

Welshman, I. R., Sisson, T. A., Jungbluth, G. L., Stalker, D. J., and Hopkins, N. K. (2001). Linezolid absolute bioavailability and the effect of food on oral bioavailability. *Biopharm. Drug Dispos.* 22 (3), 91–97. doi:10.1002/bdd.255

Wilson, D. N., Schluenzen, F., Harms, J. M., Starosta, A. L., Connell, S. R., and Fucini, P. (2008). The oxazolidinone antibiotics perturb the ribosomal peptidyl-transferase center and effect tRNA positioning. *Proc. Natl. Acad. Sci. U. S. A.* 105 (36), 13339–13344. doi:10.1073/pnas.0804276105

Woytowish, M. R., and Maynor, L. M. (2013). Clinical relevance of linezolid-associated serotonin toxicity. *Ann. Pharmacother.* 47 (3), 388–397. doi:10.1345/aph.1R386

Wu, F., Zhang, X. S., Dai, Y., Zhou, Z. Y., Zhang, C. H., Han, L., et al. (2022). Dosage strategy of linezolid according to the trough concentration target and renal function in Chinese critically ill patients. *Front. Pharmacol.* 13, 844567. doi:10.3389/fphar.2022.844567

Wunderink, R. G., Niederman, M. S., Kollef, M. H., Shorr, A. F., Kunkel, M. J., Baruch, A., et al. (2012). Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin. Infect. Dis.* 54 (5), 621–629. doi:10.1093/cid/cir895

Wunderink, R. G., Roquilly, A., Croce, M., Rodriguez Gonzalez, D., Fujimi, S., Butterton, J. R., et al. (2021). A phase 3, randomized, double-blind study comparing tedizolid phosphate and linezolid for treatment of ventilated gram-positive hospital-acquired or ventilator-associated bacterial pneumonia. *Clin. Infect. Dis.* 73 (3), e710–e718. doi:10.1093/cid/ciab032

Yang, X.-Y., Chen, L., Gu, J.-N., Zeng, C.-J., and Pan, D.-M. (2022). Linezolid-induced pure red cell aplasia: a case report. *Infect. Drug Resist.* 15, 3847–3856. doi:10.2147/IDR.S362358

Zhang, Q., Ding, Y., Shu, Y., and Chen, J. (2023). A real-world disproportionality analysis of rucaparib: post-marketing pharmacovigilance data. *BMC Cancer* 23 (1), 745. doi:10.1186/s12885-023-11201-w

Zhou, Q., Du, Z., Qu, K., Shen, Y., Jiang, Y., Zhu, H., et al. (2023). Adverse events of epidiolex: a real-world drug safety surveillance study based on the FDA adverse event reporting system (FAERS) database. *Asian J. Psychiatry* 90, 103828. doi:10.1016/j.ajp.2023.103828

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fphar.2024.1270612

OPEN ACCESS

EDITED BY
Jia-bo Wang,
Capital Medical University, China

REVIEWED BY
Michael David Gershon,
Columbia University Irving Medical Center, United States
Mustafa Gul,
Atatürk University, Türkiye

*CORRESPONDENCE
Shuanglian Wang,
wangshuanglian@sdfmu.edu.cn
Chuanyong Liu,
liucy@sdu.edu.cn

RECEIVED 01 August 2023
ACCEPTED 26 February 2024
PUBLISHED 09 April 2024

CITATION
Li S, Shi Y, Zhu J, Li J, Wang S and Liu C (2024), Protective effect of oxytocin on vincristine-induced gastrointestinal dysmotility in mice. *Front. Pharmacol.* 15:1270612. doi: 10.3389/fphar.2024.1270612

Protective effect of oxytocin on vincristine-induced gastrointestinal dysmotility in mice

Shuang Li[1], Yao Shi[2], Jianchun Zhu[1], Jingxin Li[1], Shuanglian Wang[3]* and Chuanyong Liu[1,4]*

[1]Department of Physiology, School of Basic Medical Sciences, Cheeloo Medical College, Shandong University, Jinan, China, [2]Ministry of Education Key Laboratory of Protein, School of Life Sciences, Tsinghua University, Beijing, China, [3]Medical Science and Technology Innovation Center, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [4]Provincial Key Lab of Mental Disorders, Shandong University, Jinan, China

Aims: Vincristine (VCR), an antineoplastic drug, induces peripheral neuropathy characterized by nerve damage, limiting its use and reducing the quality of life of patients. VCR causes myenteric neuron damage, inhibits gastrointestinal motility, and results in constipation or paralytic ileus in patients. Oxytocin (OT) is an endogenous neuropeptide produced by the enteric nerve system, which regulates gastrointestinal motility and exerts neuroprotective effects. This study aimed to investigate whether OT can improve VCR-induced gastrointestinal dysmotility and evaluate the underlying mechanism.

Methods: Mice were injected either with saline or VCR (0.1 mg/kg/d, i. p.) for 14 days, and OT (0.1 mg/kg/d, i.p.) was applied 1 h before each VCR injection. Gastrointestinal transit and the contractile activity of the isolated colonic segments were assessed. The concentration of OT in plasma was measured using ELISA. Immunofluorescence staining was performed to analyze myenteric neurons and reactive oxygen species (ROS) levels. Furthermore, the indicators of oxidative stress were detected. The protein expressions of Nrf2, ERK1/2, P-ERK1/2, p38, and P-p38 in the colon were tested using Western blot.

Results: VCR reduced gastrointestinal transit and the responses of isolated colonic segments to electrical field stimulation and decreased the amount of neurons. Furthermore, VCR reduced neuronal nitric oxide synthase and choline acetyltransferase immunopositive neurons in the colonic myenteric nerve plexus. VCR increased the concentration of OT in plasma. Exogenous OT pretreatment ameliorated the inhibition of gastrointestinal motility and the injury of myenteric neurons caused by VCR. OT pretreatment also prevented the decrease of

Abbreviations: ACh, acetylcholine; AUC, area under the curve; ChAT, choline acetyltransferase; CNS, central nervous system; DAG, diacylglycerol; DAPI, 4′,6′diamidino-2-phenylindole dihydrochloride hydrate; DHE, dihydroethidium; EFS, electrical field stimulation; ELISA, enzyme-linked immunosorbent assay; ENS, enteric nervous system; GITT, gastrointestinal transit time; GSH, glutathione; IP3, inositol-3-phosphate; MP, myenteric plexus; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; nNOS, neuronal NO synthase; NO, nitric oxide; NS, normal saline; Nrf2, nuclear factor erythroid 2-related factor 2; OT, oxytocin; OTR, oxytocin receptor; PBS, phosphate-buffered saline; PLC, phospholipase C, PMSF, phenylmethylsulfonyl fluoride; PVDF, polyvinylidene difluoride; ROS, reactive oxygen species; SOD, superoxide dismutase; T-AOC, total antioxidative capacity; and VCR, vincristine.

superoxide dismutase activity, glutathione content, total antioxidative capacity, and Nrf2 expression, the increase of ROS levels, and the phosphorylation of ERK1/2 and p38 MAPK following VCR treatment.

Conclusion: Our results suggest that OT pretreatment can protect enteric neurons from VCR-induced injury by inhibiting oxidative stress and MAPK pathways (ERK1/2, p38). This may be the underlying mechanism by which it alleviates gastrointestinal dysmotility.

KEYWORDS

vincristine, oxytocin, gastrointestinal motility, myenteric neurons, oxidative stress, MAPK pathways

1 Introduction

One of the primary characteristics of vincristine (VCR) is its antineoplastic properties, which are beneficial for patients. VCR has been used to treat various cancers. The second property includes its undesirable side effects, which cause pain, limiting the treatment and substantially reducing the quality of life of patients (van de Velde et al., 2021). VCR binds to β-tubulin, inhibits microtubule polymerization at low concentrations or promotes microtubule depolymerization at high concentrations, prevents the formation of mitotic spindles, arrests mitotic progression, and prevents cell division. This is the mechanism underlying the anti-tumor properties of VCR (Triarico et al., 2021). Peripheral neuropathy is the most common dose-restricting side effect of VCR, affecting not only the peripheral sensorimotor nerves but also the autonomic nervous system, increasing the likelihood of damage to visceral organs (Legha, 1986; Dorchin et al., 2013; Triarico et al., 2021). Gastrointestinal toxicity is a common complication of VCR treatment (Moudi et al., 2013; Escalante et al., 2017). Most patients receiving VCR chemotherapy suffer from gastrointestinal diseases, which usually manifest as constipation or even a paralytic ileus, which is life-threatening in severe cases (Tomomasa et al., 1999; Yasu et al., 2016; Escalante et al., 2017; Adil et al., 2021). Experimental studies have reported that VCR delays gastric emptying and inhibits gastrointestinal motility (Sninsky, 1987; Sharma, 1988; Peixoto Júnior et al., 2009; Lopez-Gomez et al., 2018), which may be related to the damage of the gastrointestinal wall and myenteric plexus by VCR ((Sninsky, 1987; Lopez-Gomez et al., 2018; Smith, 1967)). The myenteric nerve plexus within the enteric nervous system (ENS) mainly controls gastrointestinal motility, and its injury usually leads to motility disorders (Spencer and Hu, 2020). Previous results from our lab have shown that VCR can damage myenteric neurons in mice (Gao et al., 2021). This may explain why VCR impairs gastrointestinal motor function.

The classical concept suggests that oxytocin (OT) acts as a neuro-pituitary hormone that is generated in the supraoptic and paraventricular nuclei of the hypothalamus and promotes milk ejection during lactation and uterine contraction during childbirth (Soloff et al., 1979; Jurek and Neumann, 2018). In addition, OT is involved in the regulation of many physiological functions, such as social behavior, emotion, food intake, and pain perception, and exerts anti-inflammatory, antioxidative, analgesic, and neuroprotective effects in many diseases (Jurek and Neumann, 2018). At present, OT is increasingly recognized as a gastrointestinal hormone or neuropeptide that regulates the function of the gastrointestinal tract. OT is endogenously produced and contained within enteric neurons, and its receptors are widely expressed throughout the digestive tract (Monstein et al., 2004; Ohlsson et al., 2006; Shi et al., 2021). OT has been reported to regulate the development and function of enteric neurons and modulate intestinal inflammation, motility, permeability, and mucosal homeostasis (Welch et al., 2008; Qin et al., 2009; Welch et al., 2014; Chen et al., 2015; Tang et al., 2019; Hollenberg, 2021). Published studies have demonstrated the protective effect of OT on VCR-induced sciatic nerve injury (Erdogan et al., 2020; Zhu et al., 2021). Therefore, we believe that OT may ameliorate VCR-induced gastrointestinal motor dysfunction by protecting the ENS from VCR damage.

In addition to the direct damage of the nervous system, characterized by VCR-induced peripheral neuropathy, the pathological mechanisms of VCR-induced neurotoxicity are also related to changes in ion channel activity, oxidative stress, and inflammation (Tay et al., 2022). VCR treatment leads to oxidative stress in the nervous system, including the sciatic nerve, spinal cord, and brain (Chen et al., 2020; Khan et al., 2021). However, whether VCR causes oxidative stress in the intestine has not been reported yet. The inflammation-related pathways ERK1/2 and p38 MAPK are involved in VCR-induced neuropathy (Shen et al., 2015; Fumagalli et al., 2020; Gao et al., 2021; Khan et al., 2021), and the phosphorylation of ERK 1/2 and p38 MAPK kinases in the spinal cord and colonic myenteric nerve plexus is enhanced following VCR treatment (Shen et al., 2015; Gao et al., 2021; Khan et al., 2021). Oxidative stress and MAPK pathway activation contribute to myenteric neuron loss (McQuade et al., 2016; Gao et al., 2021), which may be correlated with VCR-induced enteric neuron damage. OT suppresses oxidative stress and MAPK pathway activation. It reduces the expression of genes that code the oxidative stress response in the inflammatory gut (Welch et al., 2014), inhibits the LPS-induced activation of ERK 1/2 and p38 MAPK (Yuan et al., 2016), and alleviates cisplatin-induced nephrotoxicity by inhibiting NADPH oxidase and p38 MAPK (Rashed et al., 2011). Accordingly, we hypothesized that OT might protect enteric neurons from VCR-induced injury by inhibiting oxidative stress and MAPK activation. This might be the underlying mechanism by which it alleviates gastrointestinal dysmotility.

2 Materials and methods

2.1 Experimental chemicals

VCR was ordered from Selleck Chemicals (Houston, TX, United States). OT, carmine red, and carboxymethylcellulose were

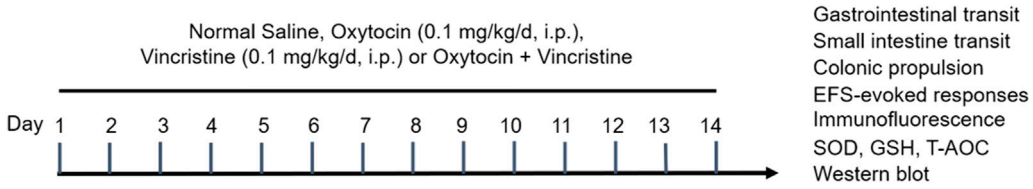


FIGURE 1
Schematic presentation of the experimental protocol. Mice were injected with normal saline (NS) or vincristine (VCR, 0.1 mg/kg/d, i. p.) for 14 consecutive days. Oxytocin (OT, 0.1 mg/kg/d, i. p.) was administered 1 h before each VCR injection.

ordered from Sigma-Aldrich Corp (St Louis, MO, United States). Isoflurane was ordered from RWD (Shenzhen, China). VCR and OT were dissolved and attenuated in normal saline (NS). Carmine red (6%) was suspended in 0.5% carboxymethylcellulose. Primary antibodies against NeuN, β III Tubulin, nNOS, choline acetyltransferase (ChAT), Nrf2, p44/42 MAPK, phospho-p44/42 MAPK, p38 MAPK, phospho-p38 MAPK, and GAPDH were ordered from Gene Tex (Irvine, United States), Cell Signaling Technology (Danvers, MA, United States), Abcam (Cambridge, UK), and Proteintech (Chicago, United States). Fluorescent secondary antibodies of Alexa Fluor 568-conjugated donkey anti-rabbit and Alexa Fluor 488-conjugated donkey anti-mouse were ordered from Invitrogen Life Technology (Foster City, CA, United States). DAPI was ordered from Beyotime Biotechnology (Shanghai, China). Dihydroethidium (DHE) was ordered from Sigma-Aldrich Corp. HRP-conjugated goat anti-rabbit secondary antibody was ordered from Zhongshan Golden Bridge Biotechnology (Beijing, China). Stripping buffer was ordered from CWBIO (Taizhou, China).

2.2 Experimental animals

Male C57BL/6J mice, aged 8–10 weeks, were ordered from Beijing Vital River Laboratory Animal Technology. The mice were kept in the Animal Center of Shangdong University with natural lighting and unconstrained access to food and water. The Medical Ethics Committee for Experimental Animals of Shandong University approved all the animal experiments (ECSBMSSDU 2020-2-006).

2.3 Experimental subgroups

The mice were randomly divided into the following four groups (Figure 1):

1) NS group: mice injected with NS (10 mL/kg/d, i. p.) for 14 days
2) OT group: mice injected with OT (0.1 mg/kg/d, i. p.) for 14 days (Zhu et al., 2021)
3) VCR group: mice injected with VCR (0.1 mg/kg/d, i. p.) for 14 days
4) OT + VCR group: mice injected with OT 1 h before each VCR injection

The mice were injected with the drugs between 8 and 11 a.m. and used for different experiments 24 h after the last injection (Supplementary Material S1: Table 1).

2.4 *In vivo* analysis of gastrointestinal tract motility

2.4.1 Total gastrointestinal transit time

Four groups of mice with six mice in each group were used to measure the total gastrointestinal transit time. At the end of the model, carmine red (6%), which was suspended in 0.5% carboxymethylcellulose, was administered to determine the total gastrointestinal transit time (GITT). The mice were fasted for 12 h prior to the analysis, but water was freely provided. Carmine red (0.2 mL/10 g) was intragastrically administered to each mouse. The GITT was the time interval between the gavage and the first red stool defecation. If no red stool was excreted until the end of the experiment (more than 10 h), the mouse was excluded.

2.4.2 Small intestinal transit

After 12 h of fasting, four groups of mice (eight mice per group) were intragastrically administered the same amount of carmine red and euthanized 30 min later by cervical dislocation. All the intestinal tubes from the pylorus to the caecum were removed immediately. The total length of the small intestine and propulsive distance of carmine red in the intestine were measured without tension, and the percentage of carmine red propulsion distance relative to the total length of the small intestine was calculated and reported as the small intestine propulsion rate.

2.4.3 Colonic propulsion

Four groups of mice (eight to nine mice per group) were anesthetized with isoflurane, and then, a glass ball with a diameter of 3 mm was placed 2 cm from the anus into the distal colon with a smooth glass pole. Subsequently, the mice were kept separately in a cage for observation. The expelling time of the glass ball was documented, which was represented as bead latency.

The GITT and glass ball expulsion time from the colon were reported as the calculated time. The small intestine propulsion rate was documented as the ratio of the carmine red propulsion distance to the length of the small intestine.

2.5 Enzyme-linked immunosorbent assay

At the end of the model, the whole blood samples from two groups of mice (four to six mice in the NS and VCR groups) were taken by eyeball extirpating, placed at room temperature for 30 min, and centrifuged at 1,000 *g* for 15 min. The liquid supernatant was carefully pipetted and used to measure the concentration of OT

TABLE 1 Experimental subgroups.

Cohort of animals	Experimental groups	Animal numbers	Experiments
1	4	6/group	Total gastrointestinal transit time and organ-bath study
2	4	8–9/group	Intestinal propulsion rate and colonic propulsion
3	2 (NS and VCR)	4–6/group	Measure of OT concentrations
4	4	4–5/group	β III Tubulin immunofluorescence staining and Western blot study
5	4	13–15/group	NeuN, nNOS, and ChAT immunofluorescence staining
6	4	3–4/group	Measure of ROS levels
7	4	4–7/group	Measure of oxidative stress indicators

using an enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's instructions.

2.6 Recording the contractile activity of the colonic segments *in vitro*

After a 12-h fast without food but with water, four groups of mice (six mice per group) were euthanized by cervical dislocation. Approximately 1.5 cm of the distal colon without mesentery was removed. Without removing the mucosa and either muscular layer, each end of the longitudinally mounted bowel segment (equivalent to the longitudinal muscle) was then tied with a thin and inelastic thread. The lower end of the segment was fixed on a hook at the bottom of the bath, and the other end was connected to a tension transducer (JH-2B, Chengdu Instrument Factory, Chengdu, China). The whole bowel segment was soaked in fresh Krebs solution (pH 7.4), which was aerated continuously with carbogen (95% O_2 + 5% CO_2) and kept at 37°C using a thermostatic water pump (ZH-Z, Zhenghu Biological Equipment Ltd., Co., Huaibe, China). The ingredients of Krebs solution were as follows (in mmol/L): NaCl 118, KC1 4.8, $NaHCO_3$ 25, NaH_2PO_4 1.0, $MgSO_4$ 1.2, glucose 11.1, and $CaCl_2$ 2.5. The change in the tension of the isolated colonic segments was recorded using a multichannel physiological recorder system (ML785-PowerLab, ADI, Sydney, Australia), and the data were visualized on a computer by Chart 5 software.

2.6.1 Response to electrical field stimulation

The colonic segments were balanced for approximately 1 h at a preload of 1 g (rinsed with fresh Krebs solution at 37°C every 15 min), and the experiment was started after their spontaneous contraction stabilized. Two platinum electrodes connected with a stimulator (SEN-7203, Nihon Kohden, Tokyo, Japan) were placed around the colonic segments. Electrical field stimulation (EFS) with a voltage of 80 V, frequency of 8 Hz, pulse width of 0.6 ms, and duration of 6 s was applied to elicit neural responses. EFS was reduplicated thrice at 10-min intervals.

EFS induced biphasic responses consisting of relaxation and contraction in our experiment. The extent of relaxation and contraction in response to EFS was evaluated by calculating the average of the area under the curve (AUC) after performing EFS thrice. The AUC was reported as g.s. The spontaneous contractions were assessed by calculating the AUC of basal contractile activity within 1 min before any stimulation.

2.7 Immunofluorescence staining

2.7.1 Cross sectioning of paraffin-embedded tissues

After modeling, the distal colon tissues were removed from four groups of mice (five to six mice per group) euthanized by cervical dislocation, rinsed with phosphate-buffered saline (PBS), and fixed with 4% paraformaldehyde all night at 4°C. After dehydration, the tissues were embedded in paraffin and dissected into serial coronal slices with a thickness of 4 μm. The paraffin sections were dewaxed in xylol, hydrated in a gradient of alcohol solutions, and then, incubated in sodium citrate buffer for 20 min for antigen retrieval. Nonspecific binding was blocked by incubating the tissues with 10% donkey serum at room temperature for 60 min. Afterward, the solution was replaced with mouse anti-β III Tubulin [2G10] (cat: ab78078, 1 μg/mL, Abcam) primary antibody and incubated at 4°C lasting all night. After washing with PBS thrice the following day, the tissues on glass slides were incubated with Alexa Fluor 488-conjugated donkey anti-mouse (cat: A-21202, 1 μg/mL, Invitrogen) fluorescent secondary antibody at room temperature under dark light for 60 min. After rinsing again, the tissue sections were stained with DAPI (cat: C1006, Beyotime) for 5 min at the ambient temperature keeping away from light. Finally, the sections on glass slides were sealed with Antifade Mounting Medium (Beyotime) and viewed with a fluorescence microscope (IX71, OLYMPUS).

2.7.2 Whole-mount myenteric plexus

Myenteric plexus (MP) whole mounts were prepared for immunofluorescence staining to assess the changes in myenteric nervous plexus. The 2-cm distal colons were removed from four groups of mice (thirteen to fifteen mice per group), cleared with cooled Krebs solution, cut longitudinally along the edge of mesentery, and pinned to a Sylgard™-lined dissecting dish. MP was prepared by eliminating the mucosal, submucosal, and circummuscular layers, followed by digestion with papain (10 mg/mL) dissolved in Krebs solution for 50 min at 37°C. Then, the tissue was rinsed thrice with PBS and stretched to twice its size under a microscope. The next step was to fix the preparation with 4% paraformaldehyde for 30 min, followed by rinsing with PBS thrice and blocking with 10% donkey serum for 60 min. These operations were performed at room temperature. After blotting the blocking solution with filter paper, the tissue was incubated with rabbit anti-NeuN [EPR12763] (cat: ab177487, 8.5 μg/mL, Abcam), mouse anti-β III Tubulin [2G10] (cat:

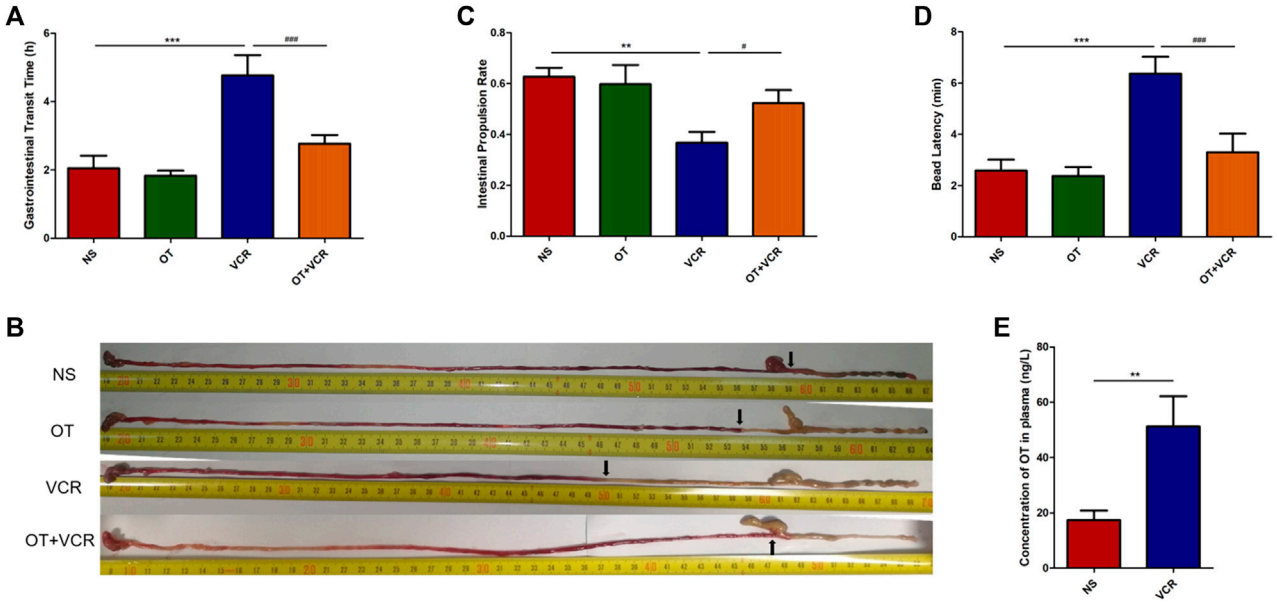


FIGURE 2
OT relieves the inhibitory effect of VCR on the gastrointestinal transit in mice. **(A)** Total gastrointestinal transit time. Mice were intragastrically administered carmine red, and the time of the first appearance of red feces were recorded (n = 5–6). **(B–C)** Small intestine transit. Mice were intragastrically administered carmine red and sacrificed 30 min later. The small intestine was removed, and the rate of carmine red propulsion was calculated (n = 8). **(B)** Original images of carmine red transport along the intestine. Arrows represent the farthest point at which carmine red is transported along the intestine. **(C)** Histogram shows the small intestinal propulsion rate. **(D)** Colonic propulsion. Mice were anaesthetized with isoflurane, and then, a 3-mm glass ball was placed 2 cm from the anus into the colon with a smooth glass pole. The expelling time of the glass ball was documented (n = 7–9). **(E)** Concentration of OT in plasma was increased in VCR-treated mice as measured by ELISA (n = 4–6). The data are expressed as the means ± SEM, and one-way ANOVA combined with Newman–Keuls or Student's t-test is used to compare the differences among two or multiple groups. *p < 0.05, **p < 0.01, and ***p < 0.001 *versus* the NS group; $^{\#}p$ < 0.05 and $^{\#\#\#}p$ < 0.001 *versus* the VCR group.

ab78078, 1 μg/mL, Abcam) and rabbit anti-nNOS [EP 1855Y] (cat: ab76067, 6 μg/mL, Abcam), or mouse anti-β III Tubulin [2G10] (cat: ab78078, 1 μg/mL, Abcam) and rabbit anti- ChAT [N1N3] (cat: GTX113164, 6.15 μg/mL, Gene Tex) primary antibodies at 4°C lasting all night. The following day, the tissue was rinsed thrice with PBS and then incubated with the same fluorescent secondary antibodies (Alexa Fluor 488-conjugated donkey anti-mouse or Alexa Fluor 568-conjugated donkey anti-rabbit) at room temperature under dark light for 60 min. After three rinses, the tissue was stained with DAPI for 5 min. Then, the tissue was rinsed again, transferred to and flattened on a glass slide, sealed with Antifade Mounting Medium, and viewed with a fluorescence microscope.

2.7.3 Measurement of reactive oxygen species

DHE was used to assess the production of reactive oxygen species (ROS). Tissue preparation was performed in the same manner as the paraffin sections. The fixed samples of colons from four groups of mice (three to four mice per group) were treated with graded dehydration and then embedded in OCT (Servicebio, China). After that, the tissues were dissected into serial frozen sections with a thickness of 10 μm and stored at −20°C for future use. Frozen sections were taken out and rewarmed at room temperature. Afterward, the colonic sections were incubated with DHE dye (cat: D7008, 5 μg/mL, Sigma-Aldrich) at 37°C under dark light for 30 min, followed by a 5 min rinse with PBS thrice. After water drying, DAPI was applied to the sections for 5 min. Then, the slides were rinsed thrice with PBS, sealed with Antifade Mounting Medium, and viewed under a fluorescence microscope.

In the immunofluorescence assay, the number of β III Tubulin-immunopositive neurons in the paraffin section and the number of NeuN-, nNOS-, and ChAT-immunopositive neurons in the MP were measured by counting 5–10 or 6–8 non-overlapping images captured from each MP or paraffin section with a ×40 objective. For ROS levels, the mean fluorescence intensity was analyzed in three non-overlapping images, which were captured with a ×20 objective.

2.8 Measurement of superoxide dismutase, glutathione, and total antioxidative capacity

After modeling, the distal colons were isolated from four groups of mice (four to seven mice per group) euthanized by cervical dislocation, rinsed with cold PBS, and stored at −80°C. The activity of superoxide dismutase (SOD), content of glutathione (GSH), and total antioxidative capacity (T-AOC) were examined with assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) following the manufacturer's instructions.

2.9 Western blot analysis

Distal colon samples from four groups of mice (four to five mice per group) were homogenized with cold RIPA lysis solution (Boster Bio, Pleasanton, CA, United States) including 1% PMSF (protease inhibitor) and 1% phosphatase inhibitor (Boster Bio, Pleasanton,

CA, United States), centrifuged at 13,800 *g* for 15 min at 4°C, and the liquid supernatant was gathered for quantitating protein concentration using a BCA assay kit (Boster, United States).

Loading buffer (5×) was added to the supernatants, followed by denaturation via seething at 100°C for 10 min. After that, the proteins were isolated with 12% polyacrylamide gel electrophoresis and then shifted to polyvinylidene difluoride (PVDF) membranes. The membranes were blocked with 5% non-fat milk at room temperature for 60 min and then cut according to the molecular weight of the target protein to incubate with rabbit anti-Nrf2 (cat: ab137550, 1 μg/mL, Abcam), rabbit anti-p44/42 MAPK (ERK1/2) (137F5) (cat: #4695, 0.084 μg/mL, CST), rabbit anti-Phospho-p44/42 MAPK (ERK1/2) (cat: #9101, 0.191 μg/mL, CST), rabbit anti-p38 MAPK (cat: #9212, 0.023 μg/mL, CST), rabbit anti-Phospho-p38 MAPK (cat: #9211, 0.046 μg/mL, CST), and rabbit anti-GAPDH (cat: 10494-1-AP, 0.3 μg/mL, Proteintech) primary antibodies at 4°C lasting all night. On the second day, the membranes were immersed in HRP-conjugated goat anti-rabbit (cat: ZB-2306, 0.2 μg/mL, Zhongshan Golden Bridge Biotechnology) secondary antibody at room temperature for 60 min. After rinsing with TBST buffer thrice, the membranes were exposed to ECL chemiluminescence reagent. Then, immunoreactive bands were visualized with the Tanon Imaging System (Tanon-4600) and analyzed using ImageJ software. The gray values of the two bands of Nrf2 were quantified (Chaudhary et al., 2021; Lan et al., 2021; Lin et al., 2021), but the absence of positive controls or antagonists was a flaw in our methodology. For proteins with close molecular weight, the developed membrane was treated with Stripping Buffer (CWBIO, Taizhou, China) and then re-incubated with new primary antibodies (Litovchick, 2020). The procedure was as follows: first, the membranes were immersed in Stripping Buffer for 30 min at 37°C with shaking to remove the primary and secondary antibodies bound to the membranes; second, they were washed thrice with TBST for 5 min at room temperature; and third, they were blocked again and subsequently incubated with new primary antibodies for the next round of Western blot experiments. The rule of preferentially detecting the target protein with low expression levels (such as phosphorylated proteins) was followed.

2.10 Data analysis

All data are expressed as the means ± SEM. Two-tailed Student's t-test or one-way ANOVA combined with the Newman–Keuls test was used to compare the differences among two or multiple groups. GraphPad Prism version 5 (La Jolla, CA, United States) was used for statistical analysis. $p < 0.05$ was identified as a statistically significant difference.

3 Results

3.1 OT pretreatment relieves the inhibitory effect of VCR on gastrointestinal transit in mice *in vivo*

The total gastrointestinal transit time, small intestinal propulsion rate, and the time of glass ball discharge from the colon were measured and compared among the four groups of mice to assess global gastrointestinal transit.

3.1.1 OT pretreatment shortens the total gastrointestinal transit time compared with VCR administration alone

One mouse was excluded from the VCR group because it did not excrete red stool at the end of the experiment. The time of the first passage of red stool in the VCR group was 4.77 ± 0.53 h, which was significantly longer than that in the NS control group (2.05 ± 0.33 h) ($p < 0.01$, Figure 2A), and it was shortened to 2.77 ± 0.23 h in the OT + VCR group compared with the VCR group ($p < 0.01$, Figure 2A). This result indicated that OT prevented the slowing of total gastrointestinal transit caused by VCR.

3.1.2 OT pretreatment increases the small intestinal propulsion rate compared with VCR administration alone

There was no significant difference in the length of the small intestine among the four groups (Supplementary Figure S1). The intestinal propulsion rate in mice from the VCR group was 0.37 ± 0.04, which was significantly lower than that of 0.63 ± 0.03 in the vehicle controls ($p < 0.01$, Figures 2B and C). Conversely, it was increased to 0.52 ± 0.05 in mice from the OT + VCR group ($p < 0.05$, Figures 2B and C). This result indicated that OT prevented the weakness of small intestinal propulsion caused by VCR.

3.1.3 OT pretreatment improves the colonic propulsion compared with VCR administration alone

The time of glass ball discharge from the colon was substantially increased from 2.59 ± 0.40 min to 6.36 ± 0.61 min in mice from the VCR group compared with the NS controls ($p < 0.01$, Figure 2D), while it was decreased to 3.30 ± 0.68 min by prior OT administration ($p < 0.01$, Figure 2D). This result indicated that OT prevented the diminution of colonic propulsion caused by VCR.

All the results from the *in vivo* study showed that OT relieved the inhibitory effect of VCR on gastrointestinal transit.

3.2 VCR treatment increases the concentration of OT in plasma

The concentration of OT in plasma was measured by ELASA, and the result showed that it was significantly increased in VCR groups (51.20 ± 0.53 ng/L) compared with NS controls (17.32 ± 3.17 ng/L) ($p < 0.01$, Figure 2E). This indicated that VCR promoted the synthesis and secretion of endogenous OT.

3.3 OT pretreatment mitigates the inhibitory effect of VCR on neuro-evoked responses in colonic segments *in vitro*

The movement of the digestive tract is mainly controlled by the ENS within the wall and regulated by the central nervous system (CNS) (Furness et al., 2014). To exclude the control of the

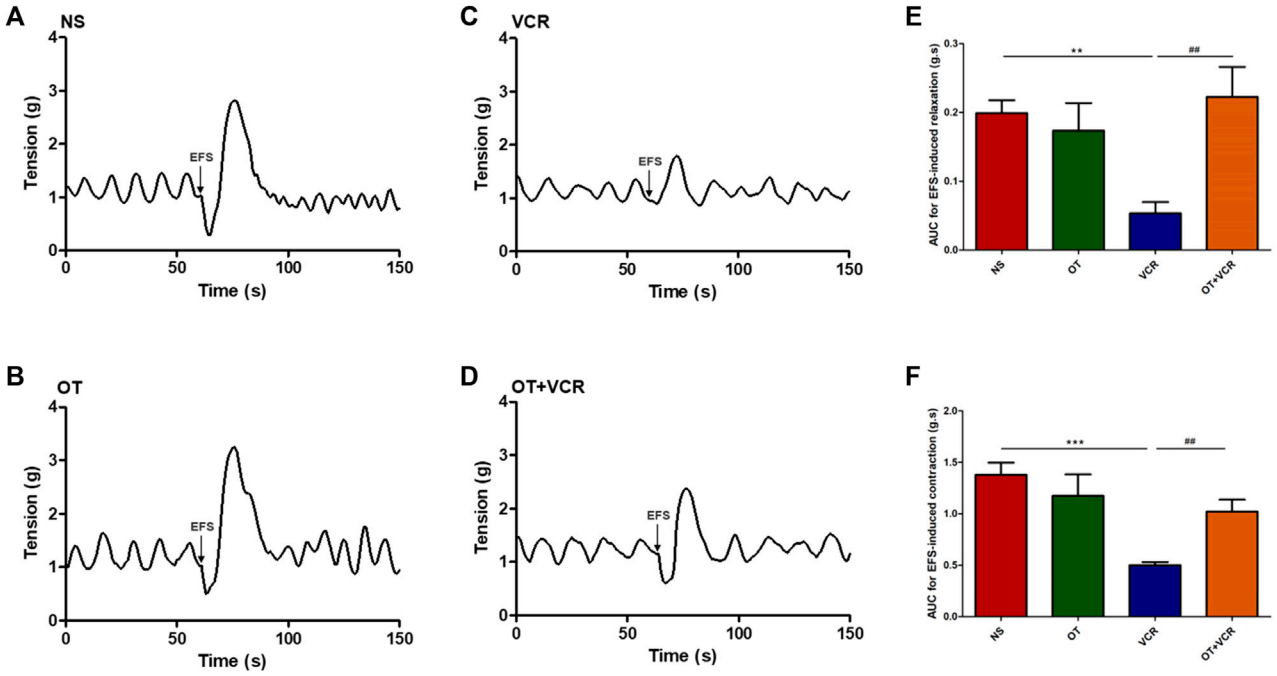


FIGURE 3
OT mitigates the restrained effect of VCR on electrical field stimulation (EFS)-induced responses of the isolated colonic segments. **(A–D)** Representative tension recordings show the EFS-induced biphasic responses consisting of relaxation and contraction in the four groups of mice: NS **(A)**, OT **(B)**, VCR **(C)**, and OT + VCR **(D)**. Arrows represent the application of EFS. **(E,F)** The area under the curve (AUC) for relaxation **(E)** and contraction **(F)** responses induced by EFS in the four groups indicates that the neurogenic relaxation and contraction of colonic segments are restrained by VCR but eliminated by prior OT treatment (n = 5–6). The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^{**}p < 0.01$ and $^{***}p < 0.001$ *versus* the NS group; $^{\#\#}p < 0.01$ *versus* the VCR group.

movement by neural pathways originating outside the alimentary tract, we recorded the contractile activity of colonic segments *in vitro* to detect neurogenic responses by applying EFS to the colon.

In this experiment, the colonic segments showed continuous and stable spontaneous contractions, and no significant difference in the spontaneous contraction of colonic segments was observed among the four groups (Supplementary Figure S2). One mouse was removed from the organ bath study because there was no continuous spontaneous activity. Representative trace from the control showed that EFS induced biphasic responses consisting of relaxation and subsequent contraction (Figure 3A), where nitric oxide (NO) was mainly responsible for the relaxation phase and acetylcholine (Ach) was mainly responsible for the contraction phase (Moralioglu et al., 2017). In the colonic segments from the VCR group, the magnitude of relaxation and contraction in response to EFS were less pronounced than those in the vehicle control group (Figure 3C). The AUC of EFS-induced relaxation was reduced from 0.20 ± 0.02 g s in the NS group to 0.05 ± 0.01 g s in the VCR group ($p < 0.01$, Figure 3E); contraction was reduced from 1.38 ± 0.11 g s to 0.50 ± 0.03 g s ($p < 0.001$, Figure 3F), indicating an inhibitory effect of VCR on EFS-evoked responses. Pretreatment with OT improved the inhibition of VCR on EFS-induced biphasic responses. The magnitude of relaxation and contraction in response to EFS was augmented in the OT + VCR group compared with the VCR group (Figure 3D). Meanwhile, the AUC of relaxation and contraction was also increased to 0.22 ± 0.04 g s and 1.02 ± 0.11 g s, respectively ($p < 0.01$, Figures 3E, F). These findings revealed that OT mitigated the restraint induced by VCR on neurogenic responses.

3.4 OT pretreatment reduces VCR-induced injury to myenteric neurons

In the ENS, the myenteric nerve plexus is mainly responsible for the coordination of muscle movements that propel the content (Spencer and Hu, 2020). Therefore, the spatial organization and the number of enteric neurons in the myenteric nerve plexus were studied by immunofluorescence staining.

3.4.1 OT pretreatment increases the numbers of colonic myenteric neurons compared with VCR administration alone

Previous results from our lab showed that VCR reduced neuron numbers in the myenteric nerve plexus (Gao et al., 2021), and this result was confirmed by immunofluorescence staining in this present study. From the photomicrographs of the colonic paraffin section and MP, we found that the numbers of β III Tubulin (neuronal marker) immunopositive neurons and NeuN (neuronal marker) immunopositive neurons were lower in the VCR group than in the vehicle controls (Figures 4A and C). The numbers of β III Tubulin$^+$ neurons in the paraffin sections were reduced from 13.03 ± 1.08 in the NS group to 5.96 ± 0.85 in the VCR group ($p < 0.01$, Figure 4B). The amounts of NeuN$^+$ neurons in the MP were reduced

from 46.18 ± 2.64 to 29.11 ± 1.34 ($p < 0.001$, Figure 4D). In contrast, the amounts of β III Tubulin$^+$ neurons and NeuN$^+$ neurons in the OT + VCR group were greater than that in the VCR group, increasing to 10.45 ± 1.23 and 38.18 ± 2.28, respectively ($p < 0.05$ and $p < 0.01$, respectively, Figures 4B and D). These results suggested that OT prevented the decrease in the amounts of intermuscular plexus neurons caused by VCR administration.

3.4.2 OT pretreatment increases the numbers of nitrergic neurons compared with VCR administration alone in the myenteric nerve plexus

NO is a primary inhibitory neurotransmitter generated by the ENS and is mainly responsible for the EFS-induced relaxation phase (Furness, 2000; Moralioglu et al., 2017). Neuronal NO synthase (nNOS) is the main source of NO in the myenteric nerve plexus (Takahashi, 2003). Therefore, the amounts of nitrergic neurons in the colon were detected by double immunofluorescence staining of MP with nNOS (red) and β III Tubulin (green). From the representative images and quantitative analysis, we observed fewer nNOS-positive neurons in the VCR group, which was 16.19 ± 1.43, than in the control group, which was 21.87 ± 1.08, but these numbers were increased to 21.21 ± 1.07 in the OT + VCR group ($p < 0.05$, Figure 5).

3.4.3 OT pretreatment increases the numbers of cholinergic neurons compared with VCR administration alone in the myenteric nerve plexus

ACh is the major excitatory neurotransmitter produced by motor neurons in the ENS and is mainly responsible for the EFS-induced contraction phase (Furness, 2000; Moralioglu et al., 2017). Therefore, cholinergic neurons in colonic MP were also detected by double immunofluorescence staining for ChAT (red), an ACh synthetase, and β III Tubulin. The results showed that the amounts of ChAT-positive neurons were also decreased in the VCR group compared with the NS group, which were reduced from 35.18 ± 1.11 to 21.08 ± 2.49, while this decrease was also prevented by pretreatment with OT, with the numbers of ChAT$^+$ neurons being 31.45 ± 4.00 ($p < 0.01$ and $p < 0.05$, respectively, Figure 6).

In conclusion, OT prevented VCR-induced decreases in the amounts of neurons, nitrergic neurons, and cholinergic neurons in the myenteric nerve plexus.

3.5 OT attenuates VCR-induced oxidative stress in mice

After VCR treatment, we found that the activity of SOD, the content of GSH, and the T-AOC in the colon samples of mice were significantly reduced (Figures 7A–C). Furthermore, Western blot results showed that Nrf2 protein expression was decreased (Figures 7D and E); the immunofluorescence assay also showed that DHE staining was enhanced and ROS levels were significantly elevated in the VCR group compared with those in the NS group (Figures 7F and G). As previously reported, in this experiment, OT pretreatment increased SOD activity, GSH content, and T-AOC; it also increased Nrf2 protein expression and significantly decreased DHE staining and ROS levels (Figure 7). These results demonstrated that OT attenuated oxidative stress in mice treated with VCR.

3.6 OT suppresses ERK1/2 and p38 MAPK activation caused by VCR

The results from Western blot have shown that VCR treatment resulted in the activation of ERK1/2 and p38 MAPK pathways, which is manifested by increased phosphorylation levels of the ERK1/2 and p38 proteins. These effects were prevented by OT pretreatment, as indicated by decreased P-ERK1/2 and P-p38 expression (Figure 8). This result suggested that OT inhibited the VCR-induced activation of the ERK1/2 and p38 MAPK pathways.

4 Discussion

The effects of OT on VCR-induced gastrointestinal dysmotility and enteric nerve injury were investigated in this study. Continuous VCR treatment for 14 days reduced the intestinal propulsion rate and prolonged the time of glass ball expelled from the colon and the time of first red feces appearance. Furthermore, VCR treatment decreased the relaxation and contraction responses of the colonic segments to EFS and reduced the numbers of total neurons and nNOS- and ChAT-immunopositive neurons in the myenteric nerve plexus. The most exciting finding was that OT improved the gastrointestinal motor function and protected against enteric nerve injury following VCR treatment. OT increased the intestinal propulsion rate, shortened the time of glass ball expelling and first red stool excretion, enhanced the reactivity of colonic segments to EFS, and increased the numbers of myenteric neurons and nNOS- and ChAT-positive neurons. Overall, OT alleviated VCR-induced changes in gastrointestinal motility and neurogenic injury. Further studies showed that OT enhanced the activity of SOD, increased the content of GSH and the T-AOC, increased the expression of Nrf2 protein, and decreased ROS levels; meanwhile, it decreased the phosphorylation levels of ERK1/2 and p38 proteins in the colon samples following VCR treatment. Therefore, OT might play a protective role by inhibiting oxidative stress and the MAPK (ERK1/2 and p38) pathways.

In clinical practice, gastrointestinal motility disorder is a known complication of VCR treatment, presenting as constipation or even paralytic ileus (Tomomasa et al., 1999; Yasu et al., 2016; Escalante et al., 2017; Adil et al., 2021). Animals treated with VCR also develop gastrointestinal motor dysfunction (Sninsky, 1987; Sharma, 1988; Peixoto Júnior et al., 2009; Lopez-Gomez et al., 2018). In the present study, the intestinal transit was altered after VCR treatment. Previous studies by us and other labs had confirmed that OT was an endogenous neuropeptide produced by the ENS (Monstein et al., 2004; Ohlsson et al., 2006; Welch et al., 2008; Shi et al., 2021), which stimulated motor activity in the stomach and colon and improved gastrointestinal dyskinesia induced by stress and hypoxia (Ohlsson et al., 2004; Li et al., 2007; Feng et al., 2009; Qin et al., 2009; Babygirija et al., 2010; Xie et al., 2011; Welch et al., 2014; Yang et al., 2019). Accordingly, we believed that OT might exert protective effects against VCR-induced intestinal transit weakening. This was proved by our results, which showed that OT pretreatment improved intestinal transit. Therefore, clinical preadministration of OT might be useful to prevent or treat intestinal motor dysfunction induced by chemotherapy. In this paper, it was

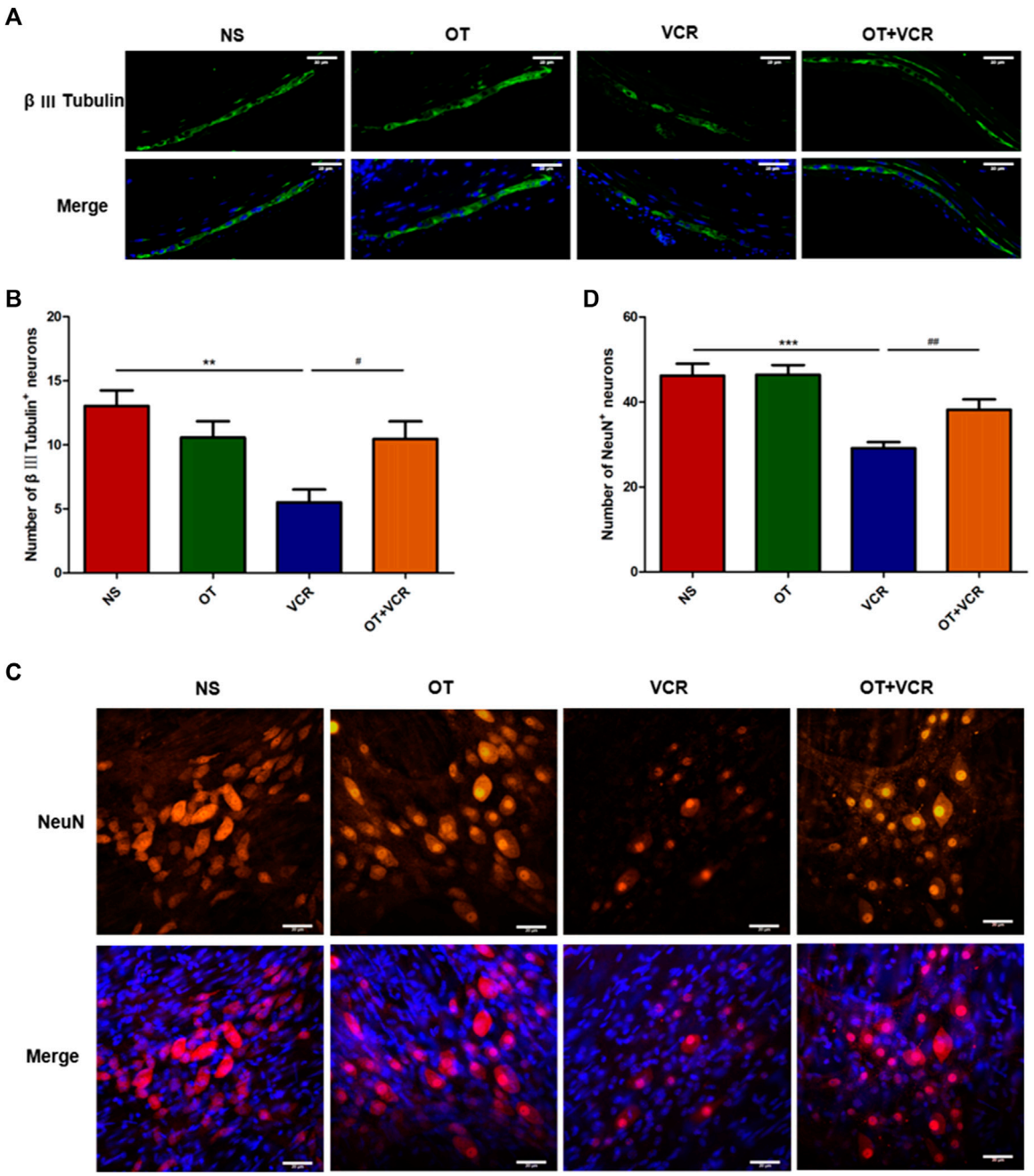


FIGURE 4
OT attenuates the decrease in the numbers of myenteric neurons induced by VCR administration. **(A)** Typical photo of immunofluorescence staining for β III Tubulin in paraffin sections of the colon. **(B)** Quantification of β III tubulin-immunopositive neurons (n = 5). **(C)** Typical photo of immunofluorescence staining for NeuN in colonic myenteric nerve plexus. **(D)** Quantification of NeuN-immunopositive neurons (n = 8–9). Scale bars = 20 μm. The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^{**}p < 0.01$ and $^{***}p < 0.001$ *versus* the NS group; $^{\#}p < 0.05$ and $^{\#\#}p < 0.01$ *versus* the VCR group.

found that OT itself did not affect gastrointestinal transit, possibly because of its short half-life (Smith et al., 2019). The regulatory effects of OT on gastrointestinal motility reported in the pervious literature were usually transient (Ohlsson et al., 2004; Li et al., 2007; Feng et al., 2009; Qin et al., 2009), whereas all experiments in this study were conducted 24 h after the last OT injection. In another study in our lab, administration of OT alone also had no effect on the peripheral pain sensitivity of mice (Zhu et al., 2021).

OT exerts biological effects by binding to its receptor (OTR). OTR is a G-protein-coupled receptor. After combining with OT, it triggers intracellular calcium release and protein kinase C activation through the PLC-IP3/DAG signaling pathway (Blanks et al., 2007; Jurek and Neumann, 2018). We found that OTR on macrophages inhibited the LPS-induced polarization through the β-arrestin 2-NF-κB pathway (Tang et al., 2019). This might be the mechanism underlying the anti-inflammatory effect of OT. Some studies indicated that the anti-

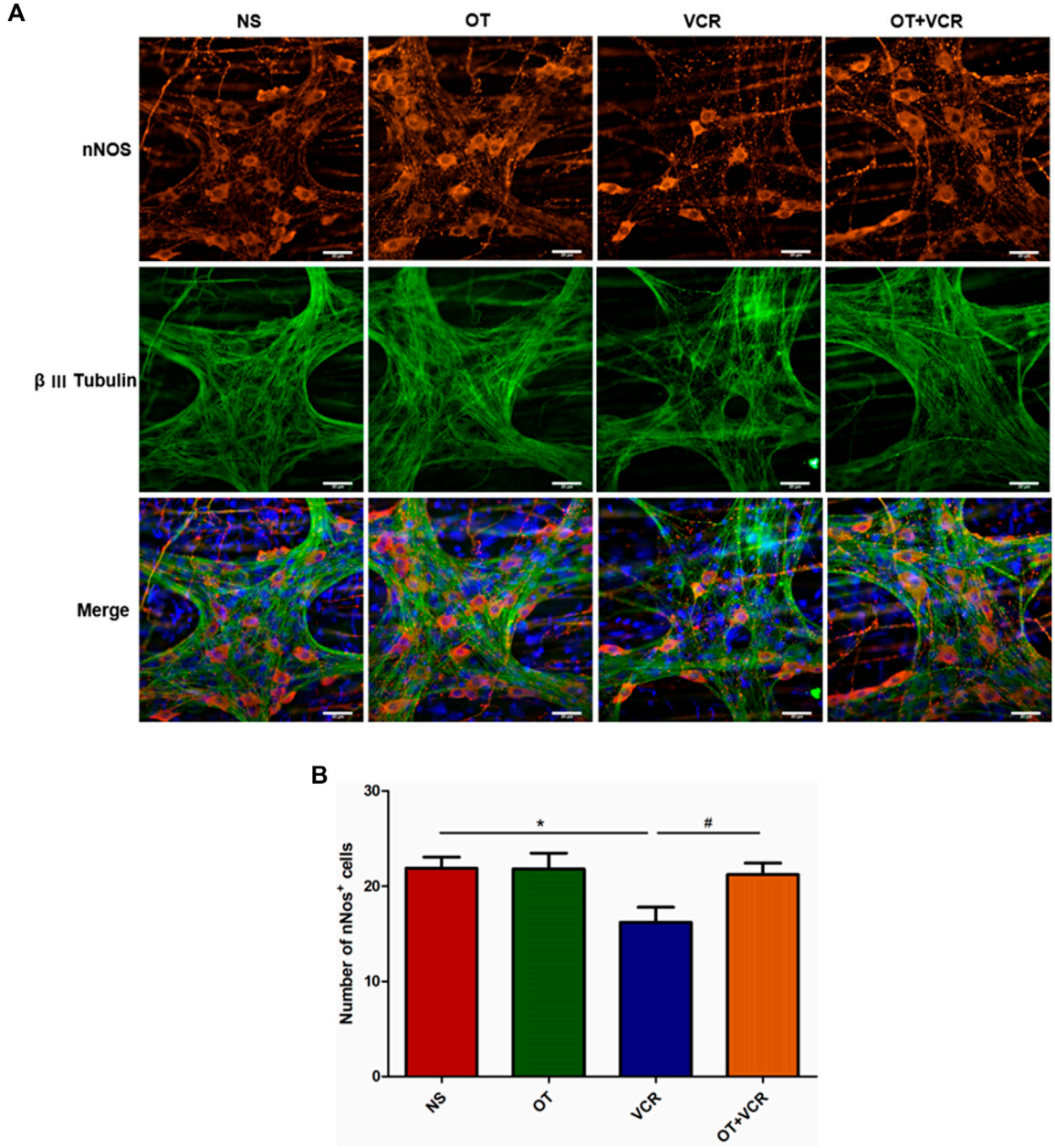


FIGURE 5
OT pretreatment increases the amounts of nNOS$^+$ neurons compared with VCR administration alone in the myenteric nerve plexus. **(A)** Typical photomicrograph of immunofluorescence staining for β III Tubulin (green) and nNOS (red) in colonic myenteric plexus. **(B)** Quantification of nNOS-immunopositive neurons (n = 5–7). Scale bars = 20 μm. The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^*p < 0.05$ *versus* the NS group; $^{\#}p < 0.05$ *versus* the VCR group.

inflammatory effect of OT might be physiological. Our previous study found that if the OTR on mononuclear macrophages was conditionally knocked out in mice, the intestinal inflammation induced by DSS was more severe (Tang et al., 2019); Kara Gross Margolis et al. also found that necrotizing enterocolitis was further aggravated after pretreatment with atosiban, an inhibitor of OTR (Gross Margolis et al., 2017). Therefore, as a neuropeptide, OT might exert endogenous inhibition on intestinal inflammation through the OT/OTR signaling system. Abnormal gastrointestinal motility is a known complication in VCR-treated patients (Tomomasa et al., 1999; Yasu et al., 2016; Adil et al., 2021). We found, for the first time, that the treatment of OT exerted a protective effect against VCR-induced gastrointestinal transit weakening. Endogenous OT might have a similar effect, as we found that the concentration of OT in plasma was significantly increased at 14 days following VCR treatment. We had previously reported that the elevated level of OT induced by D-mannose inhibited DSS-induced intestinal injury (Shi et al., 2021; Zhang et al., 2024). Therefore, we speculated that VCR treatment promoted the local synthesis and secretion of OT in the intestine, which in return might have an endogenous protective effect on VCR-induced intestinal transit weakening. This effect might be achieved through OTR.

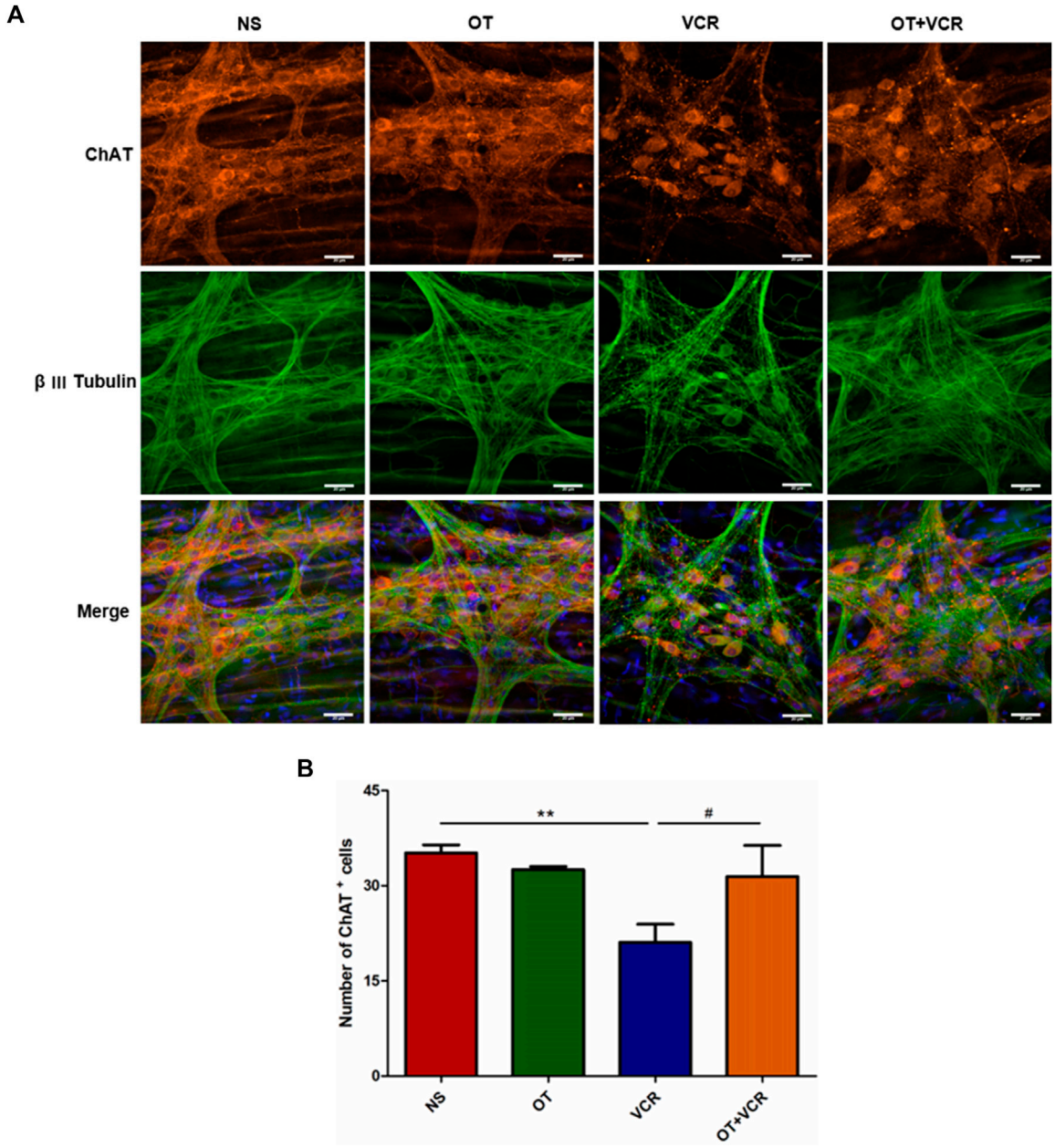


FIGURE 6
OT pretreatment increases the numbers of ChAT$^+$ neurons compared with VCR administration alone. **(A)** Typical photomicrograph of immunofluorescence staining for β III Tubulin (green) and ChAT (red) in myenteric plexus of the colon. **(B)** Quantification of ChAT-immunopositive neurons (n = 3–5). Scale bars = 20 μm. The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^{**}p < 0.01$ *versus* the NS group; $^{\#}p < 0.05$ *versus* the VCR group.

Patients undergoing chemotherapy with other drugs exhibited structural and functional changes in colonic myenteric neurons (Carbone et al., 2016). VCR also caused the alterations in the ENS (Lopez-Gomez et al., 2018; Gao et al., 2021). Therefore, we speculated that the protective effect of OT against VCR-induced intestinal transit abnormality might be related to the ENS. Immunofluorescence staining of the paraffin sections and MP of the colon showed that VCR reduced the amount of neurons in the myenteric nerve plexus, which was ameliorated by pretreatment with OT. Further studies found that OT also prevented VCR-induced loss of the number of nNOS-immunopositive and ChAT-immunopositive neurons. Based on these results, OT protected the myenteric neurons from VCR-induced damage. This might be the mechanism by which it improved intestinal transit.

The ENS plays a major part in regulating intestinal motility, among which the propulsion of chyme along the oral cavity to the anus is its physiological function. This propulsive movement is attributed to the innervation of the tissue and complex neural reflexes that contract the upstream intestinal muscles (the ascending excitatory reflex) and relax the downstream intestinal muscles (the descending inhibitory reflex), thereby facilitating the propulsive movement of digesta towards the

10.3389/fphar.2024.1270612

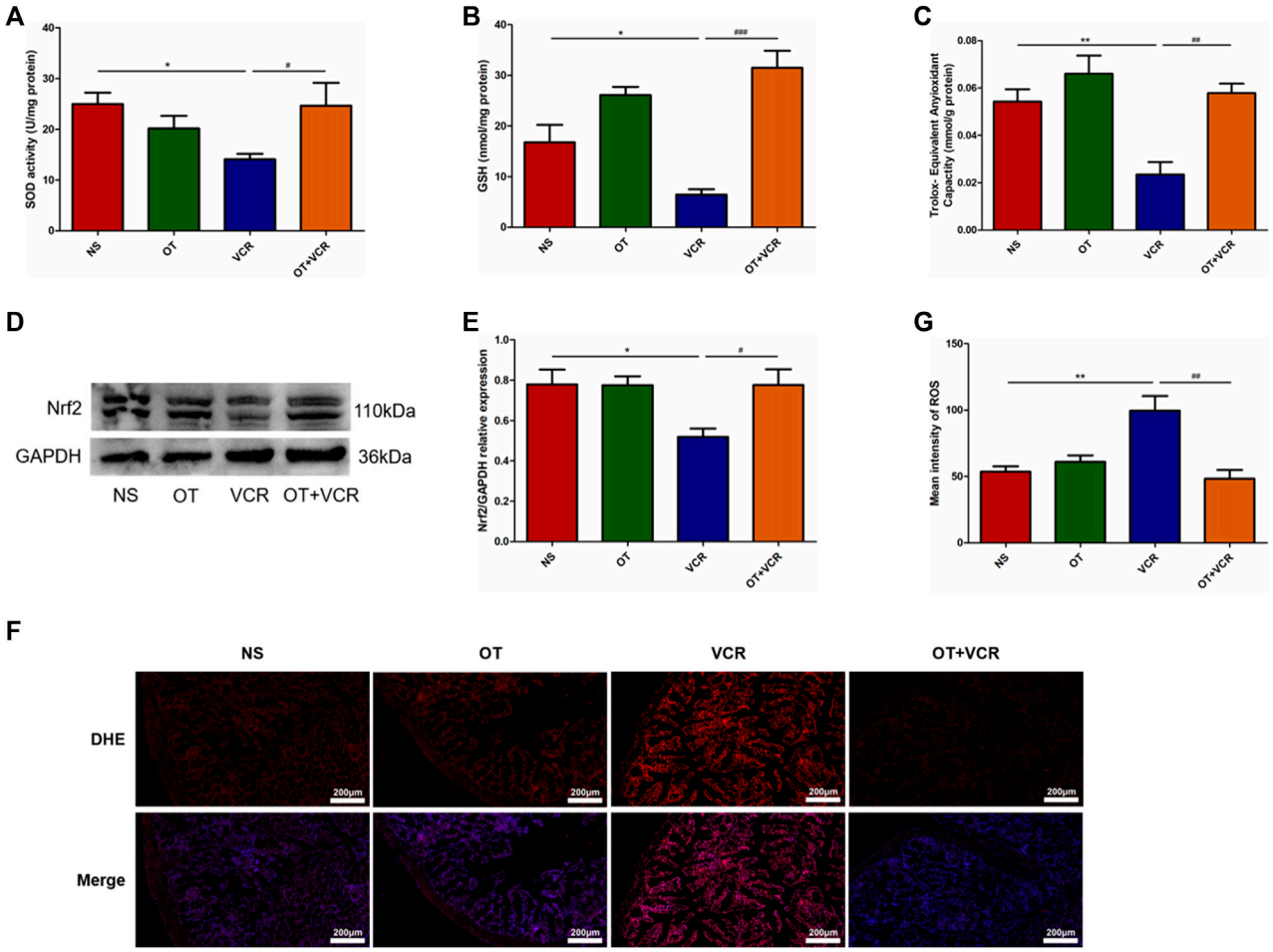


FIGURE 7
OT attenuates VCR-induced oxidative stress in mice. **(A–C)** Activity of SOD **(A)** and content of GSH **(B)** and T-AOC **(C)** in colon tissues are measured (n = 4–7). **(D)** Representative image of Nrf2 protein is detected by Western blot. **(E)** Quantification of Nrf2 relative expression levels (n = 4). **(F)** Representative image of immunofluorescence staining for DHE in colonic frozen sections. **(G)** Quantification of the mean fluorescence intensity of DHE, which represents for ROS levels (n = 3–4). Scale bars = 200 μm. The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^{*}p < 0.05$ and $^{**}p < 0.01$ *versus* the NS group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ *versus* the VCR group.

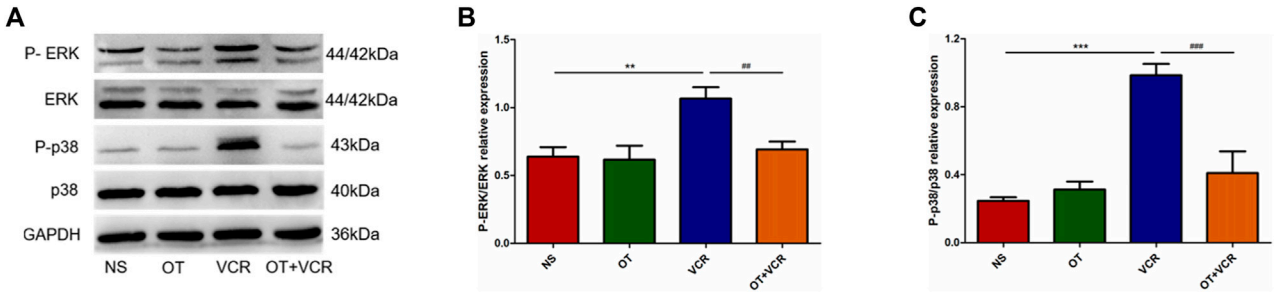


FIGURE 8
OT suppresses the VCR-induced activation of the ERK1/2 and p38 MAPK pathways. **(A)** Representative image of phosphorylated and total ERK1/2 and p38 protein tested using Western blot. **(B–C)** Quantification of phosphorylated ERK1/2 **(B)** and p38 **(C)** relative expression levels (n = 5). The data are expressed as the means ± SEM, and one-way ANOVA combined with the Newman–Keuls test is used to compare the differences among multiple groups. $^{**}p < 0.01$ and $^{***}p < 0.001$ *versus* the NS group; $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ *versus* the VCR group.

anus (Camilleri, 2021). Excitatory neurotransmitters such as ACh are involved in promoting the ascending excitatory reflex, while inhibitory neurotransmitters such as NO are involved in promoting the descending inhibitory reflex (Lecci et al., 2002). Immunofluorescence results showed that OT successfully prevented the loss of the number of nitrergic and cholinergic neurons caused by VCR. Those two types of neurons are responsible for EFS-induced relaxation and contraction responses, respectively (Moralioglu et al., 2017). In this study, we found that the responses of isolated colonic segments to EFS were attenuated after VCR treatment, suggesting that VCR might inhibit both the responses. Interestingly, OT pretreatment improved EFS-evoked responses and increased the number of $nNOS^+$ and $ChAT^+$ neurons, suggesting that OT might improve intestinal transit by alleviating VCR-induced neurogenic injuries. Unfortunately, we only examined the neurogenic responses but did not detect any myogenic responses (such as the response of the colonic segment to KCl of the expression of Ach receptors). The present results confirmed that neurogenic factors were involved in the protective effect of OT, but it did not rule out the involvement of myogenic factors. It had been found that VCR affected the response of the colon or the dimensions (Peixoto Júnior et al., 2009; Vera et al., 2017; Lopez-Gomez et al., 2018; López-Tofiño et al., 2023). OT receptors were expressed on smooth muscles cells (Qin et al., 2009), so OT might also exert a protective effect by directly acting on smooth muscles.

Lopez-Gomez L et al. found that VCR increased the proportion of nNOS-positive neurons (Lopez-Gomez et al., 2018). Our results might not contradict this, as an increase in the proportion of nNOS-positive neurons was accompanied by a decrease in their number (McQuade et al., 2016). Unfortunately, due to the defects of our methodology, the labeling of β III Tubulin antibody failed to well expose all neurons encapsulated by nerve fibers in MP preparation, so we could only count the nNOS immunoreactive neurons in the current method and could not calculate the proportion. Meanwhile, we also observed a decrease in EFS-induced relaxation such that the function of the nitrergic neurons in smooth muscle relaxation function was weakened. This weakening might be related to the disrupted gastrointestinal motility observed in the clinic.

VCR-induced neuropathy has been reported to be associated with oxidative stress. After nerve injury, antioxidant levels were reduced and ROS levels were increased in the sciatic nerve, spinal cord, and brain (Chen et al., 2020; Zhang and Xu, 2020; Khan et al., 2021). Oxidative stress contributes to the loss of myenteric neurons in individuals with chemotherapy-induced gastrointestinal dysfunction (McQuade et al., 2016). Therefore, we suggested that VCR also induced oxidative stress in the gut, which might be responsible for the reduction of myenteric neurons. We examined the expression of oxidative stress-related indicators in colon tissues and found that VCR reduced SOD activity, GSH content, T-AOC, and Nrf2 protein expression and increased ROS levels in the colon; thus, VCR might cause enteric nerve injury by inducing oxidative stress. The anti-tumor mechanism of VCR is through binding to tubulin, inhibiting microtubule function, arresting mitotic progression, and preventing cell division (Triarico et al., 2021). As an intense site of cell division, the intestinal mucosal epithelium may be one of the targets of VCR. It had been reported that the intestinal mucosal epithelium was damaged following VCR treatment. The number of necrotic cells increased, and metaphase mitotic arrest appeared in the intestinal crypts after VCR treatment, along with villus shortening and even mucosal erosion (Hobsonii et al., 1974; Beró and Jávor, 1985; Lopez-Gomez et al., 2018). These effects might disrupt the intestinal barrier function, facilitate the translocation of bacteria or toxins to intestine, and induce inflammation responses (Chelakkot et al., 2018). It was found that long-term VCR treatment led to inflammatory cells infiltration in intestinal lamina and submucosa (Beró and Jávor, 1985; Lopez-Gomez et al., 2018) and promoted the polarization of intestinal macrophages towards pro-inflammatory phenotype, which increased the release of inflammatory factors (Gao et al., 2021). It is well known that ROS production is increased during the inflammation response. So, it is possible that the VCR-induced increase of intestinal ROS might be caused by local inflammation. OT has been reported to inhibit inflammation and ROS production. It suppressed the elevation of ROS levels in H9c2 cardiomyocytes induced by ischemia–reperfusion (Gonzalez-Reyes et al., 2015), and it was involved in maintaining the intestinal epithelial barrier and restoring the intestinal epithelial injury induced by 5-FU, irradiation, and DSS (Welch et al., 2014; Chen et al., 2015). It alleviated necrotizing enterocolitis, TNBS- and DSS-induced colitis, and food allergy-induced intestinal inflammation and inhibited the expression of genes involved in oxidative stress response in the inflammatory intestine (Old et al., 2014; Welch et al., 2014; Gross Margolis et al., 2017; Tang et al., 2019; Dou et al., 2021; Yu et al., 2022). In this study, OT pretreatment reversed VCR-induced oxidative stress, manifested as the increase of SOD activity, GSH content, T-AOC, and Nrf2 protein expression and the decrease of ROS levels. This might result from the direct inhibition of intestinal ROS production by OT or the indirect reduction of ROS by alleviating intestinal epithelial damage and inflammation. Consequently, OT might exert a protective effect on VCR-induced myenteric neuron injury by ameliorating oxidative stress. Several chemical and natural compounds with antioxidant activity mitigated VCR-induced neuropathy, such as mitoquinone, a mitochondrial-targeted antioxidant, and curcumin, isolated from *Curcuma longa* (Babu et al., 2015; Chen et al., 2020). GSH had also attracted the interest of research scholars in different disciplines, for example, enzyme mechanisms, drug metabolism, radiation, and cancer, due to its multifunctional properties (Gul et al., 2000).

Previous results from our lab showed that VCR induced myenteric neuron injury by enhancing ERK1/2 and p38 MAPK phosphorylation to stimulate macrophage polarization to the pro-inflammatory phenotype, resulting in an increase in inflammatory cytokines (Gao et al., 2021). OT inhibited the LPS-induced activation of ERK1/2 and p38 MAPK in microglia (Yuan et al., 2016). OT inhibited the polarization of macrophages toward the pro-inflammatory phenotype, decreased the release of inflammatory factors, and alleviated intestinal inflammation (Tang et al., 2019). It was hinted that OT might improve VCR-induced myenteric neuron injury by inhibiting the activation of the ERK1/2 and p38 MAPK pathways. Western blot analysis showed that OT reduced the phosphorylation of ERK1/2 and p38 proteins caused by VCR, indicating that OT inhibited the VCR-induced activation of the ERK1/2 and p38 MAPK pathways. Inhibition of Ras and c-Raf1, which were the key elements in the activation of intracellular signal transduction pathways relating to the MAPK family, by

farnesyl thiosalicylic acid and GW5074 had been reported to attenuate VCR-induced neuropathy (Jaggi and Singh, 2012).

This paper documented a number of changes that accompanied VCR toxicity. Although OT pretreatment might ameliorate VCR-induced toxicity by inhibiting oxidative stress and MAPK pathways (ERK 1/2, p38), unfortunately, the detailed mechanism was not explored here.

In summary, OT can protect the enteric neurons against VCR-induced damage by inhibiting oxidative stress and the MAPK pathways (ERK 1/2, p38), which may be the underlying mechanism for relieving gastrointestinal dysmotility, but a more precise mechanism remains to be elucidated. Our study provides a basis for the search and development of drugs that may prevent or relieve the constipation or ileal injury caused by VCR, and potentially, OT will be used as a clinical treatment in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Ethics statement

The animal study was approved by the Medical Ethics Committee for Experimental Animals of Shandong University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SL: writing–original draft. YS: methodology, validation, and writing–review and editing. JZ: methodology and writing–review and editing. JL: supervision and writing–review and editing. SW: conceptualization and writing–review and editing. CL: writing–review and editing, conceptualization.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China [NSFC 32071127, 32371175].

Acknowledgments

The authors thank Shiyang Li for assisting in revising the manuscript, Yuanhao Cui for assisting in supplementary experiments, the animal medicine center of Shandong University for providing experimental animal feeding services and the Basic Medical Sciences of Shandong University for providing experimental facilities and basic materials.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1270612/full#supplementary-material

References

Adil, M. K., Ali, Z., Arshad, U., and Fawad, U. (2021). Vincristine induced neurotoxicity in children who underwent chemotherapy for acute lymphoblastic leukemia and Wilms tumor. *Pak J. Med. Sci.* 37 (5), 1331–1334. doi:10.12669/pjms.37.5.4169

Babu, A., Prasanth, K. G., and Balaji, B. (2015). Effect of curcumin in mice model of vincristine-induced neuropathy. *Pharm. Biol.* 53 (6), 838–848. doi:10.3109/13880209.2014.943247

Babygirija, R., Zheng, J., Ludwig, K., and Takahashi, T. (2010). Central oxytocin is involved in restoring impaired gastric motility following chronic repeated stress in mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298 (1), R157–R165. doi:10.1152/ajpregu.00328.2009

Beró, T., and Jávor, T. (1985). The effect of cyclophosphamide and vincristine on intestinal protein loss in rats. *Arch. Toxicol. Suppl.* 8, 117–121. doi:10.1007/978-3-642-69928-3_15

Blanks, A., Shmygol, A., and Thornton, S. (2007). Regulation of oxytocin receptors and oxytocin receptor signaling. *Seminars Reproductive Med.* 25 (1), 052–059. doi:10.1055/s-2006-956775

Camilleri, M. (2021). Gastrointestinal motility disorders in neurologic disease. *J. Clin. Investigation* 131 (4), e143771. doi:10.1172/JCI143771

Carbone, S. E., Jovanovska, V., Brookes, S. J., and Nurgali, K. (2016). Electrophysiological and morphological changes in colonic myenteric neurons from chemotherapy-treated patients: a pilot study. *Neurogastroenterol. Motil.* 28 (7), 975–984. doi:10.1111/nmo.12795

Chaudhary, S., Pothuraju, R., Rachagani, S., Siddiqui, J. A., Atri, P., Mallya, K., et al. (2021). Dual blockade of EGFR and CDK4/6 delays head and neck squamous cell carcinoma progression by inducing metabolic rewiring. *Cancer Lett.* 510, 79–92. doi:10.1016/j.canlet.2021.04.004

Chelakkot, C., Ghim, J., and Ryu, S. H. (2018). Mechanisms regulating intestinal barrier integrity and its pathological implications. *Exp. Mol. Med.* 50 (8), 103–109. doi:10.1038/s12276-018-0126-x

Chen, D., Zhao, J., Wang, H., An, N., Zhou, Y., Fan, J., et al. (2015). Oxytocin evokes a pulsatile PGE2 release from ileum mucosa and is required for repair of intestinal epithelium after injury. *Sci. Rep.* 5, 11731. doi:10.1038/srep11731

Chen, X. J., Wang, L., and Song, X. Y. (2020). Mitoquinone alleviates vincristine-induced neuropathic pain through inhibiting oxidative stress and apoptosis via the improvement of mitochondrial dysfunction. *Biomed. Pharmacother.* 125, 110003. doi:10.1016/j.biopha.2020.110003

Dorchin, M., Masoumi Dehshiri, R., Soleiman, S., and Manashi, M. (2013). Evaluation of neuropathy during intensive vincristine chemotherapy for non-Hodgkin's

lymphoma and Acute Lymphoblastic Leukemia. *Iran. J. Ped Hematol. Oncol.* 3 (4), 138–142.

Dou, D., Liang, J., Zhai, X., Li, G., Wang, H., Han, L., et al. (2021). Oxytocin signalling in dendritic cells regulates immune tolerance in the intestine and alleviates DSS-induced colitis. *Clin. Sci.* 135 (4), 597–611. doi:10.1042/CS20201438

Erdogan, M. A., Taskiran, E., Yigitturk, G., Erbas, O., and Taskiran, D. (2020). The investigation of therapeutic potential of oxytocin and liraglutide on vincristine-induced neuropathy in rats. *J. Biochem. Mol. Toxicol.* 34 (1), e22415. doi:10.1002/jbt.22415

Escalante, J., McQuade, R. M., Stojanovska, V., and Nurgali, K. (2017). Impact of chemotherapy on gastrointestinal functions and the enteric nervous system. *Maturitas* 105, 23–29. doi:10.1016/j.maturitas.2017.04.021

Feng, M., Qin, J., Wang, C., Ye, Y., Wang, S., Xie, D., et al. (2009). Estradiol upregulates the expression of oxytocin receptor in colon in rats. *Am. J. Physiol. Endocrinol. Metab.* 296 (5), E1059–E1066. doi:10.1152/ajpendo.90609.2008

Fumagalli, G., Monza, L., Cavaletti, G., Rigolio, R., and Meregalli, C. (2020). Neuroinflammatory process involved in different preclinical models of chemotherapy-induced peripheral neuropathy. *Front. Immunol.* 11, 626687. doi:10.3389/fimmu.2020.626687

Furness, J. B. (2000). Types of neurons in the enteric nervous system. *J. Auton. Nerv. Syst.* 81 (1-3), 87–96. doi:10.1016/s0165-1838(00)00127-2

Furness, J. B., Callaghan, B. P., Rivera, L. R., and Cho, H. J. (2014). The enteric nervous system and gastrointestinal innervation: integrated local and central control. *Adv. Exp. Med. Biol.* 817, 39–71. doi:10.1007/978-1-4939-0897-4_3

Gao, Y., Tang, Y., Zhang, H., Chu, X., Yan, B., Li, J., et al. (2021). Vincristine leads to colonic myenteric neurons injury via pro-inflammatory macrophages activation. *Biochem. Pharmacol.* 186, 114479. doi:10.1016/j.bcp.2021.114479

Gonzalez-Reyes, A., Menaouar, A., Yip, D., Danalache, B., Plante, E., Noiseux, N., et al. (2015). Molecular mechanisms underlying oxytocin-induced cardiomyocyte protection from simulated ischemia–reperfusion. *Mol. Cell. Endocrinol.* 412, 170–181. doi:10.1016/j.mce.2015.04.028

Gross Margolis, K., Vittorio, J., Talavera, M., Gluck, K., Li, Z., Iuga, A., et al. (2017). Enteric serotonin and oxytocin: endogenous regulation of severity in a murine model of necrotizing enterocolitis. *Am. J. Physiology-Gastrointestinal Liver Physiology* 313 (5), G386–G98. doi:10.1152/ajpgi.00215.2017

Gul, M., Kutay, F. Z., Temocin, S., and Hanninen, O. (2000). Cellular and clinical implications of glutathione. *Indian J. Exp. Biol.* 38 (7), 625–634.

Hobsonii, R. W., Jervis, H. R., Kingry, R. L., and Wallace, J. R. (1974). Small bowel changes associated with vincristine sulfate treatment: an experimental study in the Guinea pig. *Cancer* 34 (6), 1888–1896. doi:10.1002/1097-0142(197412)34:6<1888::aid-cncr2820340606>3.0.co;2-5

Hollenberg, M. D. (2021). Oxytocin: much more than childbirth and milk letdown. *Clin. Sci. (Lond).* 135 (17), 2121–2126. doi:10.1042/CS20210180

Jaggi, A. S., and Singh, N. (2012). Analgesic potential of intrathecal farnesyl thiosalicylic acid and GW 5074 in vincristine-induced neuropathic pain in rats. *Food Chem. Toxicol.* 50 (5), 1295–1301. doi:10.1016/j.fct.2012.01.038

Jurek, B., and Neumann, I. D. (2018). The oxytocin receptor: from intracellular signaling to behavior. *Physiol. Rev.* 98 (3), 1805–1908. doi:10.1152/physrev.00031.2017

Khan, A., Shal, B., Khan, A. U., Ullah, R., Baig, M. W., Ul Haq, I., et al. (2021). Suppression of TRPV1/TRPM8/P2Y nociceptors by withametelin via downregulating MAPK signaling in mouse model of vincristine-induced neuropathic pain. *Int. J. Mol. Sci.* 22 (11), 6084. doi:10.3390/ijms22116084

Lan, T., Li, Y., Fan, C., Wang, L., Wang, W., Chen, S., et al. (2021). MicroRNA-204-5p reduction in rat hippocampus contributes to stress-induced pathology via targeting RGS12 signaling pathway. *J. Neuroinflammation* 18 (1), 243. doi:10.1186/s12974-021-02299-5

Lecci, A., Santicioli, P., and Maggi, C. A. (2002). Pharmacology of transmission to gastrointestinal muscle. *Curr. Opin. Pharmacol.* 2 (6), 630–641. doi:10.1016/s1471-4892(02)00225-4

Legha, S. S. (1986). Vincristine neurotoxicity. Pathophysiology and management. *Med. Toxicol.* 1 (6), 421–427. doi:10.1007/BF03259853

Li, L., Kong, X., Liu, H., and Liu, C. (2007). Systemic oxytocin and vasopressin excite gastrointestinal motility through oxytocin receptor in rabbits. *Neurogastroenterol. Motil.* 19 (10), 839–844. doi:10.1111/j.1365-2982.2007.00953.x

Lin, Y., Xie, Y., Hao, Z., Bi, H., Liu, Y., Yang, X., et al. (2021). Protective effect of uric acid on ox-LDL-induced HUVECs injury via keap1-nrf2-ARE pathway. *J. Immunol. Res.* 2021, 5151168–5151219. doi:10.1155/2021/5151168

Litovchick, L. (2020). Stripping of the immunoblot for reprobing. *Cold Spring Harb. Protoc.* 2020 (3), 098491. doi:10.1101/pdb.prot098491

Lopez-Gomez, L., Diaz-Ruano, S., Giron, R., Lopez-Perez, A. E., Vera, G., Herradon Pliego, E., et al. (2018). Preclinical evaluation of the effects on the gastrointestinal tract of the antineoplastic drug vincristine repeatedly administered to rats. *Neurogastroenterol. Motil.* 30 (11), e13399. doi:10.1111/nmo.13399

López-Tofiño, Y., Barragán del Caz, L. F., Benítez-Álvarez, D., Molero-Mateo, P., Nurgali, K., Vera, G., et al. (2023). Contractility of isolated colonic smooth muscle strips from rats treated with cancer chemotherapy: differential effects of cisplatin and vincristine. *Front. Neurosci.* 17, 17. doi:10.3389/fnins.2023.1304609

McQuade, R. M., Carbone, S. E., Stojanovska, V., Rahman, A., Gwynne, R. M., Robinson, A. M., et al. (2016). Role of oxidative stress in oxaliplatin-induced enteric neuropathy and colonic dysmotility in mice. *Br. J. Pharmacol.* 173 (24), 3502–3521. doi:10.1111/bph.13646

Monstein, H. J., Grahn, N., Truedsson, M., and Ohlsson, B. (2004). Oxytocin and oxytocin-receptor mRNA expression in the human gastrointestinal tract: a polymerase chain reaction study. *Regul. Pept.* 119 (1-2), 39–44. doi:10.1016/j.regpep.2003.12.017

Moralioglu, S., Vural, I. M., Ozen, I. O., Ozturk, G., Sarioglu, Y., and Basaklar, A. C. (2017). Changes in cholinergic and nitrergic systems of defunctionalized colons after colostomy in rabbits. *J. Surg. Res.* 207, 63–69. doi:10.1016/j.jss.2016.08.032

Moudi, M., Go, R., Yien, C. Y., and Nazre, M. (2013). Vinca alkaloids. *Int. J. Prev. Med.* 4 (11), 1231–1235.

Ohlsson, B., Ringström, G., Abrahamsson, H., Simrén, M., and Björnsson, E. S. (2004). Oxytocin stimulates colonic motor activity in healthy women. *Neurogastroenterol. Motil.* 16 (2), 233–240. doi:10.1111/j.1365-2982.2004.00507.x

Ohlsson, B., Truedsson, M., Djerf, P., and Sundler, F. (2006). Oxytocin is expressed throughout the human gastrointestinal tract. *Regul. Pept.* 135 (1-2), 7–11. doi:10.1016/j.regpep.2006.03.008

Old, E. A., Nadkarni, S., Grist, J., Gentry, C., Bevan, S., Kim, K.-W., et al. (2014). Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. *J. Clin. Investigation* 124 (5), 2023–2036. doi:10.1172/JCI71389

Peixoto Júnior, A. A., Teles, B. C., Castro, E. F., Santos, A. A., de Oliveira, G. R., Ribeiro, R. A., et al. (2009). Vincristine delays gastric emptying and gastrointestinal transit of liquid in awake rats. *Braz J. Med. Biol. Res.* 42 (6), 567–573. doi:10.1590/s0100-879x2009000600015

Qin, J., Feng, M., Wang, C., Ye, Y., Wang, P. S., and Liu, C. (2009). Oxytocin receptor expressed on the smooth muscle mediates the excitatory effect of oxytocin on gastric motility in rats. *Neurogastroenterol. Motil.* 21 (4), 430–438. doi:10.1111/j.1365-2982.2009.01282.x

Rashed, L. A., Hashem, R. M., and Soliman, H. M. (2011). Oxytocin inhibits NADPH oxidase and P38 MAPK in cisplatin-induced nephrotoxicity. *Biomed. Pharmacother.* 65 (7), 474–480. doi:10.1016/j.biopha.2011.07.001

Sharma, R. K. (1988). Vincristine and gastrointestinal transit. *Gastroenterology* 95 (5), 1435–1436. doi:10.1016/0016-5085(88)90404-0

Shen, Y., Zhang, Z. J., Zhu, M. D., Jiang, B. C., Yang, T., and Gao, Y. J. (2015). Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. *Neurobiol. Dis.* 79, 100–110. doi:10.1016/j.nbd.2015.04.012

Shi, Y., Li, S., Zhang, H., Zhu, J., Che, T., Yan, B., et al. (2021). The effect of macrophage polarization on the expression of the oxytocin signalling system in enteric neurons. *J. Neuroinflammation* 18 (1), 261. doi:10.1186/s12974-021-02313-w

Smith, A. S., Korgan, A. C., and Young, W. S. (2019). Oxytocin delivered nasally or intraperitoneally reaches the brain and plasma of normal and oxytocin knockout mice. *Pharmacol. Res.*, 146. doi:10.1016/j.phrs.2019.104324

Smith, B. (1967). The myenteric plexus in drug-induced neuropathy. *J. Neurol. Neurosurg. Psychiatry* 30 (6), 506–510. doi:10.1136/jnnp.30.6.506

Sninsky, C. A. (1987). Vincristine alters myoelectric activity and transit of the small intestine in rats. *Gastroenterology* 92 (2), 472–478. doi:10.1016/0016-5085(87)90144-2

Soloff, M. S., Alexandrova, M., and Fernstrom, M. J. (1979). Oxytocin receptors: triggers for parturition and lactation? *Science* 204 (4399), 1313–1315. doi:10.1126/science.221972

Spencer, N. J., and Hu, H. (2020). Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. *Nat. Rev. Gastroenterol. Hepatol.* 17 (6), 338–351. doi:10.1038/s41575-020-0271-2

Takahashi, T. (2003). Pathophysiological significance of neuronal nitric oxide synthase in the gastrointestinal tract. *J. Gastroenterol.* 38 (5), 421–430. doi:10.1007/s00535-003-1094-y

Tang, Y., Shi, Y., Gao, Y., Xu, X., Han, T., Li, J., et al. (2019). Oxytocin system alleviates intestinal inflammation by regulating macrophages polarization in experimental colitis. *Clin. Sci. (Lond).* 133 (18), 1977–1992. doi:10.1042/CS20190756

Tay, N., Laakso, E. L., Schweitzer, D., Endersby, R., Vetter, I., and Starobova, H. (2022). Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. *Front. Mol. Biosci.* 9, 1015746. doi:10.3389/fmolb.2022.1015746

Tomomasa, T., Miyazawa, R., Kato, M., Hoshino, M., Tabata, M., Kaneko, H., et al. (1999). Prolonged gastrointestinal dysmotility in a patient with hemophagocytic lymphohistiocytosis treated with vincristine. *Dig. Dis. Sci.* 44 (9), 1755–1757. doi:10.1023/a:1018865916866

Triarico, S., Romano, A., Attina, G., Capozza, M. A., Maurizi, P., Mastrangelo, S., et al. (2021). Vincristine-induced peripheral neuropathy (VIPN) in pediatric tumors: mechanisms, risk factors, strategies of prevention and treatment. *Int. J. Mol. Sci.* 22 (8), 4112. doi:10.3390/ijms22084112

van de Velde, M. E., van den Berg, M. H., Kaspers, G. J. L., Abbink, F. C. H., Twisk, J. W. R., van der Sluis, I. M., et al. (2021). The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. *Cancer Med.* 10 (22), 8172–8181. doi:10.1002/cam4.4289

Vera, G., Lopez-Perez, A. E., Uranga, J. A., Giron, R., Martin-Fontelles, M. I., and Abalo, R. (2017). Involvement of cannabinoid signaling in vincristine-induced gastrointestinal dysmotility in the rat. *Front. Pharmacol.* 8, 37. doi:10.3389/fphar.2017.00037

Welch, M. G., Margolis, K. G., Li, Z., and Gershon, M. D. (2014). Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* 307 (8), G848–G862. doi:10.1152/ajpgi.00176.2014

Welch, M. G., Tamir, H., Gross, K. J., Chen, J., Anwar, M., and Gershon, M. D. (2008). Expression and developmental regulation of oxytocin (OT) and oxytocin receptors (OTR) in the enteric nervous system (ENS) and intestinal epithelium. *J. Comp. Neurology* 512 (2), 256–270. doi:10.1002/cne.21872

Xie, D. P., Yang, X., Cao, C. Y., Wang, H. H., Li, Y. X., Qin, Y., et al. (2011). Exogenous oxytocin reverses the decrease of colonic smooth muscle contraction in antenatal maternal hypoxia mice via ganglia. *Regul. Pept.* 172 (1-3), 30–34. doi:10.1016/j.regpep.2011.08.003

Yang, Y., Yu, H., Babygirija, R., Shi, B., Sun, W., Zheng, X., et al. (2019). Intranasal administration of oxytocin attenuates stress responses following chronic complicated stress in rats. *J. Neurogastroenterol. Motil.* 25 (4), 611–622. doi:10.5056/jnm19065

Yasu, T., Ohno, N., Kawamata, T., and Kurokawa, Y. (2016). Vincristine-induced paralytic ileus during induction therapy of treatment protocols for acute lymphoblastic leukemia in adult patients. *Int. J. Clin. Pharmacol. Ther.* 54 (6), 471–473. doi:10.5414/CP202584

Yu, Y., Li, J., and Liu, C. (2022). Oxytocin suppresses epithelial cell-derived cytokines production and alleviates intestinal inflammation in food allergy. *Biochem. Pharmacol.*, 195. doi:10.1016/j.bcp.2021.114867

Yuan, L., Liu, S., Bai, X., Gao, Y., Liu, G., Wang, X., et al. (2016). Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. *J. Neuroinflammation* 13 (1), 77. doi:10.1186/s12974-016-0541-7

Zhang, H., Zhao, X., Gao, Y., Shi, Y., Wei, L., Li, J., et al. (2024). d-Mannose promotes recovery from experimental colitis by inducing AMPK phosphorylation to stimulate epithelial repair. *Food and Funct.* 15, 625–646. doi:10.1039/d3fo03146b

Zhang, K., and Xu, Y. (2020). Suppressing BRD4 exhibits protective effects against vincristine-induced peripheral neuropathy by alleviating inflammation and oxidative stress. *Biochem. Biophysical Res. Commun.* 532 (2), 271–279. doi:10.1016/j.bbrc.2020.06.142

Zhu, J., Li, Y., Liang, J., Li, J., Huang, K., Li, J., et al. (2021). The neuroprotective effect of oxytocin on vincristine-induced neurotoxicity in mice. *Toxicol. Lett.* 340, 67–76. doi:10.1016/j.toxlet.2021.01.008

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 29 April 2024
DOI 10.3389/fphar.2024.1382924

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Mona, Jamaica

REVIEWED BY
Zoran Todorovic,
University of Belgrade, Serbia
Francesco Di Giacomo Barbagallo,
University of Catania, Italy
Mia Manojlovic,
University of Novi Sad, Serbia

*CORRESPONDENCE
Weizhen He,
hwzmail@yeah.net

RECEIVED 06 February 2024
ACCEPTED 27 March 2024
PUBLISHED 29 April 2024

CITATION
Chen K, Huang H, Chen Y and He W (2024), Association between atorvastatin and erectile dysfunction: a comprehensive analysis incorporating real-world pharmacovigilance and Mendelian randomization.
Front. Pharmacol. 15:1382924.
doi: 10.3389/fphar.2024.1382924

Association between atorvastatin and erectile dysfunction: a comprehensive analysis incorporating real-world pharmacovigilance and Mendelian randomization

Kaiqin Chen[1], Hesen Huang[2], Yongtai Chen[3] and Weizhen He[1]*

[1]Department of Neurosurgery, Xiang'an Hospital of Xiamen University, Xia Men, Fu Jian, China, [2]Department of Otolaryngology-Head and Neck Surgery, Xiang'an Hospital of Xiamen University, Xia Men, Fu Jian, China, [3]Department of Hepatobiliary Surgery, The Affiliated Longyan First Hospital of Fujian Medical University, Longyan, Fujian, China

Background: Atorvastatin is a commonly prescribed medication for the prevention of cardiovascular diseases. Recent observational studies have suggested a potential association between atorvastatin use and the occurrence of Erectile Dysfunction (ED). In this study, we aimed to explore the relationship between atorvastatin and ED using real-world data from the FAERS database and employed Mendelian randomization to assess causality.

Methods: To evaluate the disproportionality of atorvastatin in relation to ED, we conducted several pharmacovigilance analyses, including odds ratio (ROR), proportional reporting ratio (PRR), Bayesian Confidence propagation neural network (BCPNN), and gamma-Poisson contractile apparatus (GPS). Additionally, we employed Mendelian randomization to investigate the causal relationship between atorvastatin and ED.

Results: Pharmacovigilance disproportionality analysis revealed a significant association between atorvastatin and ED, as indicated by the following results: ROR [3.707078559, 95% CI (3.33250349, 4.123756054)], PRR [3.702969038, $\chi 2$ (669.2853829)], IC [1.870490139, IC025 (1.702813857)], and EBGM [3.656567867, EBGM05 (3.28709656)]. Furthermore, the two-sample Mendelian randomization analysis provided evidence supporting a causal relationship between atorvastatin use and ED, with an inverse variance weighted estimate of $\beta = 3.17$ (OR = 23.91, $p = 0.02 < 0.05$).

Conclusion: Based on comprehensive analyses incorporating pharmacovigilance and Mendelian randomization, our findings suggest that atorvastatin use is associated with an increased risk of ED and indicate a causal relationship. These results emphasize the importance of considering potential adverse effects, such as ED, when prescribing atorvastatin for cardiovascular

disease prevention. Further research and clinical monitoring are warranted to better understand the underlying mechanisms and develop appropriate strategies to mitigate this side effect.

KEYWORDS

atorvastatin, erectile dysfunction, real-world data analysis, adverse drug reaction, Mendelian randomization

1 Introduction

Atorvastatin, through 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition, not only lower LDL-C levels but also demonstrate pleiotropic effects like anti-inflammatory activity, endothelial function improvement, and reduction of atherosclerosis, essential in treating atherosclerotic cardiovascular diseases (ASCVDs) by interrupting inflammation within plaques and suppressing inflammatory mediator secretion (Takata et al., 2016). Consequently, it effectively lowers lipid levels within the body (Winkler et al., 2004). Despite the widespread use of statins for their efficacy in managing cholesterol production, there are lingering concerns regarding their potential side effects. A study involving eight patients prescribed various statins (simvastatin, fluvastatin, pravastatin, and atorvastatin) revealed a decrease in libido during treatment. Further examination of 2 patients assessed the patients' sex hormone levels, showing a significant reduction in testosterone levels (de Graaf et al., 2004). Zekeriya's study on the effects of rosuvastatin and atorvastatin on erectile dysfunction in hypercholesterolemic patients found that rosuvastatin had no impact on erectile dysfunction, while atorvastatin was shown to worsen erectile dysfunction (Nurkalem et al., 2014). Therefore, the effect of statins on sexual function raises concerns.

Apart from reducing lipids, atorvastatin has been observed to hinder the growth and movement of vascular smooth muscle cells, while also encouraging apoptosis. Furthermore, it improves blood rheology and viscosity, thereby enhancing cardiac, vascular endothelial, and coagulation functions (Beltrán Romero et al., 2021). Due to the fact that elevated levels of low-density lipoprotein cholesterol (LDL-C) pose an independent risk for cardiovascular disease, decreasing LDL-C levels has been connected with a lower likelihood of experiencing significant cardiovascular events (Gencer et al., 2020). Multiple research investigations have shown that aggressive methods to lower lipid levels can markedly diminish the expected risk of atherosclerotic cardiovascular disease over a span of 30 years (Pencina et al., 2020).

The European Society of Cardiology/European Atherosclerosis Society guidelines suggest that despite already low LDL-C levels, reducing LDL-C can effectively decrease cardiovascular disease (CVD) risk. The extent of risk reduction in CVD is directly linked to the extent of LDL-C level changes. The actual benefits of lowering LDL-C depend on the individual's ASCVD risk profile and the absolute reduction in LDL-C levels. Therefore, even a slight decrease in LDL-C could be beneficial for individuals at high or very high cardiovascular risk (Visseren et al., 2022). Accordingly, atorvastatin assumes a crucial role in the prevention and management of cardiovascular and cerebrovascular diseases, emerging as a cornerstone in therapeutic strategies for these clinical contexts.

Erectile dysfunction (ED) is a common issue impacting considerable portion of men globally, leading to significant distress and affecting their general wellbeing. It is defined by the persistent challenge in attaining or sustaining an erection suitable for satisfactory sexual activity. The development of ED is influenced by a range of factors, encompassing physiological, psychological, and lifestyle-related elements (Salonia et al., 2021).

However, concerns have arisen regarding the potential impact of atorvastatin on sexual function, particularly its association with ED. Some clinical observations suggested a possible link between atorvastatin and the development or exacerbation of ED symptoms (Rizvi et al., 2002; Do et al., 2009). These reports have raised questions about the mechanisms through which atorvastatin may affect erectile function, prompting further investigation into this potential relationship.

Understanding the potential relationship between atorvastatin and ED is of great clinical importance. As atorvastatin is widely prescribed and often used long-term, it is crucial to assess its impact on sexual function to ensure comprehensive patient care. Furthermore, identifying any association between atorvastatin and ED can guide healthcare professionals in managing patients who experience sexual dysfunction while on this medication.

Adverse events (AE) frequently occur with drug use, although they cannot always be directly attributed to the drug. However, a large-scale statistical, biological, and clinical analysis of AEs may reveal related causes and effects, known as ADRs (Shu et al., 2022). To facilitate this, the United States established the FDA Adverse Event Reporting System (FAERS) database in 2012. The FAERS database documents a large number of AEs and medication errors associated with human drugs and therapeutic biologics. Such research can explore ADRs and provide evidence for subsequent safe drug use.

Due to the nature of ADRs, causal reasoning is challenging. However, Nevertheless, Mendelian randomization (MR) analysis offers a way to address the constraints of conventional observational studies. MR utilizes information on genetic variations to infer causation between exposure and outcome, assessing whether an observational association is consistent with a causal effect (Walker et al., 2017). It is based on the principles of random gamete division and genetic variation, simulating the random assignment of research subjects (Levin and Burgess, 2024). Due to the challenges in determining an appropriate experimental methodology, there is a lack of studies investigating a direct causal relationship between atorvastatin and ED. Therefore, this study combines the advantages of pharmacovigilance analysis and MR analysis to explore the relationship between atorvastatin and ED.

2 Materials and methods

2.1 Data sources

Pharmacovigilance disproportional analysis data was pulled from the openly accessible FAERS database. The data extracted in this study covered all data in ASCII packets from Q1 2004–Q1 2023 (77 quarters), which were cleaned and analysed using SAS software version 9.4 (Yavne et al., 2023).

Treatment/medication code: atorvastatin data was pulled from The UK Biobank database. The dataset contained ncase: 13,851; ncontrol: 449,082, and was collected in 2018 (Sudlow et al., 2015). Erectile dysfunction data was also pulled from the EBI database (http://www.ebi.ac.uk/). The dataset contained ncase:6,175; ncontrol: 217,630, collected in 2018 (Bovijn et al., 2019). LDL-C data was pulled from the development GAWS IEU database (https://gwas.mrcieu.ac.uk/). The sample size was 173,082, and the data had been collected since 2013 (Dataset: ieu-a-300) (Willer et al., 2013).

2.2 Data processing

According to the FDA's recommended method for removing duplicate reports, select the PRIMARY-ID, CASE-ID, and FDA_DT fields from the DEMO table. Sort the data based on CASE-ID, FDA_DT, and PRIMARY-ID. For reports with the same CASE-ID, keep the one with the highest FDA_DT value. If the CASE-ID and FDA_DT are the same, keep the one with the highest PRIMARY-ID value.

Since the first quarter of 2019, each quarterly data package contains a list of reports to be removed. After deduplicating the data, remove the reports based on the CASEID in the deletion report list.

In the FAERS database, adverse reaction names are recorded using the Preferred Term (PT) terminology from the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA dictionary is updated in March and September each year, which may involve adjustments in the PT hierarchy and changes in the System Organ Class (SOC). Therefore, it is necessary to use the latest version of the MedDRA dictionary to correct the PT names in the FAERS database and obtain the updated SOC and PT from the latest version of the MedDRA dictionary.

2.3 Data analysis

2.3.1 Pharmacovigilance disproportionality analysis

Pharmacovigilance disproportionality analysis was conducted to explore the potential association between atorvastatin and ADRs using descriptive statistics. In our investigative study, we utilized this approach to identify any signals of disproportionality between atorvastatin and ADR. Four primary methods, namely, reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), were employed to assess the relationship between atorvastatin and ADR (Bate et al., 1998; van Puijenbroek et al., 2002; Rothman et al., 2004; Shu et al., 2022). These methods are commonly used in pharmacovigilance studies to evaluate the potential association between a drug and AEs.This method is further detailed below.

I. ROR method:

$$\mathrm{ROR} = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$$

$$\mathrm{SE}(\ln\mathrm{ROR}) = \sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}$$

$$95\%\mathrm{CI} = e^{\ln(\mathrm{ROR})\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

The criteria for positive signals: a≥3, 95% confidence interval (CI; the lower limit) > 1

II. PRR method:

$$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$$

$$\chi^2 = \frac{\left(|ad-bc| - \frac{a+b+c+d}{2}\right)^2 (a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$$

III. BCPNN method:

$$\mathrm{IC} = log_2\frac{p(x,y)}{p(x)p(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$$

$$\mathrm{E}(\mathrm{IC}) = log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$$

$$\mathrm{V}(\mathrm{IC}) = \frac{1}{(ln\,2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right] + \left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right] + \left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\right\}$$

$$\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$$

$$IC\text{–}2SD = E(IC)\text{–}2\sqrt{V(\mathrm{IC})}$$

$$\alpha 1 = \beta 1 = 1; \alpha = \beta = 2; \gamma 11 = 1$$

The criteria for positive signals:

1) (−): IC–2SD ≤ 0;
2) (+):0<IC–2SD ≤ 1.5;
3) (++): 1.5<IC–2SD ≤ 3;
4) (+++):IC–2SD > 3.

IV. MGPS method:

$$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$$

$$95\%\mathrm{CI} = e^{\ln(\mathrm{EBGM})\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

Criteria for positive signals: EBGM05 > 2.

The meanings of a,b,c and d can be seen in Table 1.

2.3.2 Mendelian randomisation study

According to MR theory, Instrumental variables (IVs) need to meet the following three assumptions:

TABLE 1 2 x 2 matrix.

	Target ADR	Non-target ADR	Total
Atorvastatin	a	b	a+b
Non-atorvastatin	c	d	c+d
Total	a+c	b+d	n=a+b+c+d

1) a, Frequency of target adverse reactions for the target drug population.
2) b, Total adverse reactions occurred in the target drug population.
3) c, Total number of target adverse reactions.
4) d, Total number of adverse reactions occurring in the background population.

The IVs must be strongly correlated with the exposure (correlation hypothesis).

The IVs should be independent of confounding factors that affect the exposure-outcome relationship (independence hypothesis).

The IVs can only influence the occurrence of the outcome through the exposure factors and not through any other means (exclusivity hypothesis).

For the MR data analysis, we utilized the "TwoSampleMR" package in the R. The inverse-weighted variance analysis was used to determine the causal relationship between the exposure factors and the outcome (Chen et al., 2020; Zagkos et al., 2022; Wang et al., 2023). To assess heterogeneity among the study samples, MR-Egger and inverse variance-weighted functions in Cochran's Q test were utilized, with a significance level of p >0.05 indicating non-heterogeneity. The pleiotropy was analyzed using the "mr_pleiotropy_test" function from the R package of the same name, with a significance level of p >0.05 indicatingabsence of horizontal pleiotropy.

3 Results

3.1 Descriptive results of pharmacovigilance analysis

The signal detection analysis of atorvastatin at the SOC level is presented in Table 2, revealing a comprehensive overview of its AEs. The results demonstrate that atorvastatin-related AEs are widespread, affecting a total of 27 organ systems, thus indicating their relatively common occurrence. Notably, the highest number of reported AEs were Musculoskeletal and Connective Tissue Disorders (n = 38,478), followed by General Disorders and Administration Site Conditions (n = 29,960), Investigations (n = 21,934), Nervous System Disorders (n = 20,761), and Metabolism and Nutrition Disorders (n = 15,099). These findings are consistent with the clinical observations encountered in our practice. Additionally, within the categories of reproductive system and breast disorders, we identified five distinct positive signals of adverse reactions, with a total of 1,213 reported cases.

The analysis identified several positive signals of adverse reactions, namely, Erectile Dysfunction, Genital Swelling, Haematospermia, Nipple Swelling, and Pelvic Floor Muscle Weakness. Among these, Erectile Dysfunction exhibited notable statistical indicators: (ROR: 3.707078559,95%CI(3.33250349–4.123756054), (PRR:3.702969038,χ2 (669.2853829)), (IC:1.870490139,IC025(1.702813857), (EBGM: 3.656567867,EBGM05 (3.28709656)) All four types of Erectile Dysfunction tested positive, further affirming its significance as an ADR. Therefore, Erectile Dysfunction is considered a valuable ADR to be taken into account (Table 3).

A demographic analysis of the patient population experiencing erectile dysfunction revealed that the largest proportion of participants (34.49%) belonged to the middle-aged group (45–65 years), with a total of 119 individuals. The average age of the participants was 58.39 years. Consumer reports accounted for the highest number of cases, with 124 individuals (35.94%), followed by doctors, with 107 individuals (31.01%).

Furthermore, the analysis identified the top five reporting countries for these cases, which were the United States, United Kingdom, Netherlands, Spain, and Germany (Table 4).

The frequency of annual reports documenting ED associated with the use of atorvastatin is depicted in Figure 1, revealing a notable peak of 49 cases reported in 2010 (Figure 1).

Furthermore, the onset of ED in individuals taking atorvastatin was most commonly observed within the first 30 days (n = 41) and between 181 and 360 days (n = 12) after initiating the medication. These time intervals indicate the periods during which ED symptoms were most likely to manifest following atorvastatin use (Figure 2).

3.2 Results of mendelian randomisation analysis

3.2.1 Atorvastatin-erectile dysfunction

The results of the two-sample MR analysis are presented as follows:inverse weighting analysis (β = 3.17/OR = 23.91, p = 0.02 < 0.05), MR-Egger (β = 2.25/OR = 9.51, p = 0.50), weighted median (β = 3.45/OR = 31.47, p = 0.05), simple model (β = 2.99/OR = 19.84, p = 0.37), and weighted model (β = 2.87/OR = 17.51, p = 0.31).

The inverse weighting analysis demonstrated a significant association between atorvastatin use and ED, as indicated by the p-value of 0.02 (<0.05). This finding was further supported by consistent OR (β) direction across all five statistical results.

These results suggest a potential causal relationship between atorvastatin and the development of ED, as indicated by the significant associations observed and the consistent direction of effect across different MR approaches.

The funnel plot and leave-one-out sensitivity analyses, and scatter plots of MR analyses for Atorvastatin-ED shown in Figures 3A–C.

TABLE 2 The PT signal of atorvastatin under Systematic Organ classification (SOC).

SYSTEM ORGAN CLASS(SOC)	PT (n)	Case report (n)	Case proportion (%)
Musculoskeletal and connective tissue disorders	52	38478	16.93
General disorders and administration site conditions	12	29960	13.18
Investigations	92	21934	9.65
Nervous system disorders	37	20761	9.14
Metabolism and nutrition disorders	10	15099	6.64
Gastrointestinal disorders	12	15053	6.62
Skin and subcutaneous tissue disorders	22	9306	4.09
Injury, poisoning and procedural complications	21	8961	3.94
Psychiatric disorders	3	8528	3.75
Respiratory, thoracic and mediastinal disorders	11	8159	3.59
Cardiac disorders	25	7906	3.48
Hepatobiliary disorders	33	6766	2.98
Renal and urinary disorders	7	5582	2.46
Immune system disorders	4	4944	2.18
Infections and infestations	13	4758	2.09
Vascular disorders	15	4671	2.06
Eye disorders	9	3792	1.67
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	2298	1.01
Blood and lymphatic system disorders	5	2175	0.96
Surgical and medical procedures	13	1916	0.84
Ear and labyrinth disorders	4	1601	0.70
Product issues	5	1266	0.56
Reproductive system and breast disorders	5	1213	0.53
Social circumstances	5	1179	0.52
Endocrine disorders	0	477	0.21
Congenital, familial and genetic disorders	12	306	0.13
Pregnancy, puerperium and perinatal conditions	0	174	0.08
	438	227263	100.00

The Cochran's Q test results were as follows: MR-Egger ($p > 0.05$) and inverse variance-weighted ($p > 0.05$). Our horizontal multi-effect analysis results were not statistically significant, with $p > 0.05$. However, these results exhibited good stability (Table 5).

3.2.2 LDL-C-erectile dysfunction

The two-sample MR analysis yielded the following results: inverse variance-weighted (β = 0.05 [OR = 1.05], $p = 0.25$), MR Egger (β = 0.04 [OR = 1.04], $p = 0.50$), weighted median (β = 0.11 [OR = 1.11], $p = 0.10$), simple model (β = 0.16 [OR = 1.18], $p = 0.20$), and weighted model (β = 0.10 [OR = 1.11], $p = 0.14$).

The inverse variance-weighted analysis results with $p > 0.05$ suggest that there is no significant causal relationship between LDL and ED. To assess the stability of the results, a sensitivity analysis was performed. The Cochran's Q test results for MR-Egger ($p > 0.05$) and inverse variance-weighted ($p > 0.05$) were not significant, indicating good stability (Table 6).

Figures 4A–C depict the funnel plot and leave-one-out sensitivity analyses, and scatter plots of the MR analyses conducted for the association between LDL and ED.

4 Discussion

Atorvastatin is one of the most widely used lipid-lowering drugs. Jabbari et al. found that atorvastatin can improve the prognosis of heart disease, by establishing a model-based cost-effectiveness analysis (Jabbari et al., 2020). The key pharmacological action of

TABLE 3 The PT signal of Atorvastatin under Reproductive system and Breast Disorders

PT	ROR (95%CI)	PRR (95%C)	χ^2	IC (95%CI)	IC Signal strength	EBGM (EBGM05)
Erectile dysfunction	3.707078559 (3.33250349–4.123756054)	3.702969038 (3.329340793–4.118526923)	669.2853829	1.870490139 (1.702813857–2.015942789)	(++)	3.656567867 (3.28709656)
Genital swelling	5.579288982 (3.216627557–9.677360834)	5.579027035 (3.216575735–9.676608053)	47.60524887	2.449327906 (1.266489183–2.82994912)	(+)	5.461616085 (3.1487856)
Haematospermia	4.034806581 (2.221949702–7.326747372)	4.03465969 (2.221932067–7.326272055)	24.63902939	1.99203792 (0.829036636–2.511816228)	(+)	3.97798523 (2.190658442)
Nipple swelling	8.60952786 (4.245936854–17.4576242)	8.609259993 (4.245906761–17.45666163)	51.70388947	3.055250025 (1.211234572–3.176435841)	(+)	8.312313262 (4.099360359)
Pelvic floor muscle weakness	13.56863618 (6.638947561–27.73148699)	13.56819375 (6.638888824–27.72992386)	87.53328957	3.679447689 (1.472259075–3.459437489)	(+)	12.81221217 (6.268839667)

TABLE 4 The features of reports associated with Atorvastatin-ED.

	Case report (N)	Case proportion (%)
Age		
< 18	0	0.00
≥18, <45	27	7.83
≥45, <65	119	34.49
≥65, <75	49	14.20
75≤	22	6.38
Not Specified	128	37.10
Age (quantitative)		
Mean (SD)	58.39	
Median (Q1,Q3)	58.00 (50.00, 67.00)	
Min, Max	28.00, 82.00	
Reporter		
Consumer	124	35.94
Lawyer	2	0.58
Not Specified	27	7.83
Other health-professional	46	13.33
Pharmacist	39	11.30
Physician	107	31.01
Country (TOP5)		
United States of America(%)	106	30.72
United Kiongdom(%)	70	20.29
Netherlands(%)	21	6.09
Spain(%)	17	4.93
Germany(%)	13	3.77
Outcome		
OT	227	65.80
NOT SPECIFIED	50	14.49
DS	22	6.38
HO;OT	16	4.64
DS;OT	9	2.61
HO	4	1.16
Serious report		
Serious	295	85.51
Non-Serious	50	14.49

atorvastatin is the inhibition of rate-limiting enzymes in the mevalonate pathway (Graaf et al., 2004). This pathway is a key step in the synthesis of various compounds, including cholesterol and many nonsteroidal products. Jiang et al. established a mouse model of chronic subdural haemorrhage and found that atorvastatin accelerates the absorption of Chronic Subdural Hematoma by

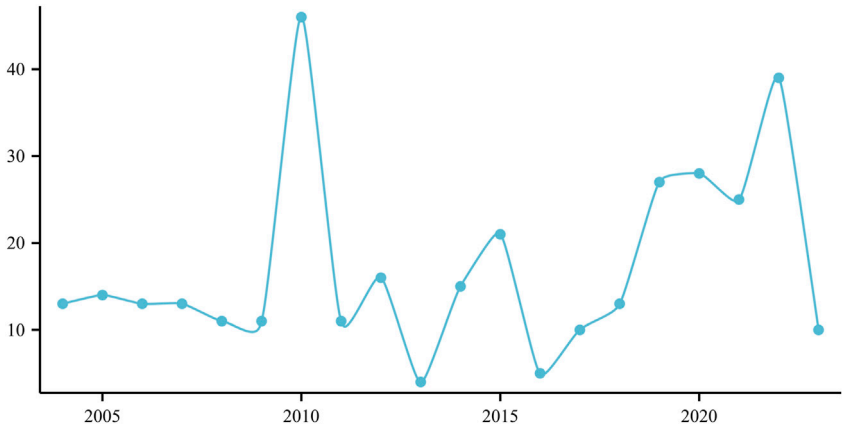


FIGURE 1
The broken line of the reporting year (Atorvastatin-ED).

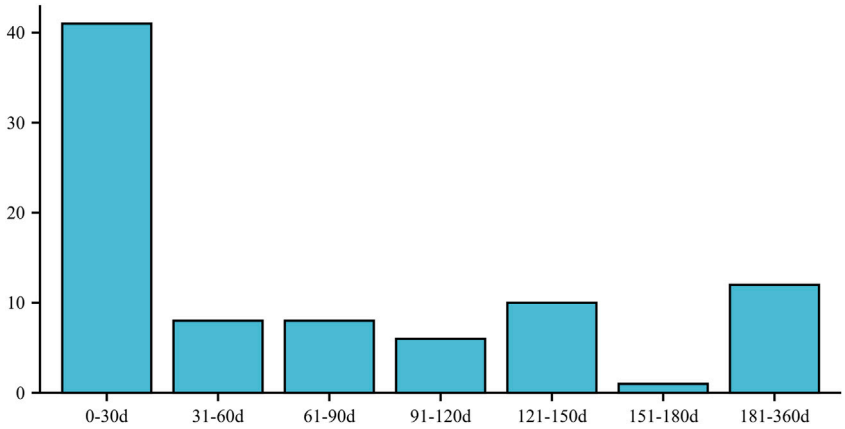


FIGURE 2
ED onset time - medication date (days).

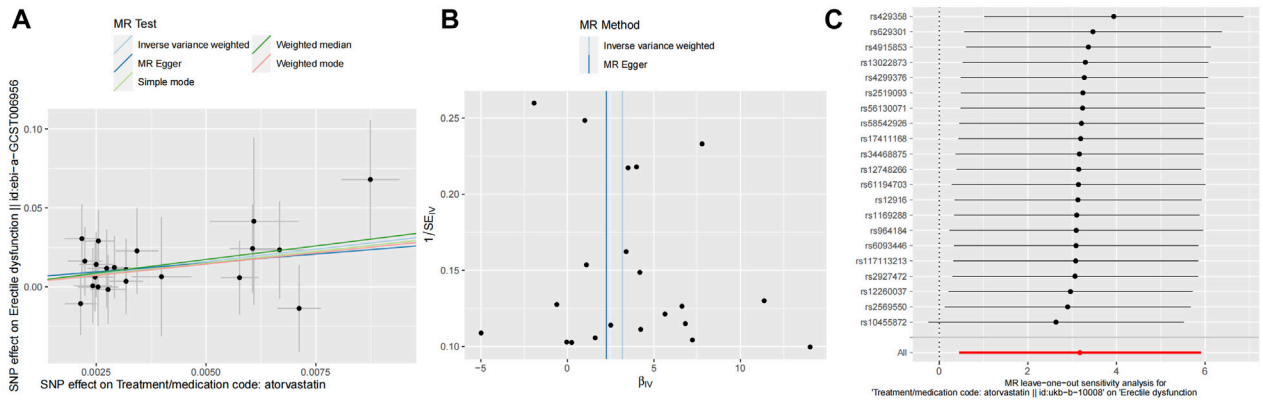


FIGURE 3
Mendelian randomized association between Atorvastatin and ED **(A)**: Scatter diagram, **(B)**: Funnel plot and **(C)**: Leave-one-out.

inducing an anti-inflammatory response and increasing Tregs in both the peripheral circulation and the brain (Quan et al., 2019). They found that a combination treatment using atorvastatin and the multikinase-targeting anticancer drug sorafenib synergistically inhibited proliferation and tumour sphere formation Gastric Cancer Stem Cells (GCSCs), in addition, GCSCs was therapeutically eliminated. This indicated that atorvastatin effectively inhibits formation of gastric cancer (Choi et al., 2022). Atorvastatin has a wide range of clinical effects; therefore, exploring its associated AEs is of practical significance.

Studies have found a potential association between atorvastatin and an increased risk of ED (Nurkalem et al., 2014). For example, a Finnish cohort study involving statin users showed a slightly elevated risk of initiating ED treatment after radical prostatectomy (Joentausta et al., 2023). Additionally, Solomon et al. discovered that patients with severe endothelial dysfunction were more likely to develop ED following statin therapy (Solomon et al., 2006). These findings suggest that ED may be an adverse reaction to atorvastatin.

Pharmacovigilance Analysis failed to verify a causal relationship between atorvastatin and ADR, as the disproportionate analysis only provided an estimate of signal strength and could neither quantify the risk nor establish causation (Zhao et al., 2023).

MR analysis employs genetic variations as IVs to evaluate the causal association between the exposure factor under study and the outcome of interest. This method has many unique advantages, such as avoiding confounding factors and high reliability (Larsson et al., 2023). Therefore, we combined the two methods, merging the ability of pharmacovigilance disproportion analysis to identify AEs with the advantage of MR for exploring causality. This provides more robust evidence for clinical decision-making. Through four pharmacovigilance analysis methods, this study found that ED (ROR:3.707078559,95% CI(3.332503494.123756054), (PRR:3.702969038,χ2 (669.2853829)), (IC:1.870490139,IC025(1.702813857), (EBGM:3.656567867,EBGM05 (3.28709656)) were effective ADRs, and it was the PT with the highest frequency. Demographic findings showed that adults aged 45–60 years were more likely to develop ED after taking atorvastatin. These people are also high-risk patients for ED in general (Corona et al., 2023).

The most common timeframe for the occurrence of AEs is within 0–30 days after administration of atorvastatin. Therefore, it is crucial to closely monitor patients' sexual function during the first month of treatment. The majority of reports regarding AEs came from patients, followed by doctors. This observation may indicate that some physicians tend to overlook changes in patients' sexual function during their clinical practice. Additionally, our MR investigation indicates a possible association between atorvastatin and ED. These results align with the outcomes derived from our pharmacovigilance monitoring analysis. Therefore, combining these two approaches can effectively explore the adverse effects of most drugs, providing more comprehensive insights into their safety profiles.

ED is a significant vascular condition linked closely with risk factors like hyperlipidemia, metabolic syndrome, diabetes, inflammation, hypertension, and vascular endothelial function (Balta and Mikhailidis, 2019). Research by Ma et al. indicates that elevated LDL levels can increase the incidence of ED in youthful males (Ma et al., 2021). Currently, nitric oxide (NO) synthesis and release play a crucial role in erectile function, being considered the primary factor in the relaxation of penile blood vessels and the corpus cavernosum (Andersson, 2011). Statin drugs induce and regulate endothelial nitric oxide synthase to increase NO production *in vitro* (Tousoulis et al., 2014). Research by Roberto suggests that PCSK9 inhibitors significantly improve lipid levels in male patients with familial hypercholesterolemia, thereby enhancing erectile function (Scicali et al., 2020). A double-blind randomized controlled trial found that treatment with simvastatin for 6 months improved erectile dysfunction (Trivedi et al., 2014). A prospective study compared the effects of rosuvastatin and atorvastatin on erectile dysfunction. They observed that atorvastatin increased the risk of erectile dysfunction (Nurkalem et al., 2014). These results suggest that different statin types may have different effects on erectile dysfunction. However, Akdeniz et al. observed a significant reduction in the number of spermatogonia and spermatocytes in male Sprague-Dawley rats following 12 weeks of atorvastatin intervention compared to the comparison group (Akdeniz et al., 2021). In their animal experiments, Bolat et al. found that atorvastatin can rapidly decrease intracavernosal pressure under 10 V stimulation in rats, lower testosterone levels, and impact sexual function (Bolat et al., 2019). In their study, Baspınar et al. found that patients on statin therapy might observe a rise in NO levels; however, a decrease in NO levels could occur when their LDL-C levels reach 100 mg/dL. This decline in NO levels at lower LDL-C concentrations could potentially worsen the incidence of ED (Baspınar et al., 2016). This may explain why ED occurs with atorvastatin rather than other types of lipid-lowering drugs.

Atorvastatin may also cause ED because of its effect on testosterone, with studies suggesting that atorvastatin may negatively affect erectile function by interfering with testosterone synthesis and metabolism and reducing testosterone levels (Bolat et al., 2019). This impact could be linked to the hindrance of the cholesterol synthesis pathway, given that cholesterol serves as a vital precursor for testosterone synthesis (Dobs et al., 2000).

Nevertheless, it is crucial to emphasize the need for additional research to confirm these mechanisms and investigate other potential variables that could impact the association between atorvastatin and ED. Factors such as individual variations, dosage, and duration of atorvastatin use should also be considered in understanding this association. Further clinical trials and lab investigations will enhance our grasp of the intricate connection between atorvastatin and ED.

Atorvastatin is often used in combination with cardiovascular drugs as a lipidlowering agent. CVD and ED share common risk factors and pathophysiological associations, such as endothelial dysfunction and inflammation (Terentes-Printzios et al., 2021). Current studies suggest a complex interaction between ED and CVD drugs. Studies have shown that cardiovascular medications such as beta-blockers can cause ED (Silvestri et al., 2023). Therefore, a simple pharmacovigilance analysis may be inaccurate. This demonstrates the limitations of pharmacovigilance analysis of real-world data. Therefore, based on the results of pharmacovigilance analysis, we introduced Mendelian randomization to further clarify the causal relationship. To further provide evidence for the relationship between atorvastatin and ED.

TABLE 5 Pleiotropy test of Mendelian randomization results (Atorvastatin-ED).

Heterogene-test						Pleiotropy-test		
MR Egger			IVW			MR Egger		
Q	Q_{df}	Q_{pval}	Q	Q_{df}	Q_{pval}	Intercept	SE	*P* val
7.477130	19	0.9912027	7.573885	20	0.9943325	0.003789579	0.01218301	0.7591461

TABLE 6 Pleiotropy test of Mendelian randomization results (LDL-ED).

Heterogene-test						Pleiotropy-test		
MR Egger			IVW			MR Egger		
Q	Q_{df}	Q_{pval}	Q	Q_{df}	Q_{pval}	Intercept	SE	*P* val
72.85954	77	0.6124935	72.88735	78	0.6424205	0.0006687527	0.004010455	0.8680021

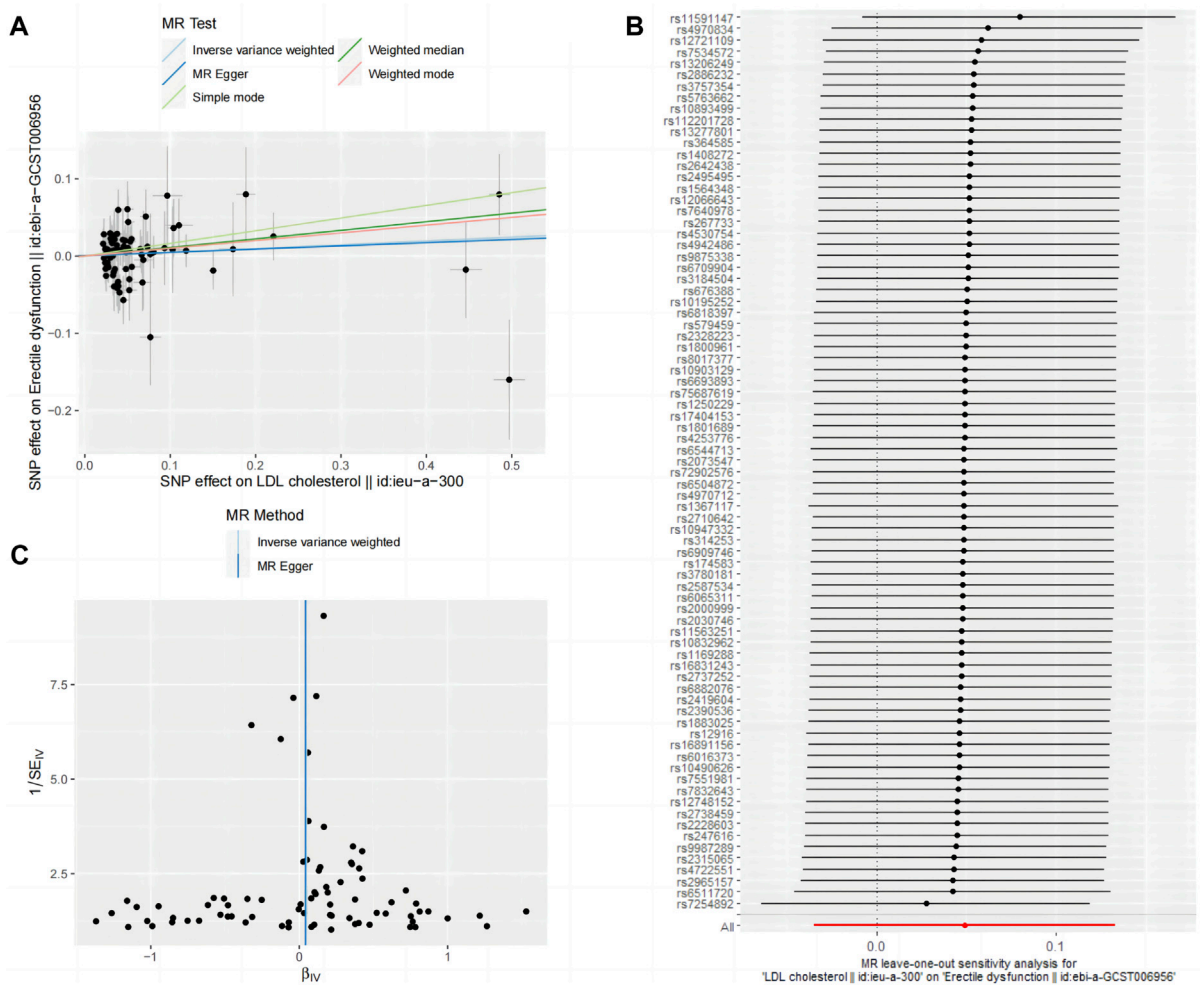


FIGURE 4
Mendelian randomized association between LDL and ED **(A)**: Scatter diagram, **(B)**: Leave-one-out and **(C)**: Funnel plot.

The efficacy and safety data for atorvastatin were initially derived from preclinical trials. Because of the relatively small sample sizes used, however, Enrolled clinical trials may not completely mirror the real-world effects of medications on individuals, especially concerning safety aspects (Zhou et al., 2023).

FAERS is dynamically updated and open to the public as a post-marketing drug safety monitoring and reporting system (Moore et al., 2020). Continuous attention to adverse drug events is helpful for evaluating the safety of drugs and making the best choice for patients during clinical decision-making. Using FAERS for pharmacovigilance analysis has the advantages of being multi-centre, providing large amounts of data, and containing many samples. However, our study has some limitations. FAERS is an open database of self-reporting systems; hence the data quality is not standardised, owing to simple differences between uploaders. This may lead to deviations in the results. On the side, confounding factors, Factors like medication dosage, treatment duration, existing health conditions, drug interactions, and specific disease types pose challenges in terms of control.

5 Conclusion

Through thorough analyses integrating pharmacovigilance and MR, our results indicate a potential causal link, suggesting that using atorvastatin is linked to a heightened risk of ED. These findings underscore the significance of taking into account possible side effects, like ED, when prescribing atorvastatin for the prevention of cardiovascular disease. The combination of pharmacovigilance monitoring and MR holds great promise in identifying previously unknown or underreported ADRs. It offers a systematic and evidence-based approach to evaluate drug safety and contributes to the ongoing efforts in improving patient care and drug regulation.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://gwas.mrcieu.ac.uk/ and https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

KC: Investigation, Writing–original draft, Writing–review and editing. HH: Software, Supervision, Writing–review and editing. YC: Conceptualization, Data curation, Writing–review and editing. WH: Investigation, Software, Validation, Writing–original draft.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by Guidance in Medical and Health Program of Xiamen, China (3502Z20224ZD1159), Guidance in Medical and Health Program of Xiamen, China (3502Z20224ZD1155).

Acknowledgments

Thank you to all the medical staff who contributed to the maintenance of the medical record database (FAERS,UKB,EBI and IEU).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Akdeniz, E., Onger, M. E., Bolat, M. S., Firat, F., Gur, M., Cinar, O., et al. (2021). Effect of atorvastatin on spermatogenesis in rats: a stereological study. *Trop. J. Pharm. Res.* 19, 2609–2614. doi:10.4314/tjpr.v19i12.19

Andersson, K. E. (2011). Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol. Rev.* 63, 811–859. doi:10.1124/pr.111.004515

Balta, S., and Mikhailidis, D. P. (2019). Endocan and erectile dysfunction. *Am. J. men's health* 13, 1557988319893889. doi:10.1177/1557988319893889

Baspınar, O., Bayram, F., Korkmaz, S., Aksu, M., Kocer, D., Dizdar, O. S., et al. (2016). The effects of statin treatment on adrenal and sexual function and nitric oxide levels in hypercholesterolemic male patients treated with a statin. *J. Clin. Lipidol.* 10, 1452–1461. doi:10.1016/j.jacl.2016.09.004

Bate, A., Lindquist, M., Edwards, I. R., Olsson, S., Orre, R., Lansner, A., et al. (1998). A Bayesian neural network method for adverse drug reaction signal generation. *Eur. J. Clin. Pharmacol.* 54, 315–321. doi:10.1007/s002280050466

Beltrán Romero, L. M., Vallejo-Vaz, A. J., and Muñiz Grijalvo, O. (2021). Cerebrovascular disease and statins. *Front. Cardiovasc Med.* 8, 778740. doi:10.3389/fcvm.2021.778740

Bolat, M. S., Bakırtaş, M., Fırat, F., Akdeniz, E., Çınar, Ö., and Erdemir, F. (2019). The effect of atorvastatin on penile intracavernosal pressure and cavernosal morphology in normocholesterolemic rats. *Turk J. Urol.* 45, 91–96. doi:10.5152/tud.2018.98048

Bovijn, J., Jackson, L., Censin, J., Chen, C. Y., Laisk, T., Laber, S., et al. (2019). GWAS identifies risk locus for erectile dysfunction and implicates hypothalamic neurobiology and diabetes in etiology. *Am. J. Hum. Genet.* 104, 157–163. doi:10.1016/j.ajhg.2018.11.004

Chen, X., Kong, J., Diao, X., Cai, J., Zheng, J., Xie, W., et al. (2020). Depression and prostate cancer risk: a Mendelian randomization study. *Cancer Med.* 9, 9160–9167. doi:10.1002/cam4.3493

Choi, Y. S., Cho, H. J., and Jung, H. J. (2022). Atorvastatin inhibits the proliferation of MKN45-derived gastric cancer stem cells in a mevalonate pathway-independent manner. *Korean J. Physiol. Pharmacol.* 26, 367–375. doi:10.4196/kjpp.2022.26.5.367

Corona, G., Cucinotta, D., Di Lorenzo, G., Ferlin, A., Giagulli, V. A., Gnessi, L., et al. (2023). The Italian Society of Andrology and Sexual Medicine (SIAMS), along with ten other Italian Scientific Societies, guidelines on the diagnosis and management of erectile dysfunction. *J. Endocrinol. Invest.* 46, 1241–1274. doi:10.1007/s40618-023-02015-5

de Graaf, L., Brouwers, A. H., and Diemont, W. L. (2004). Is decreased libido associated with the use of HMG-CoA-reductase inhibitors. *Br. J. Clin. Pharmacol.* 58, 326–328. doi:10.1111/j.1365-2125.2004.02128.x

Do, C., Huyghe, E., Lapeyre-Mestre, M., Montastruc, J. L., and Bagheri, H. (2009). Statins and erectile dysfunction: results of a case/non-case study using the French Pharmacovigilance System Database. *Drug Saf.* 32, 591–597. doi:10.2165/00002018-200932070-00005

Dobs, A. S., Miller, S., Neri, G., Weiss, S., Tate, A. C., Shapiro, D. R., et al. (2000). Effects of simvastatin and pravastatin on gonadal function in male hypercholesterolemic patients. *Metab. Clin. Exp.* 49, 115–121. doi:10.1016/s0026-0495(00)90938-7

Gencer, B., Marston, N. A., Im, K., Cannon, C. P., Sever, P., Keech, A., et al. (2020). Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 396, 1637–1643. doi:10.1016/S0140-6736(20)32332-1

Graaf, M. R., Richel, D. J., van Noorden, C. J., and Guchelaar, H. J. (2004). Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. *Cancer Treat. Rev.* 30, 609–641. doi:10.1016/j.ctrv.2004.06.010

Jabbari, A., Jafari, A., Hadian, M., and Ghasemi, M. (2020). Model-based cost-effectiveness analysis of atorvastatin drugs for prevention of cardiovascular diseases in Iran. *Int. J. Prev. Med.* 11, 57. doi:10.4103/ijpvm.IJPVM_578_18

Joentausta, R. M., Siltari, A., Rannikko, A., and Murtola, T. J. (2023). Incidence of erectile dysfunction treatment after radical prostatectomy by Statin use in Finnish Nationwide Cohort Study. *Scand. J. Urol.* 57, 53–59. doi:10.1080/21681805.2023.2168746

Larsson, S. C., Butterworth, A. S., and Burgess, S. (2023). Mendelian randomization for cardiovascular diseases: principles and applications. *Eur. Heart J.* 44, 4913–4924. doi:10.1093/eurheartj/ehad736

Levin, M. G., and Burgess, S. (2024). Mendelian randomization as a tool for cardiovascular research: a review. *JAMA Cardiol.* 9, 79–89. doi:10.1001/jamacardio.2023.4115

Ma, W. J., Qin, M., Cui, T. W., Zhang, X. P., Ke, Z. H., Pan, Z. K., et al. (2021). Relationship between the risk factors of cardiovascular disease by testing biochemical markers and young men with erectile dysfunction: a case-control study. *Transl. Androl. Urol.* 10, 724–733. doi:10.21037/tau-20-1056

Moore, T. J., Morrow, R. L., Dormuth, C. R., and Mintzes, B. (2020). US food and drug administration safety advisories and reporting to the adverse event reporting system (FAERS). *Pharm. Med.* 34, 135–140. doi:10.1007/s40290-020-00329-w

Nurkalem, Z., Yildirimtürk, Ö., Özcan, K. S., Kul, Ş., Çanga, Y., Satılmış, S., et al. (2014). The effect of rosuvastatin and atorvastatin on erectile dysfunction in hypercholesterolaemic patients. *Kardiol. Pol.* 72, 275–279. doi:10.5603/KP.a2013.0287

Pencina, M. J., Pencina, K. M., Lloyd-Jones, D., Catapano, A. L., Thanassoulis, G., and Sniderman, A. D. (2020). The expected 30-year benefits of early versus delayed primary prevention of cardiovascular disease by lipid lowering. *Circulation* 142, 827–837. doi:10.1161/CIRCULATIONAHA.120.045851

Quan, W., Zhang, Z., Li, P., Tian, Q., Huang, J., Qian, Y., et al. (2019). Role of regulatory T cells in atorvastatin induced absorption of chronic subdural hematoma in rats. *Aging Dis.* 10, 992–1002. doi:10.14336/AD.2018.0926

Rizvi, K., Hampson, J. P., and Harvey, J. N. (2002). Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam. Pract.* 19, 95–98. doi:10.1093/fampra/19.1.95

Rothman, K. J., Lanes, S., and Sacks, S. T. (2004). The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf.* 13, 519–523. doi:10.1002/pds.1001

Salonia, A., Bettocchi, C., Boeri, L., Capogrosso, P., Carvalho, J., Cilesiz, N. C., et al. (2021). European association of urology guidelines on sexual and reproductive health-2021 update: male sexual dysfunction. *Eur. Urol.* 80, 333–357. doi:10.1016/j.eururo.2021.06.007

Scicali, R., Russo, G. I., Di Mauro, M., Manuele, F., Di Marco, G., Di Pino, A., et al. (2020). Analysis of arterial stiffness and sexual function after adding on PCSK9 inhibitor treatment in male patients with familial hypercholesterolemia: a single lipid center real-world experience. *J. Clin. Med.* 9, 3597. doi:10.3390/jcm9113597

Shu, Y., He, X., Liu, Y., Wu, P., and Zhang, Q. (2022). A real-world disproportionality analysis of olaparib: data mining of the public version of FDA adverse event reporting system. *Clin. Epidemiol.* 14, 789–802. doi:10.2147/CLEP.S365513

Silvestri, A., Galetta, P., Cerquetani, E., Marazzi, G., Patrizi, R., Fini, M., et al. (2023). Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. *Eur. HEART J.* 24 (21), 1928–1932. doi:10.1016/j.ehj.2003.08.016

Solomon, H., Samarasinghe, Y. P., Feher, M. D., Man, J., Rivas-Toro, H., Lumb, P. J., et al. (2006). Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int. J. Clin. Pract.* 60, 141–145. doi:10.1111/j.1742-1241.2006.00793.x

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., et al. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 12, e1001779. doi:10.1371/journal.pmed.1001779

Takata, K., Imaizumi, S., Zhang, B., Miura, S., and Saku, K. (2016). Stabilization of high-risk plaques. *CARDIOVASC DIAGN*6 (4), 304–321. doi:10.21037/cdt.2015.10.03

Terentes-Printzios, D., Ioakeimidis, N., Rokkas, K., and Vlachopoulos, C. (2021). Interactions between erectile dysfunction, cardiovascular disease and cardiovascular drugs. *Nat. Rev. Cardiol.* 19 (1), 59–74. doi:10.1038/s41569-021-00593-6

Tousoulis, D., Psarros, C., Demosthenous, M., Patel, R., Antoniades, C., and Stefanadis, C. (2014). Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. *J. Am. Coll. Cardiol.* 63, 2491–2502. doi:10.1016/j.jacc.2014.01.054

Trivedi, D., Wellsted, D. M., Collard, J. B., and Kirby, M. (2014). Simvastatin improves the sexual health-related quality of life in men aged 40 years and over with erectile dysfunction: additional data from the erectile dysfunction and statin trial. *BMC Urol.* 14, 24. doi:10.1186/1471-2490-14-24

van Puijenbroek, E. P., Bate, A., Leufkens, H. G., Lindquist, M., Orre, R., and Egberts, A. C. (2002). A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 11, 3–10. doi:10.1002/pds.668

Visseren, F., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Bäck, M., et al. (2022). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. J. Prev. Cardiol.* 29, 5–115. doi:10.1093/eurjpc/zwab154

Walker, V. M., Davey Smith, G., Davies, N. M., and Martin, R. M. (2017). Mendelian randomization: a novel approach for the prediction of adverse drug events and drug repurposing opportunities. *Int. J. Epidemiol.* 46, 2078–2089. doi:10.1093/ije/dyx207

Wang, S., Zhu, H., Pan, L., Zhang, M., Wan, X., Xu, H., et al. (2023). Systemic inflammatory regulators and risk of acute-on-chronic liver failure: a bidirectional mendelian-randomization study. *Front. Cell Dev. Biol.* 11, 1125233. doi:10.3389/fcell.2023.1125233

Willer, C. J., Schmidt, E. M., Sengupta, S., Peloso, G. M., Gustafsson, S., Kanoni, S., et al. (2013). Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* 45, 1274–1283. doi:10.1038/ng.2797

Winkler, K., Weltzien, P., Friedrich, I., Schmitz, H., Nickell, H. H., Hauck, P., et al. (2004). Qualitative effect of fenofibrate and quantitative effect of atorvastatin on LDL profile in combined hyperlipidemia with dense LDL. *Exp. Clin. Endocrinol. Diabetes* 112, 241–247. doi:10.1055/s-2004-817970

Yavne, Y., Amar Shamir, R., Shapiro, M., and Shepshelovich, D. (2023). Evaluating the impact of black box warning updates on the reporting of drug-related adverse events: a cross sectional study of the FAERS database. *Expert Opin. Drug Saf.* 22, 463–468. doi:10.1080/14740338.2023.2172160

Zagkos, L., Dib, M. J., Pinto, R., Gill, D., Koskeridis, F., Drenos, F., et al. (2022). Associations of genetically predicted fatty acid levels across the phenome: a mendelian randomisation study. *PLoS Med.* 19, e1004141. doi:10.1371/journal.pmed.1004141

Zhao, B., Zhang, X., Chen, M., and Wang, Y. (2023). A real-world data analysis of acetylsalicylic acid in FDA Adverse Event Reporting System (FAERS) database. *Expert Opin. Drug Metab. Toxicol.* 19, 381–387. doi:10.1080/17425255.2023.2235267

Zhou, Q., Du, Z., Qu, K., Shen, Y., Jiang, Y., Zhu, H., et al. (2023). Adverse events of epidiolex: a real-world drug safety surveillance study based on the FDA adverse event reporting system (FAERS) database. *Asian J. Psychiatr.* 90, 103828. doi:10.1016/j.ajp.2023.103828

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 04 June 2024
DOI 10.3389/fmed.2024.1343483

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Orkun Tolunay,
University of Health Sciences, Türkiye
Aslınur Albayrak,
Süleyman Demirel University, Türkiye

*CORRESPONDENCE
Muhammed Yunus Bektay
✉ yunusbektay@gmail.com
Hayrettin Daşkaya
✉ h.daskaya@gmail.com

RECEIVED 14 December 2023
ACCEPTED 21 May 2024
PUBLISHED 04 June 2024

CITATION
Ayhan YE, İlerler EE, Sosyal D, Bektay MY, Karakurt S, Daşkaya H, Karaaslan K and Sancar M (2024) Assessment of drug-induced electrolyte disorders in intensive care units: a multicenter observational study.
Front. Med. 11:1343483.
doi: 10.3389/fmed.2024.1343483

Assessment of drug-induced electrolyte disorders in intensive care units: a multicenter observational study

Yunus Emre Ayhan[1], Enes Emir İlerler[2], Damla Sosyal[3], Muhammed Yunus Bektay[4,5]*, Sait Karakurt[6], Hayrettin Daşkaya[7]*, Kazım Karaaslan[7] and Mesut Sancar[2]

[1]Department of Clinical Pharmacy, Prof. Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Türkiye, [2]Department of Clinical Pharmacy, Marmara University Faculty of Pharmacy, Istanbul, Türkiye, [3]Department of Clinical Pharmacy, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye, [4]Department of Clinical Pharmacy, Faculty of Pharmacy, Istanbul University-Cerrahpasa, Istanbul, Türkiye, [5]Department of Clinical Pharmacy, Bezmialem Vakif University Faculty of Pharmacy, Istanbul, Türkiye, [6]Department of Chest Diseases and Intensive Care, Faculty of Medicine, Marmara University, Istanbul, Türkiye, [7]Department of Anesthesiology and Reanimation, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye

Objective: Electrolyte disorder (ED) is frequently encountered critically ill patients during admission or admission to the intensive care unit (ICU). This study aimed to determine the frequency of ED encountered in ICU patients to evaluate the relationship of ED with drugs.

Methods: This prospective, multicenter study was conducted in the medical and anesthesiology ICUs of two training and research hospitals and included patients with at least one ED during admission or hospitalization in the ICUs. The relationship between ED and the drug was evaluated by calculating the logistic probabilistic method scale (LPMS) and the expert panel's evaluation. The correlation between EDs and LPMS was determined using Kendal tau. A binary logistic regression model was preferred in the analysis of factors related to ED. Statistical significance was set as $p < 0.05$.

Results: A total of 117 patients were included in the study. A total of 165 EDs were detected, including at least one in 88 (75.2%) patients. According to the expert panel, 61 (21.7%) of EDs were drug-related, whereas according to the LPMS, 111 (39.6%) ($p<0.001$). Mortality (50% vs. 13.7%) and mechanical ventilation rates (52.2% vs. 17.2%) were significantly higher in patients with ED ($p<0.001$). Patients with ED had 8.352 times higher odds of exhibiting mortality (OR: 8.352, %95 CI: 1.598–43.648, p: 0.012) and need mechanical ventilation with higher odds of 3.229 (OR: 3.229 95% CI: 0.815–12.787 p: 0.045). Patient who required enteral or parenteral feeding were associated with an increased likelihood of exhibiting ED (respectively OR: 30.057, %95 CI: 2.265–398.892, p: 0.01, OR: 5.537, %95 CI: 1.406–21.800, p: 0.014).

Conclusion: EDs are very common in the ICU. Dysnatremia was detected more commonly in other EDs. It has also been found that patients with ED are more often under mechanical ventilation, have more prolonged hospitalizations, and have higher mortality rates than patients without ED. The suitability of LPMS for assessing ED-drug relationships in the ICU context is questioned.

KEYWORDS

intensive care unit, electrolyte disorder, clinical pharmacist, drug-related problems, patient safety

1 Introduction

Electrolytes play a role in many enzymatic and biochemical metabolic and hemostatic functions (1). One of the important problems in maintaining hemostasis in the body is fluid and electrolyte balance (2). Electrolyte disorder (ED) is frequently encountered in critically ill patients during admission or during hospitalization at the intensive care unit (ICU), because of treatment or multiple comorbiditie as a result of their treatment or multiple comorbidities (3).

The prevalence rates at admission to and during hospitalization in the ICU were reported as 18–33% and 11–16% for hyponatremia, 7–9%, and 6–29% for hypernatremia, respectively (4–6). Dysnatremia during ICU admission and stay has been associated with increased hospital mortality rates (5, 7). The prevalence of hypokalemia and hyperkalemia in ICU patients has been reported to be 17.4 and 12%, respectively (8). Two separate meta-analyses associated hypomagnesemia with higher mortality rates, need for mechanical ventilation, and incresead length of ICU stay (9, 10). The prevalence rates of hypocalcemia and hypercalcemia reported in ICU patients are 55–88 and 2%, respectively (11, 12). Hypercalcemia was independently associated with hospital or ICU mortality, mainly because of underlying malignancies (13). Similarly, hypocalcemia was also associated with longer ICU lengths of stay and increased mortality. Hypophosphatemia is common in the ICU, and has been observed in approximately 28% of critically ill patients (14). Hypophosphatemia is associated with longer ICU and hospital stays, increased risk of arrhythmia, and respiratory distress (15).

Diuretics, trimethoprim-sulfamethoxazole, amphotericin B, dexamethasone, ifosfamide, lithium, foscarnet, hypertonic 3% saline, and antibiotics containing sodium (fosfomycin, piperacillin-tazobactam) can be given as examples of drugs that cause hypernatremia (7, 16–18). Salbutamol, loop and thiazide diuretics; glucocorticoids, amphotericin B, and carbonic anhydrase inhibitors causes drug-induced hypokalemia (19, 20). Causes of drug-induced hyperkalemia include penicillin G, spironolactone, amiloride, trimethoprim, and angiotensin-converting enzyme inhibitors (21, 22). Among the drugs that disrupt the calcium balance, such as bisphosphonates, calcitonin, cisplatin, cyclophosphamide, cytarabine, and doxorubicin; phenytoin, phenobarbital, rifampicin, isoniazid, and furosemide can be counted (23). Lithium, Vitamin D, intoxication, and teriparatide are examples of drug-induced hypercalcemia (24). Antacids, sucralfate, phosphate binding agents, and insulin can be counted among the drugs that cause disturbances in phosphate balance (25, 26).

In the literature, studies examining drug-related ED in the adult ICU setting are limited in number. However, a study addressing this issue stated that ED is frequently seen in ICUs. Therefore, it has been attempted to increase clinicians' awareness about drugs that can potentially cause electrolyte imbalance (27).

This study aimed to determine the frequency of ED encountered in ICU patients, to evaluate its relationship with drugs, and evaluate the applicability of the current logistic probabilistic method scale (LPMS) in the ICU setting. This study aimed to determine the frequency of ED encountered in ICU patients, to evaluate its relationship with drugs, and evaluate the applicability of the current logistic probabilistic method scale (LPMS) in the ICU setting (28).

2 Materials and methods

2.1 Study design and patients

This observational multicenter prospective study was conducted in the medical and anesthesiology ICUs of two university hospital in Istanbul, Türkiye (Bezmialem Vakif University, and Marmara University) between 01.09.2022 and 01.03.2023. Patients who had at least one ED (hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypermagnesemia, hypophosphatemia, or hyperphosphatemia) at the time of admission to or during their stay in the ICU were included in the study.

2.2 Inclusion and exclusion criteria

Patients aged ≥18 years and hospitalized in the ICU for ≥24 h were included in the study. Patients with missing data and/or who did not use medication during their ICU stay were excluded from the study.

2.3 Data collection and evaluation

Patients with ED included in the study were followed daily by a longer ICU stay clinical pharmacist and intensive care physician during their ICU stay. Patient demographic information, drugs used during hospitalization, laboratory data, drug and medical history, acid–base balance, blood gas values, and fluid balance were followed up during the daily evaluations.

The possible causes of ED and its relationship with drugs were evaluated by an expert panel consisting of intensive care specialists (SK and HD) and clinical pharmacist (YEA, MYB), and the current LPMS was used as the assessment material/scale for the relationship between ED and drugs. For this purpose, intensive care specialists' evaluation was recorded to determine whether the possible cause was drug-related in patients with ED. The current LPMS of each patient with ED was also calculated by a clinical pharmacist independently of the intensive care specialists. Thus, after the intensive care specialist evaluated the relationship between ED and clinical condition, the relationship between ED and drugs was examined. As a result, each expert's evaluation was recorded independently of each other and finally discussed, and the results were decided.

LPMS evaluates the relationship between a drug and its side effects by focusing on six fundamental parameters: time of onset, exposure and re-exposure, investigation of other etiologies, risk factors for drug interaction, reaction or toxic plasma concentration at the application site or validated laboratory test, and symptomatology. The numerical sum of the statistical weights obtained from the answers to the specified parking meters is converted into probability using the logistic function. According to the *p*-value obtained afterward, the possible relationship between the side effect and the drug is interpreted (28). The evaluation process of EDs is summarized below;

1. At least two consecutive values outside the normal range were considered to be ED.

2. ED was considered to be resolved when at least two consecutive normal values were observed.
3. If the same ED is seen again after the development and resolution of ED in the same patient, it is added to the frequency of occurrence.
4. During the evaluation of the clinical etiology, if the relevant ED was not evaluated, the statements "not evaluated" and "not calculated" were added to the *p*-value of LPMS calculation part. If a result could not be reached in the evaluation made by the intensive care specialist, the statement "decision could not be made" was added.
5. In the absence of any potential drugs that could be associated with the patient's ED, the *p*-value was stated as "not calculated."
6. The local drug monograph and UpToDate® (Wolters Kluwer Health Inc., 2023) reference sources were used to evaluate the association of drugs with ED. The Sanford Guide to Antimicrobial Therapy was also used to examine the relationship between antimicrobial agents and ED.

2.4 Sample size

The study examined patients who met the inclusion criteria in the ICU during the study period (6 months). For the sample size of the study, it was decided to include a total of 115 patients in the study by adding a 15% dropout rate to the calculation made over the standard deviation 1, alpha 0.05, and 95% power values based on the monthly number of patients hospitalized in the ICU.

2.5 Data analysis

As descriptive statistics, mean, median, standard deviation, and interquartile range (IQR) or count and percentages are given for continuous variables. The frequency and percentage are given for categorical variables. The normality of continuous variables was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk test, histogram analyses, Q-Q plots, skewness and kurtosis analysis of data. It was determined that the data showed a normal distribution. The difference between groups was analyzed using independent *t*-test. Chi-square tests are used to investigate the relationship between categorical variables. The Pearson correlation coefficient was calculated in the correlation analysis. According to the correlation coefficient r value, the relationship was defined as "low" (0.01–0.29), "moderate" (0.30–0.70) and "high" (0.71–0.99). The probability status of different demographic situations and survey scores were determined by the odds ratio. Univariate logistic regression analysis was used to determine which variable(s) are significant by using $p < 0.20$. Significant variables are included in the binary logistic regression analysis. Binary logistic regression analysis was performed, and estimated risk values and confidence intervals were provided. This study was conducted to identify the variables that are useful in predicting the existence of polypharmacy. The Nagelkerke *R* square value was used to assess the model's explanatory power, and the Hosmer and Lemeshow test was used to assess the model's fit. The missing data were excluded from the analysis. All the data were statistically analyzed by using Statistical Package for Social Science (SPSS) version 26® and Jamovi version 1.6 software. Univariate and multivariate logistic regression analysis was conducted to identify factors associated with the electrolyte imbalance. Statistical, significance was set as $p < 0.05$.

3 Results

A total of 117 out of 165 hospitalized patients were included in the study. Sixty patients (51.3%) were male, the mean age was 63.7 (±16.8), and the number of comorbidities was 2 (±1.75) diseases. The most common reason for ICU admission was respiratory distress (21.9%) (Table 1).

A total of 165 EDs were detected, including at least one in 88 (75.2%) of the patients. The mean number of EDs per patient was 1.4 ± 1.57. Hyperkalemia (19.8%), hypernatremia (16.8%), and hyponatremia (13.8%) were the most common EDs in patients (Table 2).

The mean day of observation of ED during patients ICU stay was 6 (±7.96). ED lasted an average of 4.5 days (±3.16). According to the expert panel, 21.7% of EDs were drug-related, while according to the LPMS, 39.6% were drug-related. A statistically significant difference was found between the expert panel and LPMS in the rates of possible causes of ED (Table 3). According to the LPMS, the most common causes of drug-related EDs were furosemide (44.1%), sodium chloride 0.9% (11.6%), pantoprazole (9.3%), and amphotericin b (4.6%). According to the LPMS, the clinical conditions causing EDs were intake deficiency (52.9%), renal failure (15.6%), and hypervolemia (7.8%). According to the expert panel, the most common causes of drug-related EDs were furosemide (40%), pantoprazole (20%), and 0.9% sodium chloride (10%). According to the expert panel, the clinical conditions causing EDs were found to be a lack of intake (33.8%), hypovolemia (24.1%), and renal failure (8.0%).

A significant correlation was found between the total number of ED patients and the total number of days of hospitalization in the ICU (*r*: 0.457, $p < 0.001$), the number of drugs at discharge (*r*: 0.245, *p*: 0.019), mechanical ventilation status (*r*:-0.279, *p*: 0.002) and mortality status (*r*:-0.218, *p*: 0.018). No significant correlation was found between the Glasgow coma scale (GCS) score at admission, type of nutrition, renal status, number of drugs on admission, and total number of EDs in the patients. There was a statistically significant difference between the presence of ED in the patients, ICU admission GCS score, number of drugs in hospitalization, mechanical ventilation status, mortality status and total length of stay (Table 4). In addition, patients with ED (11.7 ± 9.1) had a statistically significant longer length of stay in the ICU compared with patients without ED (6.9 ± 10.2) (*p*: 0.019). In addition, mortality (50% vs. 13.7%) and mechanical ventilation rates (52.2% vs. 17.2%) were significantly higher in patients with ED than in those without ED (*p*: 0.001 and *p*: 0.001, respectively).

Binomial logistic regression analysis was performed to determine the effects of age, number of comorbidities, ICU stay, nutritional status, number of medications during ICU stay and number of medications during discharge. The logistic regression model was statistically significant, $\chi 2(6) = 26.626$, $p < 0.001$. The model explained 44.3% (Nagelkerke R^2) of the variance in ED and the model correctly classified 82.9% of cases. Sensitivity was 41.4%,

TABLE 1 Demographic characteristics of the study participants.

Variable	
Age, (Mean ± SD)	63.7 ± 16.8
Gender, *n* (%)	
Male	60 (51.3)
Female	57 (48.7)
Reasons for admission to the intensive care unit*, *n* (%)	
Convulsive seizure	4 (3.2)
Cardiac arrest	5 (4.0)
General condition disorder	7 (5.6)
Sepsis/Septic shock	9 (7.3)
Pneumonia	16 (13.0)
Post-op	21 (17.02)
Respiratory distress	27 (21.9)
Other	34 (27.6)
Comorbidities* *n* (%)	
Pulmonary embolism	7 (2.4)
Heart failure	8 (2.7)
Atrial fibrillation	10 (3.4)
Chronic kidney disease	12 (4.1)
Lung cancer	12 (4.1)
Cerebrovascular event	14 (4.8)
Chronic obstructive pulmonary disease	19 (6.6)
Other types of cancer	25 (8.7)
Coronary artery disease	26 (9.0)
Diabetes mellitus	41 (14.3)
Hypertension	51 (17.8)
Other	55 (19.2)
Admission GCS, (Mean ± SD)	*13.3 ± 3.06*
Number of comorbidity, (Mean ± SD)	*2.8 ± 1.75*
Length of stay in ICU (days), (Mean ± SD)	*10.5 ± 9.58*
Number of drugs in admission, (Mean ± SD)	*11.11 ± 4.08*
Number of drugs at discharge, (Mean ± SD)	*10.2 ± 4.41*
Nutrition type, *n* (%)	
Oral	46 (39.3)
Enteral	38 (32.5)
Parenteral	6 (5.1)
Intravenous Dextrose	27 (23.1)
Kidney status, *n* (%)	
Normal	67 (57.3)
Acute kidney failure	30 (25.6)
Hemodialysis	4 (3.4)
Continuous renal replacement therapy	16 (13.7)
Mechanical ventilation status, *n* (%)	
Yes	51 (43.6%)
Mortality, *n* (%)	
Yes	48 (41%)

*Since a patient has more than one reason for admission, this number is higher than the number of patients.
GCS, Glasgow coma scale, ICU, Intensive care unit.

specificity was 96.6%, positive predictive value was 83.3% and negative predictive value was 80.0%. The model reliability was tested with an omnibus ANOVA test for model coefficients (*p*: 0.001) and Hosmer and Lemeshow Test (*p*: 0.970). Of the 8 predictor variables, only three were statistically significant: mortality, mechanical ventilation, and nutritional status (Table 5). Patients with ED had 8.352 times higher odds of exhibiting mortality (%95 CI: 1.598–43.648, *p*: 0.012) and need mechanical ventilation with higher odds of 3.229 (95% CI: 0.815–12.787 *p*: 0.045). Patient who required enteral or parenteral feeding were associated with an increased likelihood of exhibiting ED (respectively OR: 30.057, %95 CI: 2.265–398.892, *p*: 0.01, OR: 5.537, %95 CI: 1.406–21.800, *p*: 0.014).

4 Discussion

To the best of our knowledge, this is a one of the first studies in the literature that examines EDs in the ICU and their relationship with the drugs. This study investigates the incidence of EDs in the ICU population and the role of LPMS and expert panel in evaluating the relationship between EDs and drugs. Accordingly, it was observed that EDs are common in the ICU, ED is associated with mortality. The LPMS correlates ED with medication at a higher rate than the expert panel.

Due to the severe condition of patients in the ICU, the variety of drugs used in the treatment, and many factors affecting the patient's hemodynamic stability, EDs have been widely detected in other studies (5, 6, 27, 29). Studies evaluating all EDs in the ICU are limitted. It has been demonstrated in many studies that dysnatremia is the most common ED (5, 6, 29, 30). In this study, dysnatremia was higher than hyperkalemia and hypokalemia. Sodium and potassium-related EDs are expected in the ICU due to many mechanisms such as acid–base, fluid balance, renal failure, and drugs (6, 29, 30). Less frequent follow-up of other electrolytes, such as magnesium and phosphorus, and later recognition of their symptoms may explain why EDs of these electrolytes are less frequent (14, 27). When the rates of disorders of all electrolytes examined in this study are compared with those in the literature, different rates of ED are observed. This difference may be due to differences in laboratory reference ranges for electrolytes considered in studies, frequency of monitoring, and differences in ICU populations (31).

It was observed in this study that EDs in the ICU were detected mainly in the first week of admission to the ICU and treated in an average of 4–5 days. Stelfox et al. reported the median time of detection of dysnatremia as 2 days (6). It may cause prolonged detection and treatment of ED because of hospitalizations to the ICU for severe and vital reasons. Another possibility is the treatment of EDs after the control and management of other emergencies. The presence of at least 1–2 EDs per patient and ED being statistically significantly associated with mortality require rapid control of EDs (5, 6).

Many factors can cause EDs in the ICU. Among these factors, drugs also have a certain ratio (27). However, no scale or scoring systems has been developed in the literature for associating EDs with drugs in the ICU. Therefore, the use of LPMS, one of the few scales that evaluates the relationship of side effects with the drug, was considered. In this study, EDs were associated with the drug at a higher rate than the expert panel when evaluated using LPMS. According to both the LPMS and the expert panel, the drugs

TABLE 2 Distribution of frequency of electrolyte disorders.

Electrolyte Disorders	Frequency in all ED, *n* (%)	Values of ED, Mean (min - max)	Patient, *n* (%)
Hypernatremia	28 (16.8)	149.05 (145.0–155.0)	26 (22.2)
Hyponatremia	22 (13.8)	131.45 (120.0–135.0)	21 (17.9)
Hyperkalemia	33 (19.8)	6.0 (5.14–7.10)	27 (23.1)
Hypokalemia	14 (8.4)	3.11 (2.30–3.47)	14 (12)
Hyperphosphatemia	8 (4.8)	5.82 (3.80–9.90)	8 (6.8)
Hypophosphatemia	21 (12.6)	1.86 (1.10–2.60)	20 (17.1)
Hypermagnesemia	9 (5.4)	3.0 (2.70–3.41)	8 (6.8)
Hypomagnesemia	18 (10.8)	1.54 (0.94–2.80)	17 (14.5)
Hypercalcemia	1 (0.6)	12.7	2 (1.7)
Hypocalcemia	10 (6.0)	8.5 (7.10–8.70)	9 (7.7)
Total	165 (100)		88 (75.2)

ED, Electrolyte disorder.

TABLE 3 Comparison of expert panel and LPMS decisions.

Electrolyte disorder	Expert panel decision, *n* (%)	LPMS decision, *n* (%)	*p* value
Drug-induced	61 (21.7)	111 (39.6)	<0.001
Depends on clinical situation	148 (52.8)	102 (36.4)	
Could not be evaluated/decided	71 (25.3)	138 (49.2)	
Total	280 (100)*	280 (100)*	

* More possibilities than the total number of EDs ($n = 165$) were evaluated because more than one possible cause of an ED was evaluated.
LPMS, Logistic probabilistic method scale.

and clinical factors causing EDs were determined to be quite similar. However, the causes of EDs could not be evaluated/decided in approximately half of the patients because of the complicated calculation method of LPMS and its unsuitability for use in the ICU. On the other hand, in the evaluation made with the expert panel, possible causes were revealed depending on the clinical conditions in approximately half of the EDs. However, due to the high rate of undecidable situations with LPMS and the significant proportional difference between the expert panel and LPMS, there is a need for a scale that evaluates the relationship between EDs and drugs, considering the clinical factors of the patients. In this case, the use of LPMS in the ICU is not considered appropriate and practical.

There was a positive correlation between the length of hospital stay and low GCS in ICU patients and a negative correlation between EDs and mechanical ventilation and hospitalizations, resulting in mortality. Based on this information, there is a direct relationship between the worsening of the patient's prognosis and EDs. On the other hand, in the logistic regression analysis, a significant relationship was revealed with EDs in patients being mechanically ventilated, fed by means other than oral, and hospitalizations resulting in mortality (6, 7, 29, 30, 32). Therefore, it is predicted that the outcomes of the patients will be improved by the diagnosis and management of EDs in patients hospitalized in the ICU, especially in the first week of the patient's ICU, in a shorter time (5, 30). Long-term stays in the ICU bring many complications due to the nature of the ICU environment. Therefore, long-term ICU hospitalizations, the need for mechanical ventilation, and the patient's enteral feeding tubes or parenteral nutrition conditions make the management and care of the patient more complicated (32). During this prolonged hospitalization, at ICU, the patient's acid base, fluid balance, nutritional needs, and the variability of drug treatments significantly affected the ED rates of the patients. EDs are particularly common in mechanically ventilated patients and significantly impact patient outcomes during treatment and weaning from mechanical ventilation. Patients requiring mechanical ventilation are likely to have decreased electrolyte levels. It is stated that unbalanced serum electrolytes and delay in their recovery prolong the duration of mechanical ventilation, stay in the ICU, and are associated with increased comorbidity and mortality (14, 29, 33, 34). For these reasons, it was found in this study, similar to the literature, that patients with ED were statistically significantly more likely to be under mechanical ventilation, with a longer ICU stay, and with higher mortality than patients without ED (5–7, 34).

The limitations of this study are that the relationship of ED with the drug was not controlled using different scales, and only a small number of patients were included in the study. In an environment where there are many factors affecting ED, such as the ICU, other factors, such as fluid, acid–base balance, and renal failure, which affect ED were considered in the expert panel but were not mentioned in this study because they were not the primary aim of the study. Because this was a multicenter study, there was also a difference in the frequency and order of laboratory follow-up of electrolytes in the centers. These differences may have caused inconsistencies in the ED rates. The study gains strength both in Turkey and in the literature in terms of investigating all EDs and the relationship of EDs with drugs in the patient group in the ICU. In addition, this study also included surgical, medical, cardiac, and neurological/traumatic patients without focusing only on a specific ICU patient population. The results of this study are likely to generalize to EDs in other ICU settings.

TABLE 4 Distribution of the relationship between categorical data and the presence of electrolyte disorders.

Variable	Electrolyte disorder status		*p* value
	Yes	No	
Age, *n*			
<64	34	9	0.461
≥64	54	20	
Gender, *n*			
Male	46	14	0.709
Female	42	15	
Admission GCS, *n*			
<14	24	2	0.021
≥14	33	15	
Number of comorbidity, *n*			
<3	39	13	0.962
≥3	49	16	
Length of stay in ICU (days), *n*			
<11	50	27	<0.001
≥11	38	2	
Number of drugs in admission, *n*			
<12	46	24	0.006
≥12	39	5	
Number of drugs at discharge, *n*			
<11	50	24	0.810
≥11	12	5	
Nutrition type, *n*			
Oral	38	8	0.136
Others (Enteral, Parenteral, IV Dextrose)	50	21	
Kidney status, *n*			
Normal	49	18	0.547
Others (Acute kidney failure, Hemodialysis, Continuous renal replacement therapy)	39	11	
Mechanical ventilation status, *n*			
Yes	46	5	<0.001
No	42	24	
Mortality, *n*			
Yes	44	4	<0.001
No	44	25	

GCS, Glasgow coma scale; ICU, Intensive care unit; IV, Intravenous.

5 Conclusion

In conclusion, EDs are quite common in the ICU. Dysnatremia was detected more commonly than in other EDs. It has also been found that patients with ED are more often under mechanical ventilation, with more prolonged hospitalizations, and have higher mortality rates than patients without ED. In evaluating the relationship between EDs and drugs in the ICU, it was observed that the LPMS associated EDs with the drugs at a higher rate than the expert panel. According to the LPMS and the expert panel, drugs that cause ED have been similarly identified. However, the causes of EDs in approximately half of the patients with LPMS have not been evaluated/decided. Therefore, LPMS does not appear to be a practical and appropriate scale for evaluating the ED-drug relationship in the ICU.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Marmara University. This study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YEA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. EEI: Conceptualization, Data curation, Writing – original draft. DS: Data curation, Writing – original draft. MYB: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. SK: Conceptualization, Formal analysis, Resources, Supervision, Writing – original draft, Writing – review & editing. HD: Resources, Supervision, Visualization, Writing – review & editing. KK: Visualization, Writing – review & editing. MS: Formal analysis, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors are grateful to Marmara University and Bezmialem Vakif University and all participants included in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

TABLE 5 Binary logistic regression analysis of factors related with electrolyte disorders.

Variables	Electrolyte disorder					
	Univariate analysis			Multivariate analysis		
	OR	95% CI for Odds ratio	*p* values	OR	95% CI for Odds Ratio	*p* values
Age	1.015	0.98–1.043	0.280			
Comorbidity	0.855	0.655–1.100	0.223			
ICU Stay (days)	0.922	0.858–0.990	0.025	0.953	0.893–1.016	0.142
Nutritional Status		-				
Oral feeding	*Reference*					
Enteral Feeding	9.500	1.478–61.071	0.018	30.057	2.265–398.892	0.010
Parenteral Feeding	3.800	1.296–11.144	0.015	5.537	1.406–21.800	0.014
Number Medication during ICU stay	0.854	0.754–0.969	0.014	0.944	0.801–1.113	0.494
Number of Medication during hospital discharge	0.939	0.852–1.034	0.199	1.090	0.922–1.289	0.313
Mortality						
No	*Reference*					
Yes	6.250	2.009–19.448	<0.001	8.352	1.598–43.648	0.012
Mechanical Ventilation						
No	*Reference*					
Yes	5.257	1.839–15.029	<0.001	3.229	0.815–12.787	0.045

ICU: Intensive care Unit.

Publisher's note

References

1. Kraft MD, Btaiche IF, Sacks GS, Kudsk KA. Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm*. (2005) 62:1663–82. doi: 10.2146/AJHP040300

2. Balcı AK, Koksal O, Kose A, Armagan E, Ozdemir F, Inal T, et al. General characteristics of patients with electrolyte imbalance admitted to emergency department. *World J Emerg Med*. (2013) 4:113–6. doi: 10.5847/WJEM.J.ISSN.1920-8642.2013.02.005

3. Reintam Blaser A, van Zanten ARH. Electrolyte disorders during the initiation of nutrition therapy in the ICU. *Curr Opin Clin Nutr Metab Care*. (2021) 24:151–8. doi: 10.1097/MCO.0000000000000730

4. Darmon M, Pichon M, Schwebel C, Ruckly S, Adrie C, Haouache H, et al. Influence of early Dysnatremia correction on survival of critically ill patients. *Shock*. (2014) 41:394–9. doi: 10.1097/SHK.0000000000000135

5. Funk GC, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, et al. Incidence and prognosis of Dysnatremias present on ICU admission. *Intensive Care Med*. (2010) 36:304–11. doi: 10.1007/s00134-009-1692-0

6. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired Hyponatraemia and Hypernatraemia in medical-surgical intensive care units. *Crit Care*. (2008) 12:R162–8. doi: 10.1186/cc7162

7. Lindner G, Funk GC, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis*. (2007) 50:952–7. doi: 10.1053/J.AJKD.2007.08.016

8. Bouadma L, Mankikian S, Darmon M, Argaud L, Vinclair C, Siami S, et al. Influence of Dyskalemia at admission and early Dyskalemia correction on survival and cardiac events of critically ill patients. *Crit Care*. (2019) 23:415. doi: 10.1186/S13054-019-2679-Z

9. Jiang P, Lv Q, Lai T, Feng X. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? A systematic review and Meta-analysis. *Shock*. (2017) 47:288–95. doi: 10.1097/SHK.0000000000000769

10. Upala S, Jaruvongvanich V, Wijarnpreecha K, Sanguankeo A. Hypomagnesemia and mortality in patients admitted to intensive care unit: a systematic review and Meta-analysis. *QJM*. (2016) 109:453–9. doi: 10.1093/QJMED/HCW048

11. Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? *Chest*. (2016) 149:846–55. doi: 10.1016/J.CHEST.2015.12.001

12. Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, et al. Ionized calcium concentration and outcome in critical illness. *Crit Care Med*. (2011) 39:314–21. doi: 10.1097/CCM.0B013E3181FFE23E

13. Mousseaux C, Dupont A, Rafat C, Ekpe K, Ghrenassia E, Kerhuel L, et al. Epidemiology, clinical features, and Management of Severe Hypercalcemia in critically ill patients. *Ann Intensive Care*. (2019) 9:133. doi: 10.1186/S13613-019-0606-8

14. Bugg NC, Jones JA. Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. *Anaesthesia*. (1998) 53:895–902. doi: 10.1046/J.1365-2044.1998.00463.X

15. Zhao Y, Li Z, Shi Y, Cao G, Meng F, Zhu W, et al. Effect of hypophosphatemia on the withdrawal of mechanical ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. *Biomed Rep*. (2016) 4:413–6. doi: 10.3892/BR.2016.605

16. Garofeanu CG, Mathew Weir M, Rosas-Arellano P, Henson G, Garg AX, Clark WF. Causes of reversible nephrogenic diabetes insipidus: a systematic review. *Am J Kidney Dis*. (2005) 45:626–37. doi: 10.1053/j.ajkd.2005.01.008

17. Liamis G, Christidis D, Alexandridis G, Bairaktari E, Madias NE, Elisaf M. Uric acid homeostasis in the evaluation of diuretic-induced hyponatremia. *J Investig Med*. (2007) 55:36–44. doi: 10.2310/6650.2007.06027

18. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. (2008) 52:144–53. doi: 10.1053/J.AJKD.2008.03.004

19. Greger R. Why do loop diuretics cause Hypokalaemia? *Nephrol Dial Transplant*. (1997) 12:1799–801. doi: 10.1093/NDT/12.9.1799

20. Tsai WS, Chien Ping W, Hsu YJ, Lin SH. Life-threatening hypokalemia in an asthmatic patient treated with high-dose hydrocortisone. *Am J Med Sci*. (2004) 327:152–5. doi: 10.1097/00000441-200403000-00007

21. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med*. (1996) 124:316–20. doi: 10.7326/0003-4819-124-3-199602010-00006

22. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone. a report from the Boston collaborative drug surveillance program. *JAMA*. (1973) 225:40–3. doi: 10.1001/JAMA.225.1.40

23. Body JJ, Bouillon R. Emergencies of calcium homeostasis. *Rev Endocr Metab Disord*. (2003) 4:167–75. doi: 10.1023/A:1022994104070

24. Maier JD, Levine SN. Hypercalcemia in the intensive care unit: a review of pathophysiology, diagnosis, and modern therapy. *J Intensive Care Med*. (2015) 30:235–52. doi: 10.1177/0885066613507530

25. Brown GR, Greenwood JK. Drug- and nutrition-induced hypophosphatemia: mechanisms and relevance in the critically ill. *Ann Pharmacother*. (1994) 28:626–32. doi: 10.1177/106002809402800513

26. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care*. (2010) 14:R147. doi: 10.1186/cc9215

27. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med*. (2010) 38:S253–64. doi: 10.1097/CCM.0B013E3181DDA0BE

28. Théophile H, André M, Miremont-Salamé G, Arimone Y, Bégaud B. Comparison of three methods (an updated logistic probabilistic method, the Naranjo and Liverpool algorithms) for the evaluation of routine pharmacovigilance case reports using consensual expert judgement as reference. *Drug Saf*. (2013) 36:1033–44. doi: 10.1007/S40264-013-0083-1

29. Aiyagari V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? *J Crit Care*. (2006) 21:163–72. doi: 10.1016/J.JCRC.2005.10.002

30. Polderman KH, Schreuder WO, Strack RJM, Schijndel V, Thijs LG. Hypernatremia in the intensive care unit: an Indicator of quality of care? *Crit Care Med*. (1999) 27:1105–8. doi: 10.1097/00003246-199906000-00029

31. Bennani SL, Abouqal R, Zeggwagh AA, Madani N, Abidi K, Zekraoui A, et al. Incidence, Étiologies et Facteurs Pronostiques de l'hyponatrémie En Réanimation. *Rev Med Interne*. (2003) 24:224–9. doi: 10.1016/S0248-8663(02)00811-1

32. Bigatello LM, Stelfox HT, Berra L, Schmidt U, Gettings EM. Outcome of patients undergoing prolonged mechanical ventilation after critical illness. *Crit Care Med*. (2007) 35:2491–7. doi: 10.1097/01.CCM.0000287589.16724.B2

33. Adrogué HJ, Madias NE. Hypernatremia. *N Engl J Med*. (2000) 342:1493–9. doi: 10.1056/NEJM200005183422006

34. Shah B, Mohan J. A study of electrolyte imbalance in mechanically ventilated patients. *J Pharm Negat Results*. (2023) 13:6909–15. doi: 10.47750/pnr.2022.13.S07.835

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 26 July 2024
DOI 10.3389/fphar.2024.1413944

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Carolina Dagli Hernandez,
State University of Campinas, Brazil
Michael John Calcutt,
University of Missouri, United States

*CORRESPONDENCE
Haixia Zhang,
zhx_510@hotmail.com
Hongliang Mei,
liulidemao@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 08 April 2024
ACCEPTED 25 June 2024
PUBLISHED 26 July 2024

CITATION
Qiao Y, Chen Y, Wang Q, Liu J, Guo X, Gu Q, Ding P, Zhang H and Mei H (2024), Safety profiles of doxycycline, minocycline, and tigecycline in pediatric patients: a real-world pharmacovigilance analysis based on the FAERS database.
Front. Pharmacol. 15:1413944.
doi: 10.3389/fphar.2024.1413944

Safety profiles of doxycycline, minocycline, and tigecycline in pediatric patients: a real-world pharmacovigilance analysis based on the FAERS database

Yanli Qiao[1,2†], Yechao Chen[1,2†], Qiaoyun Wang[1,2], Jingrui Liu[2], Xiaohui Guo[1,2], Qiaoling Gu[1,2], Peng Ding[1,2], Haixia Zhang[3,4*] and Hongliang Mei[4*]

[1]Department of Pharmacy, Nanjing Drum Tower Hospital, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu, China, [2]School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu, China, [3]School of Pharmacy, Faculty of Medicine, Macau University of Science and Technology, Taipa, Macau SAR, China, [4]Department of Pharmacy, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Introduction: Recently, the rise of antibiotic resistance has prompted a reconsideration of tetracyclines. However, existing studies are inadequate in assessing the pediatric safety of this class of antibiotics. To address the gap, our study aims to comprehensively assess the safety of tetracyclines in children.

Methods: Adverse event (AE) reports from January 2005 to September 2023 were obtained from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, and reporting odds ratio (ROR) was performed to identify potential risk signals in children under 18 years old who were administered any of the three tetracyclines: doxycycline, minocycline, and tigecycline.

Results: A total of 1903 AE cases were included in our study: 782 for doxycycline, 981 for minocycline, and 140 for tigecycline. Doxycycline and tigecycline were predominantly associated with "general disorders and administration site conditions" and "gastrointestinal disorders," while minocycline was more frequently linked to "skin and subcutaneous tissue disorders" and "gastrointestinal disorders." Psychiatric risks predominantly included depression, suicidal ideation, and suicide attempt. In the category of skin and subcutaneous tissues, 30.88% of the minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) cases resulted in death, alongside a high occurrence of co-occurring AEs such as multiple organ dysfunction syndrome, Type 1 Diabetes Mellitus (T1DM), and autoimmune thyroiditis. As for the endocrine system, both doxycycline and minocycline were found to potentially increase the risk of thyroid dysfunction. For children under the age of 8, doxycycline was associated with tooth discoloration (N = 7, ROR = 20.11%, 95% CI: 9.48–42.67), although it remained unclear whether the discoloration was permanent.

Conclusion: Our findings indicated that for pediatric patients, the majority of results were in line with the prescribing information and previous studies, and minocycline tended to cause more frequent and severe AEs than doxycycline.

However, it is noteworthy that exceptions were found for psychiatric disorders and thyroid dysfunction associated with doxycycline, which are not mentioned in its FDA prescribing information. Additionally, further safety studies on tigecycline are still needed for children. When prescribing tetracyclines to pediatric patients, a careful risk-benefit assessment is crucial.

KEYWORDS

tetracyclines, children, pharmacovigilance, FAERS, reporting odds ratio

1 Introduction

Tetracyclines are broad-spectrum antibiotics, exhibiting activity against a wide range of Gram-positive and Gram-negative bacteria, atypical organisms such as *Chlamydia*, *Mycoplasma*, Spirochetes, and *Rickettsia*, as well as protozoan parasites, and the mechanism of action involves inhibiting protein synthesis by preventing the attachment of aminoacyl-tRNAs to the A site of the 30S subunit of ribosomes (Chopra and Roberts, 2001). In addition to their antibacterial activity, tetracyclines can also inhibit metalloproteinases and exhibit anti-inflammatory, antiapoptotic, and antioxidant effects (Orylska-Ratynska et al., 2022).

The first tetracycline antibiotic, chlortetracycline, was first reported in the scientific literature in 1948 (Bryer et al., 1948). Following the initial breakthrough, several tetracyclines, including tetracycline, doxycycline, and minocycline, became staples in antimicrobial therapy. Despite their initial success, the rise of tetracycline-resistant bacteria and the introduction of alternative antibiotics, such as cephalosporins and fluoroquinolones, led to a decline in the use of tetracyclines (Chopra and Roberts, 2001; Emmerson and Jones, 2003; LaPlante et al., 2022). The clinical landscape remained stagnant for over 3 decades following the U.S. Food and Drug Administration (FDA) approval of minocycline in 1971, with no new tetracyclines entering the market.

With the rise of antibiotic multi-drug resistance, the imperative to combat this global health challenge has reignited interest in the tetracycline class. The FDA approval of third-generation tetracyclines—tigecycline in 2005, eravacycline and omadacycline in 2018—marks a promising resurgence (Wenzel et al., 2005; Zhanel et al., 2016; Watkins and Deresinski, 2019). Moreover, tetracyclines remain highly effective against atypical pathogens, necessitating a reevaluation of their role in current medical practices (Smilack, 1999).

However, there is a notable scarcity of comprehensive safety studies on tetracyclines in pediatric patients. Currently, doxycycline and minocycline are predominantly prescribed for treating moderate to severe inflammatory acne in children (Zaenglein et al., 2016). However, due to limited research and concerns about tooth discoloration, their use is contraindicated in children under 8 years old (Patheon Pharmaceuticals Inc, 2017; Mayne Pharma, 2022). Tigecycline is not advised for children due to the potential for higher all-cause mortality rates observed in adult trials (McGovern et al., 2013; Shen et al., 2015; Pfizer Inc, 2020). Additionally, the safety and efficacy of omadacycline and eravacycline in pediatric patients have not yet been established (Paratek Pharmaceuticals, 2021; Tetraphase Pharmaceuticals, 2018). Nonetheless, because of the scarcity of other effective antimicrobials, tigecycline has become a useful alternative as a drug of last resort for serious infections, including in children, caused by multi-drug resistant (MDR) and extensively drug-resistant organisms (XDR) (Song et al., 2018). For children under 8 years old, doxycycline and minocycline may be necessary when treating infections like macrolide-resistant *Mycoplasma pneumoniae* (Chou et al., 2019; Ishiwada et al., 2023; National Health Commission of the People's Republic of China, 2023). Additionally, doxycycline is considered the first-line treatment for Lyme disease and Rocky Mountain spotted fever in children of all ages (American Academy of Pediatrics, 2018; Lantos et al., 2021; Meissner and Steere, 2022). To fill the gap in safety knowledge for pediatric use of tetracyclines, our study focused on the safety profiles of doxycycline, minocycline, and tigecycline, which are more commonly prescribed to this age group. We utilized data from the FDA's Adverse Event Reporting System (FAERS) for this analysis.

2 Methods

Data Source: FAERS is one of the world's largest spontaneous reporting databases for adverse reactions to marketed drugs and therapeutic biologics. It contains a vast number of adverse event (AE) reports utilized for post-marketing safety monitoring, excelling in detecting serious and rare adverse drug event signals (Rodriguez et al., 2001). The majority of reports come from healthcare professionals, patients, and pharmaceutical manufacturers. The coding of these reports employs the MedDRA (Medical Dictionary for Regulatory Activities) (Version 26.1) preferred terms (PTs). In MedDRA, while a single PT can be associated with multiple system organ classes (SOCs), it is linked to only one primary SOC. In our study, the primary SOC was utilized to categorize PTs.

Study Design: This study collected data from the FAERS database covering the period from January 2005 to September 2023. To eliminate duplicates, the study followed the FDA guidelines: if CASEIDs (identifiers for FAERS cases) were the same, the report with the latest FDA_DT (the date the FDA received the case) was retained, and if both the CASEID and FDA_DT were the same, the report with the higher PRIMARYID (the unique identifier for FAERS reports) was selected (Wei et al., 2022).

The study focused on three tetracyclines: doxycycline, minocycline, and tigecycline, targeting pediatric patients under 18 years old. Only AE reports with reported roles of drugs as "suspect" (either the primary or the secondary suspect) were included. Additionally, a drug event combination was established by combining all AE reports associated with each of the three drugs. Given the lack of uniform standards for drug naming within the

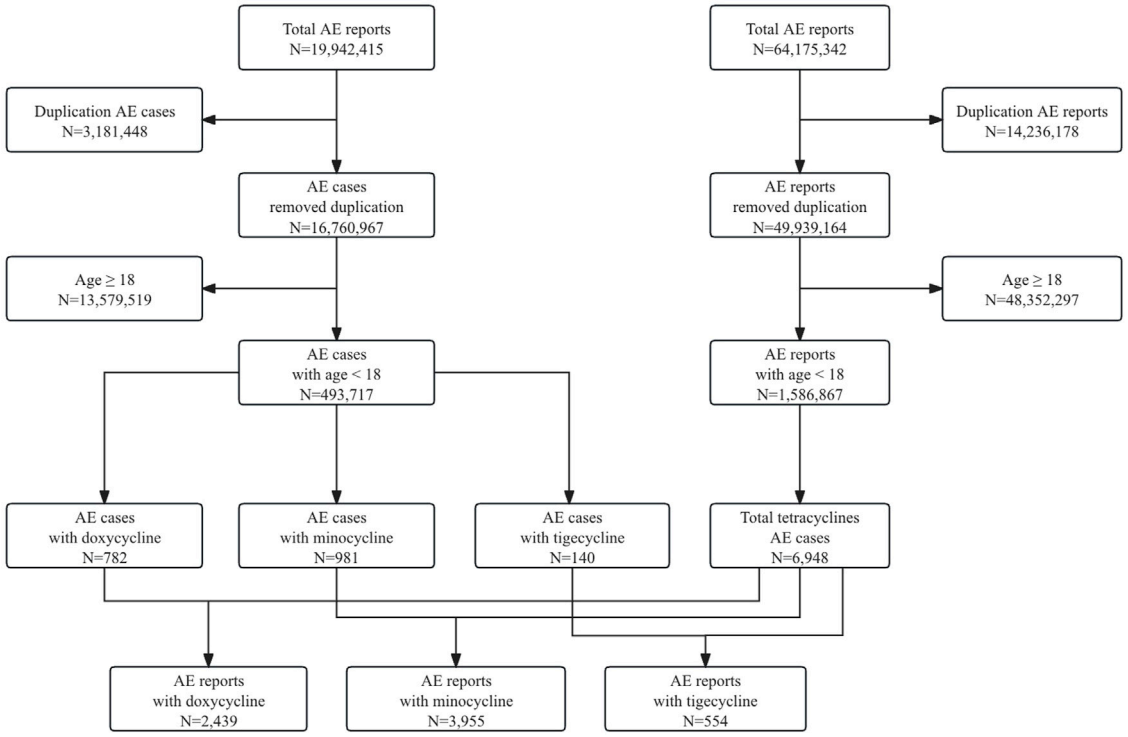


FIGURE 1
Flowchart of data processing in our study. A detailed description of the selection process of adverse events for doxycycline, minocycline, and tigecycline in pediatric patients in the Food and Drug Administration Adverse Event Reporting System (FAERS).

FAERS system, coupled with the diverse backgrounds of reporters and the variety of report formats, multiple names for the same drug can exist within the system. Therefore, this study utilized the PharnexCloud database (https://www.pharnexcloud.com/) to search and compile the generic names, brand names, and research codes of these three tetracyclines approved by the FDA as of 30 September 2023. By employing the compiled list (Supplementary Table S1) to conduct searches in the FAERS database, the objective was to extract relevant drug data as comprehensively as possible, thereby ensuring data integrity.

Signal Detection: Based on the disproportionality analysis method, a widely used signal detection method in the pharmacovigilance study, risk signals for the target drugs were mined using the Reporting Odds Ratio (ROR), with the statistical measures being the ROR and its 95% confidence intervals (CI) (Candore et al., 2015; Zhou et al., 2023). The formulas for calculating the ROR and the 95% CI are as follows:

$$ROR = \frac{a/c}{b/d}$$

$$ROR_{95\%\,\mathrm{CI}} = e^{\ln(ROR)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

In the formulas, (a) is the count of AE reports of interest related to the suspected drug, (b) is the count of other AE reports for the same suspected drug, (c) is the count of AE reports of interest for all other drugs, and (d) is the count of other AE reports for all other drugs. It was considered statistically significant and deemed a potential signal if a potential risk signal met the following criteria: 1) number of reports≥3, 2) the lower limit of the 95% CI>1. A higher ROR value indicates a stronger association between tetracyclines and AEs.

Statistical Analysis: Descriptive statistics were employed for data analysis. Continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables were reported as frequencies and percentages. Data management and statistical analysis were performed using Microsoft Excel 2021 (Microsoft Corporation, Redmond, Washington, United States) and R software version 4.3.1.

3 Results

3.1 The baseline characteristics of the children treated with tetracyclines

Between January 2005 and September 2023, FAERS received a total of 19,942,415 AE reports. After deduplication, 16,760,967 reports remained. Out of these, 493,717 pertained to pediatric patients, and ultimately, 6,948 met our inclusion criteria, involving 1,903 cases. Among the drugs studied, minocycline had the highest number of reports (N = 2,439), followed by doxycycline (N = 3,955), and tigecycline (N = 554), with corresponding case counts of 981, 782, and 140, respectively. The detailed data processing workflow is shown in Figure 1.

The baseline characteristics of children treated with doxycycline, minocycline, and tigecycline in FAERS are

10.3389/fphar.2024.1413944

TABLE 1 The baseline characteristics of children treated with doxycycline, minocycline, and tigecycline in FAERS.

Characteristics	doxycycline (N = 782)	minocycline (N = 981)	tigecycline (N = 140)
Age group, (y)			
Median (Q1, Q3)	15 (12,16)	16 (14,17)	7 (5,14)
0–7	103 (13.17%)	15 (1.53%)	71 (50.71%)
8–18	679 (86.83%)	966 (98.47%)	69 (49.29%)
Gender			
Male	362 (46.29%)	399 (40.67%)	76 (54.29%)
Female	409 (52.30%)	567 (57.80%)	62 (44.29%)
Missing	11 (1.41%)	15 (1.53%)	2 (1.43%)
Country			
United States	411 (52.56%)	699 (71.25%)	24 (17.14%)
United Kingdom	82 (10.49%)	41 (4.18%)	9 (6.43%)
Canada	55 (7.03%)	51 (5.20%)	7 (5.00%)
China	1 (0.13%)	2 (0.20%)	27 (19.29%)
Netherlands	2 (0.26%)	0	23 (16.43%)
Outcomes			
Death	21 (2.69%)	78 (7.95%)	33 (23.57%)
Life Threatening	57 (7.29%)	60 (6.12%)	15 (10.71%)
Hospitalization	237 (30.31%)	290 (29.56%)	32 (22.86%)
Disability	14 (1.79%)	15 (1.53%)	0
Required Intervention	2 (0.26%)	12 (1.22%)	0
Other serious events	308 (39.39%)	231 (23.55%)	25 (17.86%)
Unknown	143 (18.29%)	15 (1.53%)	2 (1.43%)
Received year			
2005–2007	39	60	2
2008–2010	45	117	8
2011–2013	52	123	6
2014–2016	152	174	12
2017–2019	177	257	42
2020–2022	250	206	58
2023 (Q1-Q3)	67	44	12
Indication (top5)			
1	Acne(N = 281)	Acne(N = 691)	*Mycobacterium abscessus* Infection (N = 38)
2	Lyme Disease (N = 38)	Confluent and Reticulate Papillomatosis (N = 12)	Mastoiditis (N = 37)
3	Acne Conglobata (N = 26)	Folliculitis (N = 11)	Sepsis (N = 10)
4	Relapsing Fever (N = 15)	Infective Pulmonary Exacerbation of Cystic Fibrosis (N = 8)	Pneumonia (N = 9)
5	Sclerotherapy (N = 13)	*Mycobacterium abscessus* Infection (N = 7)	*Acinetobacter* Infection (N = 6)

(FAERS: the FDA Adverse Event Reporting System).

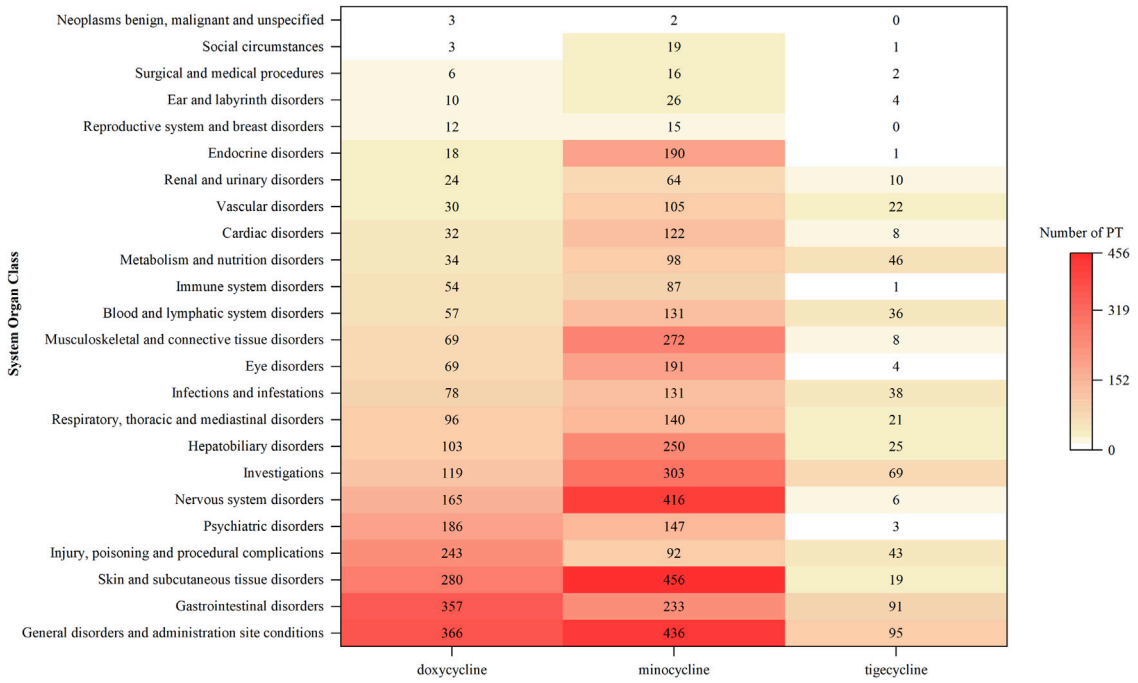


FIGURE 2
The number of AE reports at SOC levels with significant signal PTs in at least one drug. (AE: adverse event; SOC: system organ class; PT: preferred term).

presented in Table 1. The median age was 7 years for tigecycline (IQR: 5–14 years), 15 years for doxycycline (IQR: 12–16 years), and 16 years for minocycline (IQR: 14–17 years). In terms of gender distribution, the proportion of female patients was slightly higher than male patients, at 52.30% and 57.80%, respectively, for doxycycline and minocycline, whereas tigecycline showed a higher proportion of male patients at 54.29%. The majority of the reports for doxycycline and minocycline were from the United States, accounting for 52.56% and 71.25% respectively, while for tigecycline, China had the highest reports at 19.29%. It is important to note that within FAERS, a single PRIMARYID may correspond to multiple outcomes. For the purpose of baseline statistical analysis, the most severe outcome associated with each PRIMARYID was selected. Notably, over 40% of the reports for all these drugs indicated serious outcomes, including death, life-threatening events, disability, congenital anomaly, or hospitalization, with tigecycline showing the highest incidence at 57.14%. As for pediatric fatalities in FAERS, tigecycline accounted for 23.57%, significantly exceeding those for doxycycline at 2.69% and minocycline at 7.95%. In addition, from 2005 to 2022, we observed a predominant trend of a gradual increase in the number of AE reports per 3-year period.

Further analysis of tigecycline-related fatal cases (N = 33) revealed that 27 cases (81.81%) involved PTs such as drug ineffective, drug ineffective for unapproved indication, treatment failure, drug resistance, intentional product use issue, multiple drug resistance, and product use issue. The median age was 6 years (IQR: 0–8 years). The top three indications were sepsis (N = 8), pneumonia (N = 5), and *Acinetobacter* infection (N = 4). The top three countries with the highest number of fatalities were China (N = 13), Greece (N = 7), and the United Kingdom (N = 4).

Regarding the indications of the AE reports, doxycycline was primarily prescribed for acne (N = 281), Lyme disease (N = 38), and acne conglobata (N = 26); minocycline was most frequently used for acne (N = 691), confluent and reticulated papillomatosis (N = 12), and folliculitis (N = 11); tigecycline was mainly used to treat *Mycobacterium abscessus* infection (N = 38), mastoiditis (N = 37), and sepsis (N = 10).

3.2 Tetracycline-related SOCs in pediatric patients

The number of AE reports at SOC levels with significant signal PTs in at least one drug is detailed in Figure 2. There were 24 SOCs involved in children, excluding "Pregnancy, Puerperium and Perinatal Conditions," "Product Issues," and "Various Congenital, Familial, and Genetic Disorders." The affected SOCs varied slightly among the tetracyclines. Specifically, doxycycline mainly influenced "General Disorders and Administration Site Conditions" (N = 366), "Gastrointestinal Disorders" (N = 357), and "Skin and Subcutaneous Tissue Disorders" (N = 280). Minocycline chiefly impacted "Skin and Subcutaneous Tissue Disorders" (N = 456), "General Disorders and Administration Site Conditions" (N = 436), and "Nervous System Disorders" (N = 416). Tigecycline primarily focused on "General Disorders and Administration Site Conditions" (N = 95), "Gastrointestinal Disorders" (N = 91), and "Various Investigations" (N = 69).

10.3389/fphar.2024.1413944

TABLE 2 The top 20 PTs (highlighted in bold) with significant risk signals based on the number of AE reports for doxycycline, minocycline, and tigecycline, respectively.

SOC	PT	Doxycycline			Minocycline			Tigecycline		
		Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)
Gastrointestinal disorders	vomiting	●	**56**	**1.82 (1.39-2.37)**	●	38	0.75 (0.54-1.03)	●	**26**	**3.81 (2.57-5.64)**
	nausea	●	**32**	**1.83 (1.29-2.59)**	●	**48**	**1.69 (1.27-2.25)**	●	**28**	**7.33 (5.01-10.72)**
	colitis ulcerative	●	**30**	**9.17 (6.38-13.17)**	●	2	0.37 (0.09-1.47)	●	0	0.00
	dysphagia	●	**25**	**8.31 (5.59-12.35)**	●	5	1.01 (0.42-2.42)	●	2	2.88 (0.72-11.55)
	oesophageal ulcer	●	**23**	**389.61 (233.96-648.80)**	●	1	48.26 (6.11-381.02)	●	0	0.00
	oesophagitis	●	**19**	**55.53 (34.76-88.72)**	●	1	1.66 (0.23-11.85)	●	0	0.00
	abdominal pain upper	●	**19**	**2.33 (1.49-3.67)**	●	11	0.83 (0.46-1.50)	●	1	0.54 (0.08-3.82)
	pancreatitis	●	1	0.47 (0.07- 3.37)	●	1	1.47 (0.61-3.53)	●	**6**	**12.72 (5.68-28.48)**
	pancreatitis acute	●	3	2.14 (0.69- 6.66)	●	4	1.76 (0.66-4.71)	●	**7**	**22.39 (10.60-47.31)**
Nervous system disorders	headache	●	28	1.34 (0.92-1.94)	●	**78**	**2.33 (1.86-2.91)**	●	0	0.00
	idiopathic intracranial hypertension	●	12	14.62 (8.25-25.94)	●	**69**	**58.18 (45.17-74.92)**	●	0	0.00
	intracranial pressure increased	●	**17**	**13.58 (8.39-21.98)**	●	**28**	**13.96 (9.57-20.36)**	●	0	0.00
	dizziness	●	12	1.30 (0.74-2.30)	●	**28**	**1.88 (1.30-2.73)**	●	0	0.00
Psychiatric disorders	depression	●	**30**	**3.71 (2.58-5.32)**	●	11	0.83 (0.46-1.49)	●	0	0.00
	suicidal ideation	●	**22**	**3.15 (2.07-4.80)**	●	6	0.52 (0.23-1.17)	●	0	0.00
	suicide attempt	●	**16**	**2.28 (1.39-3.73)**	●	3	0.26 (0.08-0.81)	●	0	0.00
Hepatobiliary disorders	cholangitis sclerosing	●	**26**	**190.93 (123.62-294.89)**	●	2	7.18 (1.77-29.05)	●	0	0.00
	drug-induced liver injury	●	7	5.85 (2.78-12.33)	●	**48**	**26.23 (19.57-35.16)**	●	0	0.00
	autoimmune hepatitis	●	3	10.53 (3.37-32.95)	●	**35**	**90.72 (62.96-130.73)**	●	0	0.00
	hepatotoxicity	●	3	2.19 (0.71-6.81)	●	**8**	**3.62 (1.81-7.27)**	●	**21**	**71.55 (46.05-111.18)**
Skin and subcutaneous tissue disorders	drug reaction with eosinophilia and systemic symptoms	●	13	4.21 (2.44-7.28)	●	**136**	**29.64 (24.85-35.36)**	●	1	1.42 (0.20-10.07)
	neutrophilic dermatosis	●	**23**	**1818.21 (840.46-3933.45)**	●	0	0.00	●	0	0.00
	photosensitivity reaction	●	**16**	**26.09 (15.81-43.03)**	●	3	2.91 (0.93-9.06)	●	0	0.00
	urticaria	●	10	0.92 (0.50-1.72)	●	**40**	**2.30 (1.68-3.15)**	●	5	2.05 (0.85-4.94)
	dermatitis	●	4	2.28 (0.85- 610.00)	●	4	1.41 (0.53-3.75)	●	5	12.68 (5.25-30.64)

(Continued on following page)

TABLE 2 (*Continued*) The top 20 PTs (highlighted in bold) with significant risk signals based on the number of AE reports for doxycycline, minocycline, and tigecycline, respectively.

SOC	PT	Doxycycline			Minocycline			Tigecycline		
		Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)
Endocrine disorders	hyperthyroidism	●	13	33.49 (19.17-58.50)	●	**58**	**111.12 (83.17-148.46)**	●	0	0.00
	thyroiditis	●	1	7.12 (0.99-51.08)	●	**50**	**439.78 (296.79-651.67)**	●	0	0.00
Blood and lymphatic system disorders	lymphadenopathy	●	1	0.48 (0.07-3.40)	●	**27**	**8.15 (5.56-11.94)**	●	0	0.00
	neutropenia	●	6	0.90 (0.40- 2.01)	●	2	0.18 (0.05-0.74)	●	**5**	**3.33 (1.38-8.04)**
	thrombocytopenia	●	2	0.39 (0.10- 1.55)	●	13	1.56 (0.90-2.69)	●	**9**	**7.82 (4.04-15.12)**
	bone marrow failure	●	10	5.19 (2.78- 9.68)	●	1	0.32 (0.04-2.25)	●	**8**	**18.47 (9.17-37.20)**
Musculoskeletal and connective tissue disorders	arthralgia	●	15	2.22 (1.34-3.70)	●	**63**	**5.87 (4.57-7.55)**	●	0	0.00
	lupus-like syndrome	●	3	12.52 (4.00-39.25)	●	**43**	**146.32 (103.47-206.93)**	●	0	0.00
	arthropathy	●	0	0.00	●	2	1.64 (0.41-6.56)	●	**6**	**35.74 (15.91-80.26)**
Respiratory, thoracic and mediastinal disorders	dyspnoea	●	**23**	**1.78 (1.18-2.69)**	●	20	0.95 (0.61-1.48)	●	4	1.36 (0.51-3.64)
General disorders and administration site conditions	pyrexia	●	18	0.60 (0.38-0.95)	●	**77**	**1.60 (1.28-2.01)**	●	5	0.73 (0.30-1.77)
	fatigue	●	14	1.10 (0.65-1.86)	●	**40**	**1.95 (1.43-2.66)**	●	6	2.08 (0.93-4.66)
	multiple organ dysfunction syndrome	●	4	1.10 (0.41-2.92)	●	**34**	**5.85 (4.16-8.21)**	●	4	4.85 (1.81-12.99)
Injury, poisoning and procedural complications	intentional overdose	●	**16**	**1.82 (1.12-2.98)**	●	1	0.07 (0.01-0.49)	●	0	0.00
Investigations	alanine aminotransferase increased	●	2	0.42 (0.11-1.70)	●	**33**	**4.39 (3.11-6.19)**	●	3	2.82 (0.91-8.77)
	aspartate aminotransferase increased	●	3	0.71 (0.23-2.20)	●	**31**	**4.59 (3.22-6.55)**	●	1	1.04 (0.15-7.42)
	weight decreased	●	11	1.73 (0.95-3.12)	●	**27**	**2.63 (1.80-3.84)**	●	2	1.38 (0.34-5.53)
	transaminases increased	●	7	3.57 (1.70-7.50)	●	18	5.71 (3.58-9.09)	●	**6**	**13.57 (6.06-30.40)**
	blood cholesterol increased	●	0	0.00	●	4	2.81 (1.05-7.52)	●	**8**	**41.05 (20.33-82.87)**
Metabolism and nutrition disorders	hypertriglyceridaemia	●	0	0.00	●	6	5.48 (2.45-12.27)	●	**17**	**117.12 (71.66-191.43)**
	hyperkalaemia	●	0	0.00	●	0	0.00	●	**5**	**22.77 (9.41-55.10)**
	decreased appetite	●	14	1.63 (0.96- 2.76)	●	17	1.22 (0.76-1.96)	●	**7**	**3.61 (1.71-7.61)**

(Continued on following page)

TABLE 2 (*Continued*) The top 20 PTs (highlighted in bold) with significant risk signals based on the number of AE reports for doxycycline, minocycline, and tigecycline, respectively.

SOC	PT	Doxycycline			Minocycline			Tigecycline		
		Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)	Risk signal	N	ROR (95%CI)
Eye disorders	papilloedema	●	7	7.56 (3.59-15.94)	●	**40**	**28.25 (20.48-38.95)**	●	0	0.00
Immune system disorders	jarisch-herxheimer reaction	●	**29**	**795.54 (467.85-1352.73)**	●	0	0.00	●	0	0.00

●: PT with a significant risk signal; ●: PT without a significant risk signal.
To facilitate comparison, we listed the ROR for the corresponding PTs of each drug, with bold text indicating that the PT is among the top 20 for the drug.
(PT: preferred term; AE: adverse event; SOC: system organ class; ROR: reporting odds ratio; CI: confidence intervals).

TABLE 3 The characteristics of pediatric patients treated with doxycycline, minocycline, and tigecycline, including the outcomes of IIH/ICP, suicidal ideation/suicide attempts, DRESS, thyroid dysfunction, and dental staining (specific to children under 8 years old).

Characteristics	IIH/ICP	Suicidal ideation/suicide attempts	DRESS	Thyroid dysfunction	Dental staining under 8 years old
Number					
total	117	44	150	77	7
doxycycline	28	35	13	14	7
minocycline	89	8	136	63	0
doxycycline + minocycline	0	1	0	0	0
tigecycline	0	0	1	0	0
Gender					
Female	92 (78.63%)	22 (50.00%)	86 (57.33%)	47 (61.04%)	5 (71.43%)
Male	24 (20.51%)	22 (50.00%)	64 (42.67%)	30 (38.96%)	2 (28.57%)
Missing	1 (0.85%)	0	0	0	0
Median age, (y)	15 [13,16]	15 [14,16]	15 [14,17]	16 [16,16]	4 [3.5,5.5]
Median time to the onset, (d)					
total	53 [17,172]				
doxycycline	151 [72,196]				
minocycline	31 [16,122]	9 [7.5,12]	36 [20,49]		

(IIH: idiopathic intracranial hypertension; ICP: increased intracranial pressure; DRESS: drug reactions with eosinophilia and systemic symptoms).

For each drug, we selected the top 20 PTs based on the number of reports that exhibited a significant risk signal and categorized them by SOC. After compiling the results for the three drugs, we listed the ROR for the corresponding PTs of each drug to facilitate comparison, with bold text indicating that the PT is among the top 20 for the drug. The results are presented in Table 2. In Table 2, we excluded signals that were clearly irrelevant to the drugs, such as death, drug ineffective, condition aggravated, treatment failure, drug resistance, sepsis, and off-label use. Additionally, for a comprehensive overview of the significant risk signals associated with each drug, please refer to Supplementary Table S2.

3.2.1 Gastrointestinal disorders

Gastrointestinal disorders in this study commonly presented with vomiting, nausea, ulcerative colitis, dysphagia, esophageal ulcer, esophagitis, upper abdominal pain, pancreatitis, and acute pancreatitis. Doxycycline was associated with all of these conditions except pancreatitis and acute pancreatitis, showing RORs of 1.82, 1.83, 9.17, 8.31, 389.61, 55.53, and 2.33, respectively, which were higher than those associated with minocycline. Minocycline only exhibited a risk for nausea, with an ROR of 1.69. Tigecycline was associated with vomiting, nausea, pancreatitis, and acute pancreatitis, with RORs of 3.81, 7.33, 12.72, and 22.39, respectively.

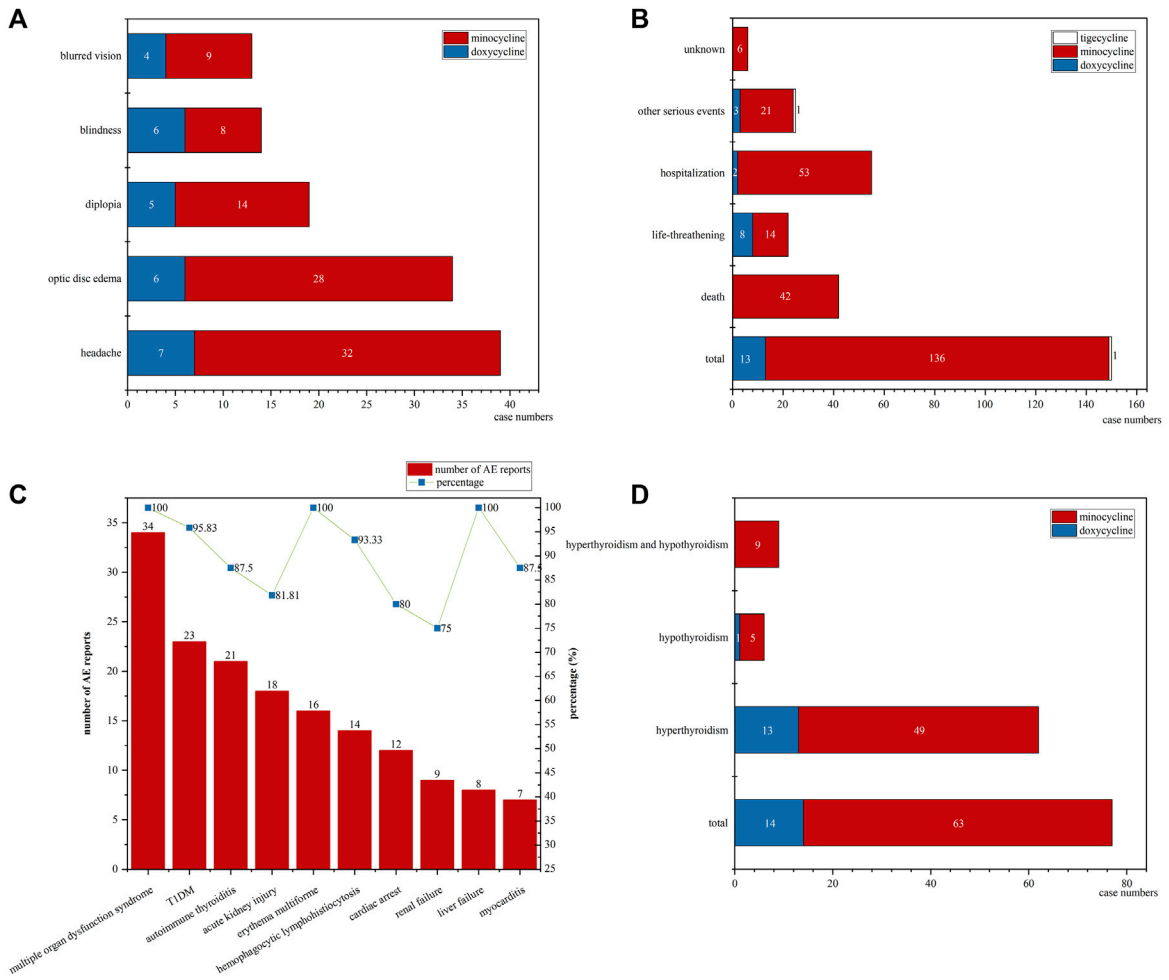


FIGURE 3
The details of IIH/ICP, DRESS, and thyroid dysfunction cases: **(A)** The co-occurring AEs in IIH/ICP cases; **(B)** The outcomes distribution in all DRESS cases; **(C)** The number of co-occurring AEs and their respective percentages of the total reports for each AE in minocycline-associated DRESS cases; **(D)** The distribution of hyperthyroidism and hypothyroidism among thyroid dysfunction cases. (IIH: idiopathic intracranial hypertension; ICP: increased intracranial pressure; DRESS: drug reactions with eosinophilia and systemic symptoms; AE: adverse event).

3.2.2 Nervous system disorders

Nervous system disorders in this study primarily manifested as headache, idiopathic intracranial hypertension (IIH), increased intracranial pressure (ICP), and dizziness. Minocycline was associated with all of these risks, exhibiting RORs of 2.33, 58.18, 13.96, and 1.88, respectively, which were higher than those associated with doxycycline. Doxycycline was specifically linked to IIH and ICP, with RORs of 14.62 and 13.58, respectively. No significant signals were observed for tigecycline.

In pediatric patients diagnosed with either IIH or ICP, a total of 117 cases were identified, as detailed in Table 3 and illustrated in Figure 3A. Among these, 28 were linked to doxycycline, while 89 were associated with minocycline. Females, accounting for 78.63% of the cases, were affected more frequently. The median age of these patients was 15 years. The median time to onset of the symptoms was 31 days for minocycline and 53 days for doxycycline. The co-occurring AEs in these patients included headache in 39 patients (doxycycline: 7, minocycline: 32), optic disc edema in 34 patients (doxycycline: 6, minocycline: 28), diplopia in 19 patients (doxycycline: 5, minocycline: 14), blindness in 14 patients (doxycycline: 6, minocycline: 8), and blurred vision in 13 patients (doxycycline: 4, minocycline: 9).

3.2.3 Psychiatric disorders

In our study, psychiatric disorders were predominantly characterized by depression, suicidal ideation, and suicide attempt. These risks were exclusively associated with doxycycline, with RORs of 3.71, 3.15, and 2.28, respectively. No significant risk signals were identified for minocycline and tigecycline.

For pediatric patients experiencing suicidal ideation and suicide attempts, the characteristics are detailed in Table 3. In total, 44 cases were reported, with 35 cases linked to doxycycline, 8 cases to minocycline, and one case associated with both medications. Fortunately, there were no fatalities among these children. The male-to-female ratio was 1:1. The median age of these patients was 15 years, and the youngest was 11 years old. Notably, the median onset time of symptoms associated with minocycline was only 9 days (95% CI: 7.5–12 days). Unfortunately, the data related to the onset time for doxycycline were incomplete.

3.2.4 Hepatobiliary disorders

Hepatobiliary disorders in this study typically presented as sclerosing cholangitis, drug-induced liver injury, autoimmune hepatitis, and hepatotoxicity. For minocycline, the primary risks identified included drug-induced liver injury, autoimmune hepatitis, and hepatitis, with RORs of 26.23, 90.72, and 3.62, respectively. These RORs were notably higher compared to those associated with doxycycline. The identified risks for doxycycline included sclerosing cholangitis, drug-induced liver injury, and autoimmune hepatitis, with RORs of 190.93, 5.85, and 10.53, respectively. Tigecycline was specifically associated with a risk of hepatotoxicity, with an ROR of 71.55.

3.2.5 Skin and subcutaneous tissue disorders

In our study, skin and subcutaneous tissue disorders were typically characterized by drug reactions with eosinophilia and systemic symptoms (DRESS), neutrophilic dermatosis, photosensitivity reaction, urticaria, and dermatitis. Among the evaluated drugs, tigecycline was only associated with a risk of dermatitis. Minocycline exhibited stronger AE signals compared to doxycycline in DRESS and urticaria risk signals, with RORs of 29.64 *versus* 4.21 for DRESS and 2.30 *versus* 0.92 for urticaria. Additionally, unlike minocycline and tigecycline, doxycycline also showed risk signals for neutrophilic dermatosis and photosensitivity reaction, with RORs of 1818.21 and 26.09, respectively.

Focusing on pediatric DRESS cases, we detail the results in Table 3 and illustrate them in Figures 3B,C. Our research identified a total of 150 cases: 13 associated with doxycycline, 136 with minocycline, and only 1 with tigecycline, accounting for 0.38%, 13.86%, and 0.71% of the total AE reports for each drug, respectively. Females represented the majority of affected patients, comprising 57.33% of the cases. The median age was 15 years. For minocycline cases, the median time to onset of DRESS symptoms was 36 days (95% CI: 20–49 days). The outcomes of these cases are shown in Figure 3B. Doxycycline was not associated with any fatalities but was associated with 8 life-threatening cases. In stark contrast, minocycline had a more severe impact, being linked to 42 deaths, which accounted for 30.88% of the drug's DRESS cases, and 14 life-threatening cases.

In the minocycline-related DRESS cases, our study also analyzed their co-occurring AEs, with the results displayed in Figure 3C. We observed 34 instances of multiple organ dysfunction syndrome, 23 of Type 1 Diabetes Mellitus (T1DM), 21 of autoimmune thyroiditis, 18 of acute kidney injury, 16 of erythema multiforme, 14 of hemophagocytic lymphohistiocytosis, 12 of cardiac arrest, 9 of renal failure, 8 of liver failure, and 7 of myocarditis. Remarkably, these instances corresponded to 100%, 95.83%, 87.50%, 81.81%, 100%, 93.33%, 80.00%, 75.00%, 100.00%, and 87.50% of the total reports for each PT. Interestingly, although we observed 38 cases of autoimmune hepatitis and 46 of lupus-like syndrome, none of these conditions were noted in the minocycline-related DRESS cases.

3.2.6 Endocrine disorders

In our study, the most prominent risk signals in endocrine disorders were hyperthyroidism and thyroiditis. The RORs for these conditions in association with minocycline were 111.12 and 439.78, respectively, which were significantly higher than those for doxycycline. For doxycycline, the primary risk signal was hyperthyroidism, with an ROR of 33.49. No significant risk signals were observed for tigecycline.

For thyroid dysfunction, including both hyperthyroidism and hypothyroidism, the details are presented in Table 3 and illustrated in Figure 3D. A total of 77 cases were identified. Of these, 14 were related to doxycycline and 63 to minocycline. The doxycycline-related cases comprised 13 cases of hyperthyroidism and 1 of hypothyroidism. The minocycline-related cases included 49 with hyperthyroidism, 5 with hypothyroidism, and 9 with both conditions. Females, accounting for 61.04%, were more frequently affected. In addition, the median age was 16 years.

3.3 Dental staining risks in children under 8 years old linked to tetracyclines

Focused on children under 8 years old, our study assessed tetracycline-related dental staining risks. In this age group, we collected 103 doxycycline-associated cases, 15 minocycline-associated cases, and 71 tigecycline-associated cases in total. The characteristics of dental staining within this age group are detailed in Table 3. Specifically, we identified 7 instances linked to doxycycline (ROR = 107.16%, 95% CI: 49.67–231.18), with the median age being 4 years (95% CI: 3.5–5.5 years); no cases were reported for minocycline and tigecycline. However, due to incomplete data and inherent limitations of the FAERS database, the duration of these treatments and the permanence of the dental discoloration remain unclear.

4 Discussion

In this study, we employed the ROR method to detect adverse reaction signals from the FAERS database, aiming to assess the safety of tetracyclines in pediatric populations.

From January 2005 to September 2023, we observed a predominantly gradual increase in the number of AE reports per 3-year period, underscoring the critical need for ongoing monitoring and evaluation of the safety of these drugs in children. Additionally, our analysis revealed that both doxycycline and minocycline were reported more frequently in female children, consistent with previous research (Martins et al., 2021). Notably, the severity of adverse reactions attributed to minocycline significantly exceeded those to doxycycline, aligning with prior studies (Smith and Leyden, 2005; Tasina et al., 2011; Lebrun-Vignes et al., 2012; Martins et al., 2021). Furthermore, we discovered that the fatalities associated with tigecycline accounted for 23.57% of the cases in our study.

Previous studies in adult populations have indicated that tigecycline is associated with an increased risk of all-cause mortality (McGovern et al., 2013; Shen et al., 2015; Pfizer Inc, 2020). In pediatric care, tigecycline is predominantly utilized for treating infections caused by MDR/XDR pathogens, with most of these patients being in the Intensive Care Unit (ICU). The severity of MDR/XDR infections and the underlying diseases may lead to higher mortality rates in immunocompromised patients, particularly in pediatric patients (Song et al., 2018). Previous reports indicate that the all-cause mortality rate in children

treated with tigecycline varies between 18% and 40% (Ozkaya-Parlakay et al., 2020; Song et al., 2018; Zeng et al., 2017). In our study, given that 81.81% of tigecycline-related fatal cases involved PTs such as drug ineffective, drug ineffective for unapproved indication, treatment failure, drug resistance, intentional product use issue, multiple drug resistance, and product use issue, we are unable to assess the risk of death in children using tigecycline, and further research is needed. Additionally, the limited number of reports on tigecycline also restricted us to fully evaluate its safety in pediatric cases.

After the disproportionality analysis, it was observed that, apart from the risks of psychiatric disorder, the other 23 SOCs were all documented in their respective FDA prescribing information (Patheon Pharmaceuticals Inc, 2017; Mayne Pharma, 2022; Pfizer Inc, 2020). It is important to note that while the FDA prescribing information does not mention psychiatric risks associated with doxycycline, the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has documented depression, anxiety, and hallucination as rare side effects of doxycycline (Medsafe, 2023). The prevalent adverse reactions align with the findings from prior research: gastrointestinal responses are mainly associated with doxycycline and tigecycline, whereas minocycline is more frequently linked to neurological disorders and diseases of the skin and subcutaneous tissues.

4.1 Psychiatric risks in children

Our research has indicated a potential increase in psychiatric risks associated with the use of doxycycline in children, which is not currently mentioned in its FDA prescribing information. Specifically, our findings suggested a possible link between doxycycline and symptoms such as depression, suicidal ideation, and suicide attempt. To our knowledge, our study appears to be the first to identify the psychiatric risks of tetracyclines in pediatric patients. Previous case reports documented several severe psychiatric reactions to doxycycline in adults. Dyer described a 19-year-old female student from Cambridge University who developed paranoia and tragically committed suicide after taking doxycycline to prevent malaria (Dyer, 2020). Additionally, Healy et al. detailed three cases: two males, neither with a history of mental illness or substance abuse, committed suicide after taking doxycycline for 6 days and 8 weeks, respectively. Genetic testing revealed the former had the CYP2C19*2 heterozygous genotype, which is associated with diminished cytochrome P450 enzyme activity. Intriguingly, his two brothers also suffered severe anxiety after using doxycycline, and the symptom resolved after discontinuation of the medication. The third case involved a 33-year-old woman who developed suicidal thoughts on the third day after taking doxycycline for recurrent acne, which subsided after discontinuing the medication (Atigari et al., 2013). It is important to note that these previous case reports predominantly involve doxycycline, with no reported cases yet involving minocycline.

Notably, while our findings indicated a correlation between doxycycline and increased psychiatric risks in children, establishing a direct cause remains challenging. This is partly due to confounding factors, such as existing psychiatric illnesses, the use of additional medications, the sensitive stage of adolescence, and the illnesses being treated with tetracyclines, which might have psychiatric implications. Previous studies have shown that conditions like acne and Lyme disease, which are often treated with these antibiotics, also increase psychiatric risks (Eichenfield et al., 2021; Fallon et al., 2021). Therefore, more thorough and methodical research is essential to fully understand the relationship between tetracyclines and psychiatric risks.

4.2 Risk of DRESS in children

Our study has shown that both doxycycline and minocycline may elevate the risk of DRESS, with minocycline demonstrating stronger AE signals compared to doxycycline. DRESS syndrome, a severe drug-induced hypersensitivity reaction, is typically characterized by rash, fever, blood test abnormalities, and internal organ damage. This condition affects children disproportionately more than adults, typically manifesting as a measles-like rash 2–8 weeks after the initiation of drug therapy. The syndrome carries a mortality risk of up to 10%, primarily due to complications such as liver damage or myocarditis (Manieri et al., 2023; Wei et al., 2023). Following the cessation of the causative medication, approximately 5.9%–16% of patients may suffer long-term effects, including organ dysfunction and autoimmune conditions like autoimmune thyroiditis, hepatitis, and T1DM (Wei et al., 2023). These ongoing symptoms might result from the formation of doxycycline/minocycline-melanin complexes. A study found that minocycline can still be detected in the blood 17 months after discontinuing minocycline treatment (Maubec et al., 2008).

Utilizing data from the French Pharmacovigilance Database and marketing authorization holders for the years 1985–2007, focused on the general population, previous research found that the prevalence of minocycline-induced DRESS varied between 4% and 8% (Lebrun-Vignes et al., 2012). Furthermore, earlier studies have shown that the mortality rate for DRESS is 5.4% in pediatric patients, compared to 10% in adults (Manieri et al., 2023; Wei et al., 2023). Our analysis revealed that 13.86% of pediatric cases associated with minocycline developed DRESS, with 30.88% of these cases resulting in fatalities in the FAERS database. However, the precise prevalence and mortality rate of minocycline-induced DRESS in children still necessitates further research, owing to the FAERS database's inherent limitations and the scarcity of previous studies.

In our analysis of co-occurring AEs in minocycline-associated DRESS cases, we observed a significantly high number of multiple organ dysfunction syndrome, T1DM, and autoimmune thyroiditis, which are all long-term sequelae. However, studies detailing these long-term sequelae of minocycline-associated DRESS remain limited. Lan et al. documented a case of a 13-year-old girl who developed DRESS after minocycline treatment for acne, which led to a liver transplant and the diagnosis of autoimmune T1DM, requiring ongoing insulin therapy (Lan et al., 2016). Similarly, Brown et al. reported a 15-year-old female adolescent who developed DRESS 4 weeks after starting minocycline therapy for acne, resulting in autoimmune hyperthyroidism 7 weeks later and autoimmune T1DM 7 months after discontinuing minocycline therapy (Brown et al., 2009). Furthermore, our study found no instances of DRESS coinciding with autoimmune hepatitis or lupus-

like syndrome, suggesting that minocycline could induce autoimmunity even without causing DRESS, aligning with previous findings (El-Hallak et al., 2008).

4.3 Thyroid dysfunction in children

In prior studies, numerous reports have highlighted thyroid pigment deposition associated with minocycline use, yet instances of thyroid dysfunction were seldom reported in these cases (Goto et al., 2022). Additionally, contrary to the common association of thyroid dysfunction with autoimmune thyroiditis, non-autoimmune thyroid dysfunctions have been less frequently reported (Benjamin and Calikoglu, 2007). Our research identified 77 cases of thyroid dysfunction, with 14 related to doxycycline and 63 to minocycline. Notably, none of these cases were reported to have autoimmune thyroiditis. Among the limited case reports available, instances involving adults were rare (Tacon et al., 2008), whereas adolescents were comparatively more frequent (Benjamin and Calikoglu, 2007; Pollock et al., 2016; Millington et al., 2019). Researchers Pollock et al. and Millington et al. reported three and nine adolescent cases, respectively, who developed thyroid dysfunction following acne treatment, with one case related to doxycycline and eleven to minocycline. Most patients' thyroid function normalized within 4.5 months after stopping the medication. However, one case of minocycline-associated hypothyroidism persisted for more than 4.5 years after discontinuation (Pollock et al., 2016; Millington et al., 2019). Despite this, thyroid dysfunction warnings are not included in the package insert for doxycycline and are mentioned only as "cases of abnormal thyroid function have been reported" for minocycline (Patheon Pharmaceuticals Inc, 2017; Mayne Pharma, 2022).

4.4 IIH risk in children

IIH is a serious medical condition characterized by elevated intracranial pressure, predominantly affecting young, overweight women, presenting symptoms like headaches, pulsatile tinnitus, and visual issues including peripheral vision loss, transient vision blurring, and diplopia (Grech et al., 2020). In cases of IIH triggered by tetracyclines, both the duration of symptoms and outcomes vary considerably after medication discontinuation (Martins et al., 2021; Passi et al., 2022). While some reports indicate symptoms may resolve spontaneously after stopping the medication, there are also cases of permanent vision loss and persistent visual impairment (Somech et al., 1999; Paramo and Leishangthem, 2023). In our research, though the long-term outcome of these symptoms was beyond our study's scope, we observed 14 cases of blindness linked to doxycycline (6 cases) and minocycline (8 cases), highlighting the potential severity of IIH's impact.

4.5 Potential risks of dental discoloration from tetracyclines in children below 8 years

In our research on children below 8 years, we observed dental discoloration exclusively in cases treated with doxycycline (ROR = 107.16%, 95% CI: 49.67–231.18). However, both the duration of the treatment and the permanence of the staining remained uncertain. Contrary to our findings, a recent review involving 338 children under 8 years old found no significant difference in dental discoloration between the doxycycline-treated group and the control group (Stultz and Eiland, 2019). A case report also described reversible tooth staining in a 6-year-old girl treated with doxycycline (Joshi et al., 2020). In 2018, the American Academy of Pediatrics (AAP) revised their guidelines in the Red Book, stating that doxycycline can be administered for short durations (i.e., 21 days or less) regardless of the patient's age. Additionally, the Red Book removed the warning about potential tooth discoloration for doxycycline, although it remains for tetracycline (American Academy of Pediatrics, 2018). Currently, doxycycline is recommended as the treatment of choice for Lyme disease and Rocky Mountain spotted fever in children of all ages (American Academy of Pediatrics, 2018; Meissner and Steere, 2022). With the increasing use of doxycycline in this age group, additional safety studies would be beneficial. As for minocycline and tigecycline, although our study did not detect a risk signal of tooth staining, there are related case reports in children under 8 years. Reported dental discoloration in a 7-year-old girl after treatment with minocycline as a root canal medication. Despite the improvement in the cervical shade following three walking bleaching procedures, the tooth did not return to its original shade (Kim et al., 2010). Zhu et al. observed mild yellow discoloration in two children under 8 years old after discontinuing tigecycline for 4 years (Zhu et al., 2021).

Our study has several limitations. Firstly, the FDA does not require a direct causal link between AEs and medications, limiting our ability to establish a definitive cause-and-effect relationship. Secondly, FAERS is a voluntary reporting system, resulting in potential gaps in data quality, accuracy, or completeness. Thirdly, the FDA does not receive a product's all AE reports. The reports in the database may also be influenced by factors like product longevity and public awareness. Therefore, FAERS data cannot be used to calculate the incidence of an AE in the population. Fourthly, the ROR method we employed, although straightforward, is particularly sensitive to individual data points, and the statistic fluctuates greatly if the cell frequency is small. Hence, we focused on AEs with higher case counts to reduce false positives. Finally, our analysis was exclusively restricted to the safety signals of doxycycline, minocycline, and tigecycline in pediatric use, and other tetracyclines were excluded due to the limited number of reports.

5 Conclusion

Using real-world data from the FAERS, this study evaluated the safety profiles of three tetracyclines in pediatric patients. Our findings indicated that for pediatric patients, the majority of results were in line with the prescribing information and previous studies, and minocycline tended to cause more frequent and severe AEs than doxycycline. However, it is noteworthy that exceptions were found for psychiatric disorders and thyroid dysfunction associated with doxycycline, which are not mentioned in its prescribing information. Additionally, further safety studies on tigecycline

are still needed for children. When prescribing tetracyclines to pediatric patients, a careful risk-benefit assessment is crucial. We advise closely monitoring mental health, immune function, thyroid, liver, eye, and dental health.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YQ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing–original draft. YC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing–original draft. QW: Data curation, Methodology, Writing–original draft. JL: Data curation, Writing–original draft. XG: Writing–original draft, Data curation. QG: Writing–original draft. PD: Writing–original draft. HZ: Conceptualization, Funding acquisition, Project administration, Writing–review and editing. HM: Conceptualization, Funding acquisition, Project administration, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was funded by Jiangsu Pharmaceutical Association—HENGRUI hospital pharmacy fund scientific research project (No: H202107); Nanjing Pharmaceutical Association—CHANGZHOU SIYAO hospital pharmacy scientific research fund grant project (No: 2021YX004); National Natural Science Foundation of China (No: 81903870); Nanjing Municipal Health Science and Technology Development Special Fund Project Plan—Key Medical Science and Technology Development Project (No: ZKX23020).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1413944/full#supplementary-material

References

American Academy of Pediatrics (2018). *Red Book: 2018 report of the committee on infectious diseases*. Elk Grove Village, IL: American Academy of Pediatrics, 905–906. doi:10.1542/9781610021470

Atigari, O. V., Hogan, C., and Healy, D. (2013). Doxycycline and suicidality. *BMJ Case Rep.* 2013, bcr2013200723. doi:10.1136/bcr-2013-200723

Benjamin, R. W., and Calikoglu, A. S. (2007). Hyperthyroidism and lupus-like syndrome in an adolescent treated with minocycline for acne vulgaris. *Pediatr. Dermatol* 24 (3), 246–249. doi:10.1111/j.1525-1470.2007.00395.x

Brown, R. J., Rother, K. I., Artman, H., Mercurio, M. G., Wang, R., Looney, R. J., et al. (2009). Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch. Dermatol* 145 (1), 63–66. doi:10.1001/archdermatol.2008.521

Bryer, M. S., Schoenbach, E. B., Chandler, C. A., Bliss, E. A., and Long, P. H. (1948). Aureomycin; experimental and clinical investigations. *J. Am. Med. Assoc.* 138 (2), 117–119. doi:10.1001/jama.1948.02900020013004

Candore, G., Juhlin, K., Manlik, K., Thakrar, B., Quarcoo, N., Seabroke, S., et al. (2015). Comparison of statistical signal detection methods within and across spontaneous reporting databases. *Drug Saf.* 38 (6), 577–587. doi:10.1007/s40264-015-0289-5

Chopra, I., and Roberts, M. (2001). Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol. Mol. Biol. Rev.* 65 (2), 232–260. doi:10.1128/MMBR.65.2.232-260.2001

Chou, C. C., Shen, C. F., Chen, S. J., Chen, H. M., Wang, Y. C., Chang, W. S., et al. (2019). Recommendations and guidelines for the treatment of pneumonia in Taiwan. *J. Microbiol. Immunol. Infect.* 52 (1), 172–199. doi:10.1016/j.jmii.2018.11.004

Dyer, C. (2020). Doxycycline: coroner calls for MHRA to review side effects after student jumped from plane. *BMJ* 371, m4102. doi:10.1136/bmj.m4102

Eichenfield, D. Z., Sprague, J., and Eichenfield, L. F. (2021). Management of acne vulgaris: a review. *JAMA* 326 (20), 2055–2067. doi:10.1001/jama.2021.17633

El-Hallak, M., Giani, T., Yeniay, B. S., Jacobs, K. E., Kim, S., Sundel, R. P., et al. (2008). Chronic minocycline-induced autoimmunity in children. *J. Pediatr.* 153 (3), 314–319. doi:10.1016/j.jpeds.2008.03.013

Emmerson, A. M., and Jones, A. M. (2003). The quinolones: decades of development and use. *J. Antimicrob. Chemother.* 51 (Suppl. 1), 13–20. doi:10.1093/jac/dkg208

Fallon, B. A., Madsen, T., Erlangsen, A., and Benros, M. E. (2021). Lyme borreliosis and associations with mental disorders and suicidal behavior: a nationwide Danish cohort study. *Am. J. Psychiatry* 178 (10), 921–931. doi:10.1176/appi.ajp.2021.20091347

Goto, Y., Ohba, K., Sasaki, S., and Nishino, N. (2022). Minocycline and black thyroid. *QJM* 115 (6), 403–404. doi:10.1093/qjmed/hcac113

Grech, O., Mollan, S. P., Wakerley, B. R., Alimajstorovic, Z., Lavery, G. G., and Sinclair, A. J. (2020). Emerging themes in idiopathic intracranial hypertension. *J. Neurol.* 267 (12), 3776–3784. doi:10.1007/s00415-020-10090-4

Ishiwada, N., Shinjoh, M., Kusama, Y., Arakawa, H., Ohishi, T., Saitoh, A., et al. (2023). Guidelines for the management of respiratory infectious diseases in children in Japan 2022. *Pediatr. Infect. Dis. J.* 42 (10), e369–e376. doi:10.1097/INF.0000000000004041

Joshi, G., Dhingra, D., Pandav, S. S., and Kaushik, S. (2020). Doxycycline-induced staining of teeth and malar rash in a child. *J. Postgrad. Med.* 66 (1), 54. doi:10.4103/jpgm.JPGM_454_19

Kim, J. H., Kim, Y., Shin, S. J., Park, J. W., and Jung, I. Y. (2010). Tooth discoloration of immature permanent incisor associated with triple antibiotic therapy: a case report. *J. Endod.* 36 (6), 1086–1091. doi:10.1016/j.joen.2010.03.031

Lan, J., Lahoti, A., and Lew, D. B. (2016). A severe case of minocycline-induced DRESS resulting in liver transplantation and autoimmune sequelae. *Ann. Allergy Asthma Immunol.* 116 (4), 367–368. doi:10.1016/j.anai.2015.12.010

Lantos, P. M., Rumbaugh, J., Bockenstedt, L. K., Falck-Ytter, Y. T., Aguero-Rosenfeld, M. E., Auwaerter, P. G., et al. (2021). Clinical practice guidelines by the infectious diseases society of America (IDSA), American Academy of neurology (AAN), and American college of rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. *Clin. Infect. Dis.* 72 (1), e1–e48. doi:10.1093/cid/ciaa1215

LaPlante, K. L., Dhand, A., Wright, K., and Lauterio, M. (2022). Re-establishing the utility of tetracycline-class antibiotics for current challenges with antibiotic resistance. *Ann. Med.* 54 (1), 1686–1700. doi:10.1080/07853890.2022.2085881

Lebrun-Vignes, B., Kreft-Jais, C., Castot, A., and Chosidow, O. (2012). Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br. J. Dermatol* 166 (6), 1333–1341. doi:10.1111/j.1365-2133.2012.10845.x

Manieri, E., Dondi, A., Neri, I., and Lanari, M. (2023). Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome in childhood: a narrative review. *Front. Med. (Lausanne)* 10, 1108345. doi:10.3389/fmed.2023.1108345

Martins, A. M., Marto, J. M., Johnson, J. L., and Graber, E. M. (2021). A review of systemic minocycline side effects and topical minocycline as a safer alternative for treating acne and rosacea. *Antibiot. (Basel)* 10 (7), 757. doi:10.3390/antibiotics10070757

Maubec, E., Wolkenstein, P., Loriot, M. A., Wechsler, J., Mulot, C., Beaune, P., et al. (2008). Minocycline-induced DRESS: evidence for accumulation of the culprit drug. *Dermatology* 216 (3), 200–204. doi:10.1159/000112926

Mayne Pharma (2022). Prescribing information of DORYX®. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050795s030lbl.pdf (Accessed April 8, 2024).

McGovern, P. C., Wible, M., El-Tahtawy, A., Biswas, P., and Meyer, R. D. (2013). All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. *Int. J. Antimicrob. Agents* 41 (5), 463–467. doi:10.1016/j.ijantimicag.2013.01.020

Medsafe (2023). Prescribing information of DOXINE®. Available at: https://www.medsafe.govt.nz/profs/datasheet/d/doxinetab.pdf (Accessed April 8, 2024).

Meissner, H. C., and Steere, A. C. (2022). Management of pediatric Lyme disease: updates from 2020 Lyme guidelines. *Pediatrics* 149 (3), e2021054980. doi:10.1542/peds.2021-054980

Millington, K., Charrow, A., and Smith, J. (2019). Case series: minocycline-associated thyroiditis. *Horm. Res. Paediatr.* 92 (4), 276–283. doi:10.1159/000502843

National Health Commission of the People's Republic of China (2023). Guidelines for the diagnosis and treatment of Mycoplasma pneumoniae pneumonia in children(2023 edition). *Inter J. Epidemiol. Infect. Dis.* 50 (02), 79–85. doi:10.3760/cma.j.cn331340-20230217-00023

Orylska-Ratynska, M., Placek, W., and Owczarczyk-Saczonek, A. (2022). Tetracyclines-an important therapeutic tool for dermatologists. *Int. J. Environ. Res. Public Health* 19 (12), 7246. doi:10.3390/ijerph19127246

Ozkaya-Parlakay, A., Gulhan, B., Kanik-Yuksek, S., Guney, D., Gonulal, D., Demirtas, G., et al. (2020). Tigecycline therapy in pediatric patients with multidrug resistant bacteremia. *Enferm. Infecc. Microbiol. Clin. (Engl Ed)* 38 (10), 471–473. doi:10.1016/j.eimc.2019.12.018

Paramo, R., and Leishangthem, L. (2023). Optic atrophy secondary to minocycline-induced idiopathic intracranial hypertension. *BMJ Case Rep.* 16 (3), e252731. doi:10.1136/bcr-2022-252731

Passi, S. F., Butcher, R., Orme, D. R., Warner, J. E. A., Stoddard, G. J., Crum, A. V., et al. (2022). Increased incidence of pseudotumor cerebri syndrome among users of tetracycline antibiotics. *J. Neuroophthalmol.* 42 (3), 323–327. doi:10.1097/WNO.0000000000001536

Paratek Pharmaceuticals Inc. (2021). Prescribing information of NUZYRA®. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209816s011,209817s010lbl.pdf (Accessed May 25, 2024).

Patheon Pharmaceuticals Inc (2017). Prescribing information of MINOCIN®. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050649s027lbl.pdf (Accessed April 8, 2024).

Pfizer Inc (2020). Prescribing information of TYGACIL®. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021821s049lbl.pdf (Accessed April 8, 2024).

Pollock, A. J., Seibert, T., and Allen, D. B. (2016). Severe and persistent thyroid dysfunction associated with tetracycline-antibiotic treatment in youth. *J. Pediatr.* 173, 232–234. doi:10.1016/j.jpeds.2016.03.034

Rodriguez, E. M., Staffa, J. A., and Graham, D. J. (2001). The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Saf.* 10 (5), 407–410. doi:10.1002/pds.615

Shen, F., Han, Q., Xie, D., Fang, M., Zeng, H., and Deng, Y. (2015). Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. *Int. J. Infect. Dis.* 39, 25–33. doi:10.1016/j.ijid.2015.08.009

Smilack, J. D. (1999). The tetracyclines. *Mayo Clin. Proc.* 74 (7), 727–729. doi:10.4065/74.7.727

Smith, K., and Leyden, J. J. (2005). Safety of doxycycline and minocycline: a systematic review. *Clin. Ther.* 27 (9), 1329–1342. doi:10.1016/j.clinthera.2005.09.005

Somech, R., Arav-Boger, R., Assia, A., Spirer, Z., and Jurgenson, U. (1999). Complications of minocycline therapy for acne vulgaris: case reports and review of the literature. *Pediatr. Dermatol* 16 (6), 469–472. doi:10.1046/j.1525-1470.1999.00106.x

Song, Y., Hu, L., Shu, Q., Ye, J., Liang, J., Chen, X., et al. (2018). Tigecycline salvage therapy for critically ill children with multidrug-resistant/extensively drug-resistant infections after surgery. *Int. J. Infect. Dis.* 75, 82–88. doi:10.1016/j.ijid.2018.08.007

Stultz, J. S., and Eiland, L. S. (2019). Doxycycline and tooth discoloration in children: changing of recommendations based on evidence of safety. *Ann. Pharmacother.* 53 (11), 1162–1166. doi:10.1177/1060028019863796

Tacon, L., Tan, C. T., Alvarado, R., Gill, A. J., Sywak, M., and Fulcher, G. (2008). Drug-induced thyroiditis and papillary carcinoma in a minocycline-pigmented black thyroid gland. *Thyroid* 18 (7), 795–797. doi:10.1089/thy.2008.0048

Tasina, E., Haidich, A. B., Kokkali, S., and Arvanitidou, M. (2011). Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect. Dis.* 11 (11), 834–844. doi:10.1016/S1473-3099(11)70177-3

Tetraphase Pharmaceuticals Inc. (2018). Prescribing information of XERAVA®. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf (Accessed May 25, 2024).

Watkins, R. R., and Deresinski, S. (2019). Omadacycline: a novel tetracycline derivative with oral and intravenous formulations. *Clin. Infect. Dis.* 69 (5), 890–896. doi:10.1093/cid/ciz242

Wei, B. M., Fox, L. P., Kaffenberger, B. H., Korman, A. M., Micheletti, R. G., Mostaghimi, A., et al. (2023). Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Part I. Epidemiology, pathogenesis, clinicopathological features, and prognosis. *J. Am. Acad. Dermatol.* 90, 885–908. doi:10.1016/j.jaad.2023.02.072

Wei, C., Liu, Y., Jiang, A., and Wu, B. (2022). A pharmacovigilance study of the association between tetracyclines and hepatotoxicity based on Food and Drug Administration adverse event reporting system data. *Int. J. Clin. Pharm.* 44 (3), 709–716. doi:10.1007/s11096-022-01397-5

Wenzel, R., Bate, G., and Kirkpatrick, P. (2005). Tigecycline. *Nat. Rev. Drug Discov.* 4 (10), 809–810. doi:10.1038/nrd1857

Zaenglein, A. L., Pathy, A. L., Schlosser, B. J., Alikhan, A., Baldwin, H. E., Berson, D. S., et al. (2016). Guidelines of care for the management of acne vulgaris. *J. Am. Acad. Dermatol* 74 (5), 945–973. doi:10.1016/j.jaad.2015.12.037

Zeng, J., Zhang, L., Gao, M., Wu, J., Wu, H., Chen, J., et al. (2017). Tigecycline treatment in an infant with extensively drug-resistant *Acinetobacter baumannii* bacteremia. *Int. J. Infect. Dis.* 61, 23–26. doi:10.1016/j.ijid.2017.05.013

Zhanel, G. G., Cheung, D., Adam, H., Zelenitsky, S., Golden, A., Schweizer, F., et al. (2016). Review of eravacycline, a novel fluorocycline antibacterial agent. *Drugs* 76 (5), 567–588. doi:10.1007/s40265-016-0545-8

Zhou, C., Peng, S., Lin, A., Jiang, A., Peng, Y., Gu, T., et al. (2023). Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* 59, 101967. doi:10.1016/j.eclinm.2023.101967

Zhu, Z., Yu, Q., Qi, G., Yang, J., Ni, Y., Ruan, W., et al. (2021). Tigecycline-induced tooth discoloration in children younger than eight years. *Antimicrob. Agents Chemother.* 65 (9), e0085421. doi:10.1128/AAC.00854-21

frontiers | Frontiers in Pharmacology

TYPE Brief Research Report
PUBLISHED 19 August 2024
DOI 10.3389/fphar.2024.1407228

OPEN ACCESS

EDITED BY
Jia-bo Wang,
Capital Medical University, China

REVIEWED BY
Zili Xie,
Icahn School of Medicine at Mount Sinai, United States
Jiayu (Daisy) Ye, Stanford University, United States

*CORRESPONDENCE
Moumita Bhaumik,
drmoumitabhaumik@gmail.com

RECEIVED 26 March 2024
ACCEPTED 29 July 2024
PUBLISHED 19 August 2024

CITATION
Sikdar S, Mitra D, Das O, Bhaumik M and Dutta S (2024) The functional antagonist of sphingosine-1-phosphate, FTY720, impairs gut barrier function.
Front. Pharmacol. 15:1407228.
doi: 10.3389/fphar.2024.1407228

The functional antagonist of sphingosine-1-phosphate, FTY720, impairs gut barrier function

Sohini Sikdar[1], Debmalya Mitra[2], Oishika Das[1], Moumita Bhaumik[1]* and Shanta Dutta[1]

[1]Division of Immunology , ICMR-National Institute for Research in Bacterial Infections (NIRBI), Kolkata, India, [2]Center of Radiological Research, Columbia University Irving Medical Center, New York, NY, United States

FTY720 or fingolimod is a known functional antagonist of sphingosine-1-phosphate (S1P), and it is effective in treating multiple sclerosis and preventing inflammatory bowel disease (IBD). Evidence shows that its use in mice can increase the susceptibility to mucosal infections. Despite the significant contribution of S1P to barrier function, the effect of the administration of FTY720 on the mucosal barrier has never been investigated. In this study, we looked into how FTY720 therapy affected the function of the gut barrier susceptibility. Administration of FTY720 to C57BL/6 mice enhances the claudin-2 expression and reduces the expression of claudin-4 and occludin, as studied by qPCR, Western blot, and immunofluorescence. FTY720 inhibits the Akt–mTOR pathway to decrease occludin and claudin-4 expression and increase claudin-2 expression. FTY720 treatment induced increased colonic inflammation, with notably greater immune cell infiltration, colon histopathology, and increased production of TNF-α, IFN-γ, CXCL-1, and CXCL-2 than that in control mice. Taking into account the close association of "the leaky gut" and gut dysbiosis among the major diseases, we therefore can infer that the vigilance of gut pathology should be maintained, where FTY720 is used as a treatment option.

KEYWORDS

FTY720, sphingosine-1-phosphate, occludin, claudin-4, gut permeability

Introduction

The mammalian gut is a multilayer system with an immunological barrier within and a physical barrier outside, thus enabling the gut microbiome to maintain equilibrium within the body. The gut barrier that maintains these luminal compounds needs to be considered. Bioactive phospholipid sphingosine-1-phosphate (S1P) has pleiotropic properties, which help in cell–cell integration (Santacreu et al., 2019), epithelial barrier regulation (Weigel et al., 2023), cell proliferation (Chen et al., 2017), migration (Chen et al. (2017) and Wang et al. (1999)), and survival (Van Brocklyn and Williams, 2012). S1P is ubiquitous in cells (Maceyka and Spiegel (2014), Le Stunff et al. (2004), and Schmidt et al. (2019)) and produced by key enzyme sphingosine kinase (SPHK) (Imamura et al. (2001) and Pulkoski-Gross et al. (2015)). SPHK catalyzes the ATP-dependent phosphorylation of sphingosine (Sph) and exists in two isoforms: SPHK1 and SPHK2 (Hatoum et al. (2017), Alemany et al.

(2007), and Liu et al. (2000)). S1P is reported to play an important role in tolerance by regulating innate immunity by acting through one or more than one of its five known receptors (S1PR1–S1PR5) (Chun et al., 2002), which are G-protein-coupled receptors (GPCRs) (Goetzl et al. (2000), and Hla et al. (2001)). FTY720 or fingolimod inhibits lymphocyte egress from the thymus, spleen, and lymph nodes (LNs) into the bloodstream and lymphatic system by modulating S1P signaling, thus restricting lymphocyte trafficking to target tissues (Chiba, 2005). When FTY720 enters the body, it is phosphorylated (FTY720-P) and binds to S1PR (Wang et al., 1999; Van Brocklyn and Williams, 2012; Chen et al., 2017; Santacreu et al., 2019; Weigel et al., 2023) and internalizes the receptors, except S1PR3, preventing its downstream signaling (Sykes et al., 2014). Interestingly, FTY720-P can only activate S1PR3, which is mostly present in neutrophils, monocytes, macrophages, and B cells (Bryan and Del Poeta, 2018), inducing further downward signaling (Sensken et al., 2008). Additionally, it influences the migration of dendritic cells (DCs) (Han et al., 2015), modulates DC-mediated pro-inflammatory signaling (Zeng et al., 2012), and is a potent suppressor of regulatory T-cell (Treg) proliferation (Wolf et al., 2009). Whether FTY720 regulates lymphocyte recirculation *in vivo* in an agonistic or a functional antagonistic manner, or in both, is still up for debate (Blanc et al., 2015). The FDA has authorized the medication FTY720 (trade name Gilenya) to treat multiple sclerosis relapse (Sharma et al., 2011). Several reports showed the protective efficacy of FTY720 in various preclinical models like oxazolone (Daniel et al., 2007a), TNBS (Daniel et al., 2007b), and DSS-induced murine models of colitis (Deguchi et al., 2006), as well as IL-10-deficient mouse model (Mizushima et al., 2004). FTY720 is in clinical trial for inflammatory bowel disease (IBD) patients (Danese et al., 2018). Furthermore, it showed therapeutic efficacy in the treatment of graft-versus-host disease (Ryu et al. (2020) and Gauthier et al. (2018)) and rheumatoid arthritis (Tsunemi et al. (2010) and Nakano et al. (2022)) in mouse and viral infection models (Miyamoto et al., 2001). FTY720 prevents colitis by modulating the colitogenic $CD4^{+}$T cells from the bone marrow (Fujii et al., 2008). However, being a structural homolog of S1P, which helps in promoting barrier function, the effect of FTY720 on the mucosal barrier has never been elucidated.

The body's largest interaction with the outside world is the gastrointestinal epithelium, which effectively creates a barrier that limits the mucosa's ability to absorb luminal toxins and antigens while permitting nutrient and water absorption. Epithelial cells use both the paracellular and transcellular transport pathways to form this specific barrier (Laksitorini et al., 2014). The paracellular route, however, which is controlled by the tight junction (TJ), is in charge of the highest level of apical cell–cell adhesion and has drawn the most attention for its function in controlling mucosal permeability in both healthy and pathological settings (Paradis et al., 2021). The TJ (also referred to as zonula occludens) controls the most apical cell-to-cell adhesion between neighboring epithelial and endothelial cells (Furuse (2010) and Bazzoni and Dejana (2004)). These TJ proteins include integral and transmembrane proteins, including the claudins, occludin, and junctional adhesion molecules (JAMs), which extend into the intercellular space and regulate the gate function, and cytoskeletal linker proteins, such as cingulin, ZO-1, ZO-2, and ZO-3, which anchor TJ-integral membrane proteins to the cell cytoskeleton (Heinemann and Schuetz (2019) and Heinemann and Schuetz (2019)). An uncontrolled flow of antigens across the intestinal epithelium and a malfunctioning intestinal barrier can tax the immune system of those who are vulnerable and alter the host–microbe balance, which can set off inflammatory processes in the gut or make mucosal infections more likely (Meddings (2008) and Yu et al. (2012)). A recent report showed that FTY720 therapy blunts the mucosal adaptive immune response, including the generation of Th1 cytokines, and impairs innate immunological responses, making mice more susceptible to *Citrobacter rodentium* infection (Murphy et al., 2012). However, the study did not assess the effect of FTY720 on the barrier function.

This study is designed and intended to investigate the effect of continuous dosing of FTY720 on the gut functional phenotype in a mouse model. We studied the TJ protein expression, gut permeability, and immune response in the gut of FTY720-treated mice compared with untreated control. Our results showed FTY720-treated mice exhibited downregulation of multiple TJ proteins, leading to an increase in gut permeability and inflammation, and these are associated with the inhibition of the AKT–mTOR signaling pathway. The mucosa of the mice shows indications of inflammation, including crypt hyperplasia, goblet cell loss, and immune cell infiltration at the crypt region. Our data clearly showed that continuous treatment with FTY720 increases the possibility of gut barrier disruption. To our knowledge, this is the first report indicating that FTY720 may jeopardize the critical barrier function and induce an immune response.

Materials and methods

Chemicals and reagents

Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco (Thermo Fisher Scientific). FTY720 (cat #SML0700) was purchased from Sigma-Aldrich. The cytokine detection ELISA kits were purchased from BD Biosciences (United States) and R&D Systems (United States). Primers were purchased from Integrated DNA Technologies. All the polyclonal antibodies for β-actin (sc-47778), occludin (ab216327), claudin-4 (ab53156), and claudin-2 (ab53032) and secondary anti-IgG (ab97080 and ab97023) antibodies were purchased from Santa Cruz Biotechnology and Abcam. For immunohistochemistry, an anti-MPO (PA5-16672, Invitrogen) antibody was used. Secondary IgG Alexa Fluor 488 (ab150081, Abcam) was used for TJ immunofluorescence. Rapamycin (cat #13346) was purchased from Cayman Chemical. The following antibodies were purchased and used for performing *in vitro* Western blot assay: p-Akt 1/2/3 (Ser 473) (cat #AF0016; Affinity), Akt (cat #GTX121937; GeneTex), P-mTOR (Ser 2,448) (D9C2) (cat #5536T; Cell Signaling Technology), and mTOR (7C10) (cat #2983S; Cell Signaling Technology). FACS antibodies used in immunofluorescence were as follows: FITC-CD3 (cat #100204; BioLegend), PerCP-CD19 (cat #115532; BioLegend), FITC-CD11b (cat #11-0112-85; eBioscience), and A700-Ly-6G (cat#127621; BioLegend).

Mice and animal ethics

C57BL/6 mice (6 weeks old) were procured from the ICMR-NICED Animal Facility of the institute. All the protocol for the study was approved by the Institutional Animal Ethics Committee of ICMR-NICED, Kolkata, India (PRO/151/July 2018–June 2021). Experiments were carried out in accordance with the guidelines laid down by the committee for the purpose of the control and supervision of experiments on animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi, India.

Treatment with FTY720

All mice were housed in cages containing straw bedding and held in pathogen-free facilities maintained at 24 °C with a 50% relative humidity and 12-h light:dark cycle. All mice had *ad libitum* access to standard rodent chow. The mice were divided into two groups (i.e., control and FTY720; n = 5/group). Mice in the FTY720 group were provided 3 mg/kg body weight (Choi et al., 2011) (Rau et al., 2011) of FTY720 orally for 14 days, whereas mice from the control group were provided normal saline. Food and water consumption was monitored throughout the experimental period. The body weights of the mice were also measured at regular time intervals. The mice were euthanized on day 15.

Gut permeability assay

On the day of euthanasia, mice from both the control and treated groups were force-fed 44 mg/100 g body weight FITC-labeled 4-kDa dextran (FD-4; MW, 4,000 Da; Sigma-Aldrich; Merck KGaA) via gavage following fasting overnight (Liu et al. (2020), Chakraborty et al. (2023), and Kang et al. (2017)). After 4 h of FD-4 administration, blood was collected and centrifuged at 2,500 × g for 10 min at 4°C to collect the serum. The fluorescence intensity of FD-4 in the serum was determined using a multimode reader at an excitation and emission wavelength of 485 nm and 520 nm, respectively. Subsequently, a standard curve was generated using serial dilutions of FD-4 from 1,000 μg/mL to 0.

Bacterial translocation

A 40 mg portion of mice liver was collected under aseptic conditions after the mice were euthanized. Liver samples were washed in 200 μL PBS containing gentamicin (50 μg/mL) and then homogenized in ice-cold PBS. A measure of 100 μL of each tissue homogenate was spread onto the nutrient agar and incubated at 37°C for 24 h. The number of bacterial colonies was counted based on the dilution factor and expressed as colony-forming unit (CFU). CFU/g of tissue denoted the amount of bacterial translocation.

Real-time PCR

RNA was extracted using TRIzol Reagent (Invitrogen, Massachusetts, United States) from each colon sample and quantified using a NanoDrop 8000 Spectrophotometer (Thermo Fisher Scientific, United States). A measure of 0.5 μg of RNA was taken for reverse transcription with oligo dT primers, dNTPs, RNase inhibitor, and MuLV reverse transcriptase according to the kit manual (PrimeScript 1st strand cDNA Synthesis Kit, Takara Bio) to synthesize cDNA. Quantitative PCR was conducted using the SYBR green master mix (TB Green Premix Ex Taq-II) and ROX reagent in a real-time PCR system, and the ΔCt values were calculated to determine relative changes in target genes. The primer sets used were as follows: GAPDH (>NM_001411843.1) (5′ACCCAGAAGACTGTGGATGG3′) (Tm = 59.01); (5′CACATTGGGGTAGGAACAC3′) (Tm = 55.49), product length = 170; occludin (>NM_001360538.1) (5′TCACTTTTCCTGCGGTGACT3′) (Tm = 59.53); (5′GGGAACGTGGCCGATATAATG3′) (Tm = 58.93), product length = 138; claudin-4 (>NM_009903.2) (5′TCGTGGGTGCTCTGGGGATGCTT3′) (Tm = 65.0); (5′GCGGATGACGTTGTGAGCGGTC3′) (Tm = 62.8), product length = 170; claudin-2 (>NM_001410421.1) (5′TATGTTGGTGCCAGCATTGT3′) (Tm = 58.08); (5′TCATGCCCACCACAGAGATA3′) (Tm - 58.12), product length = 205; claudin-1 (>NM_016674.4) (5′ATGCAAAGATGTTTTGCCACAG3′) (Tm = 58.60); 5′TACAAATTCCCATTGCAGCCC3′) (Tm = 59.17), product length = 210; junctional adhesion molecule-A (JAM-A) (>NM_172647.2) (5′CTGATCTTTGACCCCGTGAC3′) (Tm = 58.27); (5′ACCAGACGCCAAAAATCAAG3′) (Tm = 56.9), product length = 187; mucin-2 (>NM_023566.4) (5′ATGTCCTGACCAAGAGCGAA3′) (Tm = 56.2); (5′GATTTGAAGGCCACCACGTT3′) (Tm = 56.0), product length = 142; cathelicidin (>NM_009921.2) (5′GGCAGCTACCTGAGCAATGT3′) (Tm = 59.6); (5′CTGTGCACCAGGCTCGTTA3′) (Tm = 59.8), product length = 122; and hepcidin (>NM_032541.2) (5′AGGGCAGACATTGCGATACC3′) (Tm = 57.5); (5′GCAACAGATACCACACTGGGA3′) (Tm = 57), product length = 111.

Cell culture

HT-29 cells, the human colorectal adenocarcinoma cells (kind gift from Dr. Sushmita Bhattacharya, ICMR-NICED), were cultured in DMEM with high glucose, supplemented with 10% FBS with 100 U/mL penicillin and 100 μg/mL streptomycin in humidified air/CO_2 (5% CO_2) at 37 °C within tissue culture flasks. Cell viability with FTY720 treatment at different doses was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. HT-29 cells were seeded with a density of 10^6 cells/well and grouped into control, FTY720 (20 μM), and rapamycin (500 nM) groups, and incubated for 48 h. Thereafter, the cells were lysed with RIPA lysis buffer (5M NaCl, 0.5M EDTA, 1M Tris-HCl (pH 8.0), 0.5% Tween-20, 10% SDS, PMSF, and dH_2O), followed by Western blotting, as described below.

SDS PAGE and Western blotting

Colonic sections were washed with PBS and homogenized in RIPA lysis buffer. The total protein concentration of the sample was determined using Thermo Scientific™ Pierce™ BCA Protein Assay Kit (23225). A measure of 30–50 μg of each lysate was loaded into

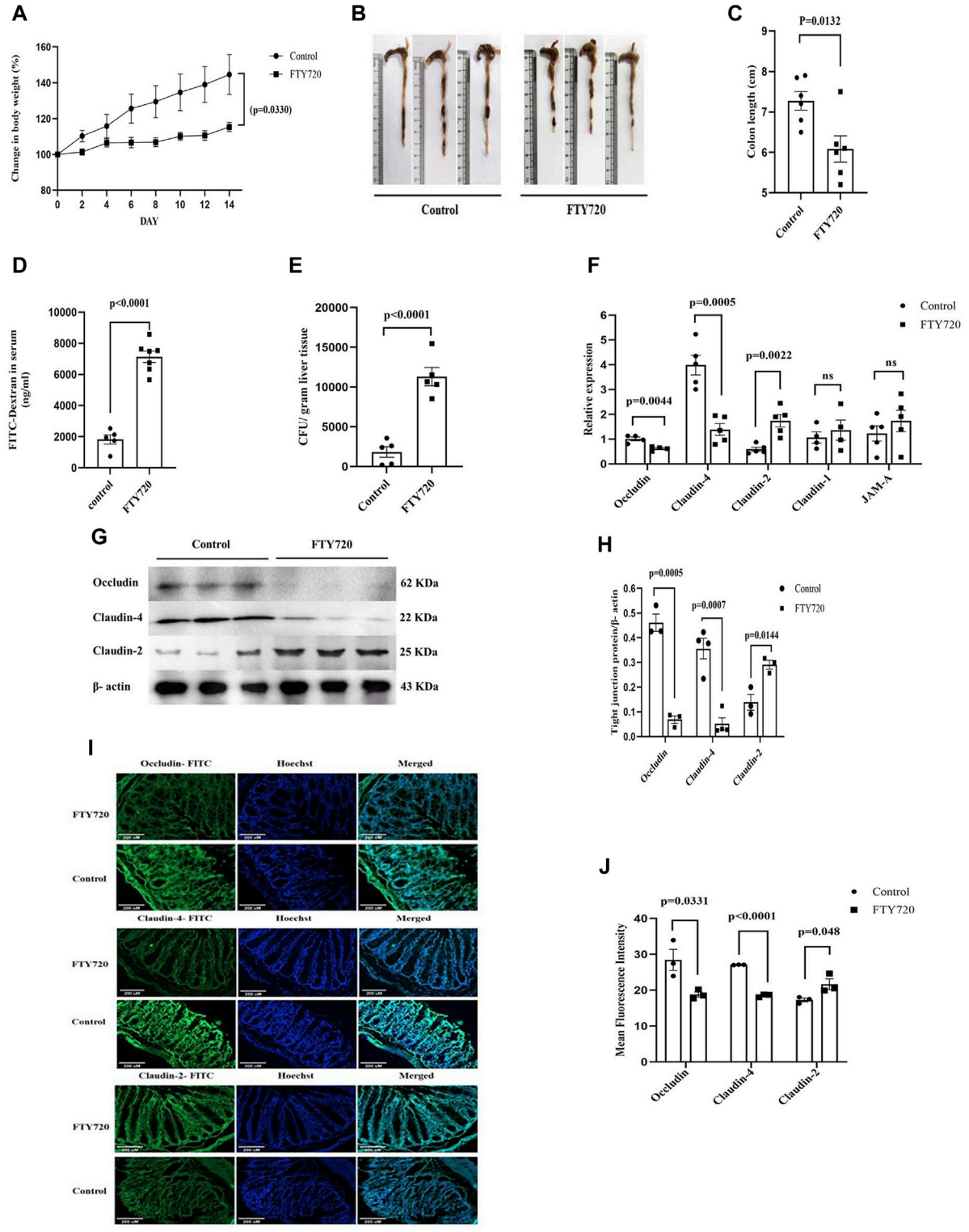


FIGURE 1
C57BL/6 mice were divided into control and FTY720 (3 mg/kg body weight) groups. After 14 days of continual dosing of FTY720, mice from both groups were euthanized. **(A)** The percentage change in body weight, **(B)** representative image of colon length, and **(C)** colon length of control mice and FTY720-treated mice were recorded. **(D)** After 4 h of oral administration of FITC dextran (44 mg/kg), there was a significant increase in FITC concentration in the sera among the FTY720 mice compared to that of the control mice. **(E)** The gut bacterial translocation in the liver was assessed by bacterial colony counting on a nutrient agar plate. **(F)** Real-time PCR data for tight junction-associated proteins: occludin, claudin-4, claudin-2, claudin-1, and JAM-A. **(G)** Western blot images of occludin, claudin-4, claudin-2, and, as internal control, β-actin from the colonic lysates of both control and FTY720 groups (full blot images are provided in Supplementary Figure S1). **(H)** Densitometric analysis of the Western blot images of occludin, claudin-4, and claudin-2. **(I)** Immunofluorescent images of colonic sections from control and FTY720 mice. Colon sections were stained with FITC-tagged (green)
(*Continued*)

FIGURE 1 (Continued)
anti-occludin, anti-claudin-4, and anti-claudin-2 antibodies. Hoechst (blue) was used to stain the nucleus. Merged images represent the dual stains. **(J)** Densitometric analysis of the fluorescent intensity of the images. n ≥ 3 animals were taken per group; these data are represented as the mean ± SEM. *p* values were calculated with respect to the control.

polyacrylamide gel (concentration of acrylamide was used according to the molecular weight of the target protein). After segregation, the proteins were transferred onto the PVDF membrane (IPVH00010, Millipore); 5% BSA in TBST was used as the blocking reagent. The membrane was incubated overnight with specific primary antibodies at 4°C. Then, the membrane was washed and incubated with AP/HRP-conjugated secondary antibody for 2 h at room temperature and detected using NBT BCIP substrate solution (Thermo Scientific)/chemiluminescent HRP substrate (Immobilon Western, Millipore). The HRP substrate-developed blots were visualized using the ChemiDoc Imaging System (Bio-Rad). Densitometric analysis of the protein bands was performed using ImageJ software.

Immunofluorescence staining and imaging

Colon samples from each group were collected and fixed in 4% paraformaldehyde. Paraffin-embedded 5-μm-thick sections were generated. The sections were then de-paraffinized in xylene and rehydrated with graded ethanol, followed by distilled water. A measure of 1 mM EDTA buffer (pH 8.0) was used for antigen retrieval. The sections were then permeabilized with 0.1% sodium citrate and 0.5% Triton-X in TBST. The sections were incubated with blocking buffer (5% animal sera in TBST) at room temperature. The primary antibodies were added to the sections (1:200 for TJ antibodies and 1:50 for FACS antibodies) and incubated overnight at 4°C. The sections were then washed and incubated with the Alexa Fluor 488-conjugated secondary antibody for 2 h at room temperature, and counterstained with Hoechst 33342 (1 μg/mL) for 10 min at RT and then washed. The sections were mounted and visualized using a Carl Zeiss microscope equipped with a CCD camera, and the images were processed using ZEN software (Gumber et al., 2014). The fluorescence intensity of the target proteins was measured using ImageJ software.

Histopathologic examination of the proximal colon

The proximal colon samples were fixed in 4% paraformaldehyde for 48 h at 4 °C. The fixed tissues were then dehydrated through graded alcohols and embedded in paraffin, and routine microtomy was then carried out to generate 5-mM sections. The sections, in turn, were stained with hematoxylin and eosin for later microscopic examination (Chakraborty and Bhaumik, 2020).

Enzyme-linked immunosorbent assay for cytokine and chemokine profiling

To measure the inflammatory markers, that is, cytokines and chemokines, colon tissues were homogenized in PBS and centrifuged at 10,000 *g* for 1 min to collect the supernatants devoid of any tissue debris. The protein concentration of the lysates was quantified using the BCA Protein Assay Kit (Thermo Scientific™ Pierce™, United states). A measure of 50 μg lysate from each animal sample was used to perform ELISA for CXCL-1 (R&D Systems; DY453-05), CXCL-2 (R&D Systems; DY452-05), TNF-α (BD OptEIA; 555268), and IFN-γ (BD OptEIA; 555138) according to the manufacturer's instructions.

Statistical analysis

All experiments were conducted in triplicate, and data are expressed as the mean ± SEM. In Figures 1, 2, Student's *t*-test was used, and in Figure 3, one-way ANOVA was used using GraphPad Prism 8 software (GraphPad Software Inc., San Diego, CA, United States). Differences with $p < 0.05$ were considered significant.

Results and discussion

Having strong immunosuppressive potential, FTY720 was approved as the first oral immunomodulatory drug for multiple sclerosis (Cohen et al. (2010) and Kappos et al. (2010)). This discourse attempts to shed light on the understanding of the effect of FTY720 on gut physiology. A multitude of evidence showed that S1P critically regulates the barrier function of mammalian cells (Kono et al., 2008) and that S1P manipulates the proteins that are involved in cell-to-cell adhesion (Greenspon et al., 2011). Adult C57BL/6 mice were divided into two groups: one group of mice received 3 mg/kg body weight FTY720 daily through oral gavage (FTY720-treated mice), and the other group was fed saline (control mice). FTY720 used in our study is completely water soluble; therefore, a vehicle control other than water was not required. The dose of FTY720 administration was previously used to treat multiple sclerosis in mice (Choi et al., 2011). All the animals received food and water *ad libitum*. Interestingly, the FTY720-treated mice did not exhibit any significant increase in body weight (Figure 1A), indicating stagnancy in growth. The gut length was significantly reduced in FTY720-treated mice compared to the control mice (Figures 1B, C). The function of the intestinal barrier, as investigated by FITC dextran permeability (Figure 1D), revealed that the intestinal permeability of FTY720-treated mice was 4.7 times higher ($p < 0.0001$) than that of the control mice.

The increase in barrier permeability was further confirmed by studying the translocation of bacteria in the liver (Figure 1E). It was observed that a significant number of bacteria were translocated to the liver in FTY720-treated mice compared to the control mice. The translocation of bacteria

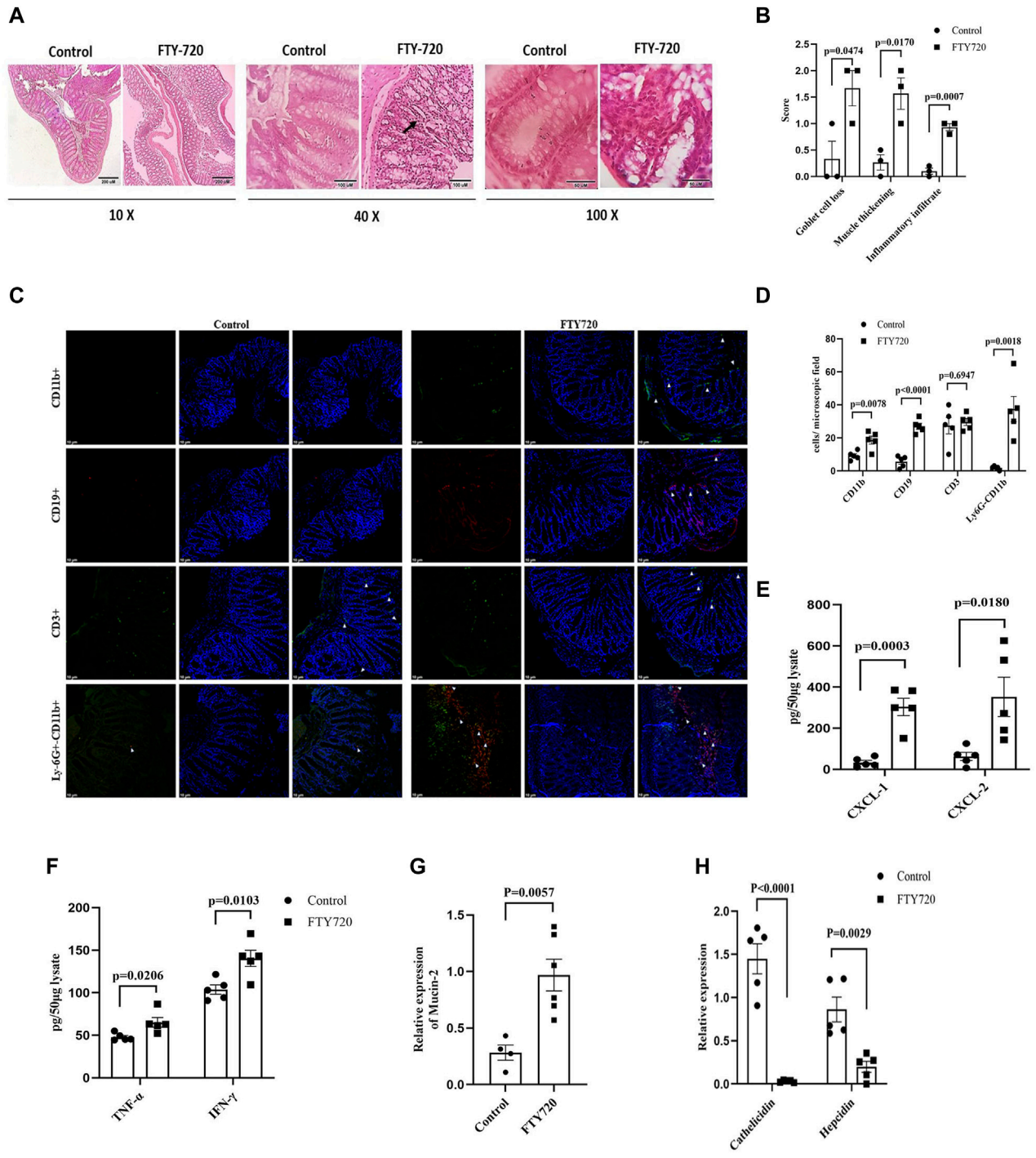


FIGURE 2
(A) Hematoxylin and eosin-stained colonic sections of mice from control and FTY720 groups (from left to right at 10 ×, 40 ×, and 100 × magnification, with the scale bar to the bottom right) for histological analysis. **(B)** Disease scores for goblet cell loss, muscle thickening, and infiltration of inflammatory cells. **(C)** Immunofluorescence of colon sections of FTY720 mice and control mice using FITC-conjugated anti-CD11b antibody, PerCP-conjugated anti-CD19 antibody, and FITC-conjugated anti-CD3 and A700-conjugated anti-Ly6G antibody. **(D)** The number of cells per microscopic field is represented. **(E)** CXCL-1 and CXCL-2 production in the gut tissue of FTY720 and control mice as measured by ELISA. **(F)** TNF-α and IFN-γ production in the gut tissue of FTY720 and control mice as measured by ELISA. **(G)** Real-time PCR analysis for mucus production regulating gene mucin-2. **(H)** Real-time PCR analysis for antimicrobial peptide cathelicidin and hepcidin from the colonic tissue of FTY720 and control mice. All the experiments were carried out with n ≥ 3 animals, and the graphs are presented as the mean ± SEM. *p*-values were calculated with respect to the control.

to the liver is an indication that FTY720 may predispose the individual to major complications and play a role in chronic liver disease. We looked at the group of proteins called occludin, classes of claudins (claudin-4, claudin-2, and claudin-1), and JAM-A that are associated with intestinal permeability (Figure 1F).

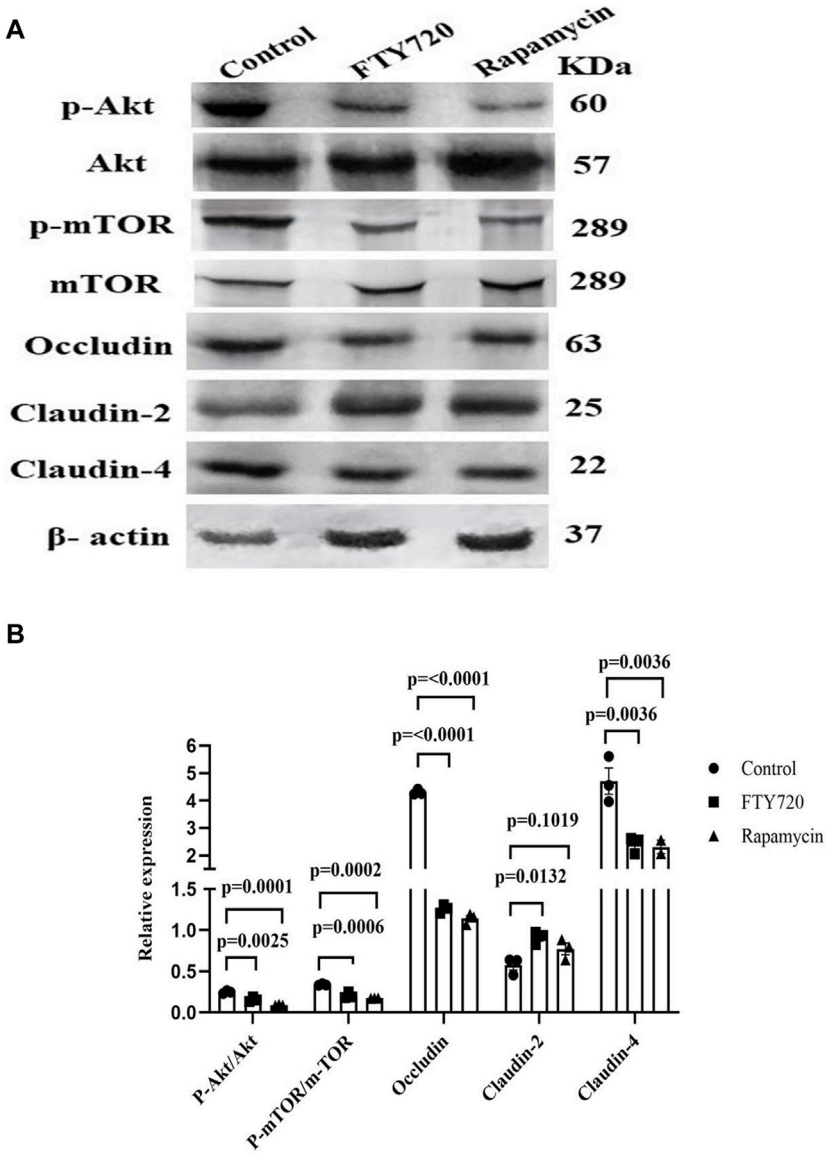


FIGURE 3
FTY720 inhibits Akt-mTOR to downregulate occludin and claudin-4 expression and upregulate claudin-2 expression in HT-29 cells. **(A)** HT-29 cells were treated with or without either FTY720 (20 μM) or rapamycin (500 nM) for 48 h. Thereafter, the cells were lysed, and Western blotting was conducted for p-AKT, AKT, p-mTOR, mTOR, occludin, claudin-2, claudin-4, and β-actin. **(B)** Densitometric analysis is represented for p-Akt/Akt, p-mTOR/mTOR, occludin/β-actin, claudin-2/β-actin, and claudin-4/β-actin (the full blot images are provided in Supplementary Figure S3).

qPCR analysis of the expression of these proteins in the colon revealed a 2-fold reduction in occludin expression and a 2.9-fold decrease in claudin-4 expression, whereas a significant 2.92-fold increase in claudin-2 expression was observed in FTY720-treated mice compared to control mice, and claudin-1 and JAM-A expression remained unaltered. The results were validated by western blot analysis (Figures 1G, H) (full blot images are provided in Supplementary Figure S1) and immunofluorescence (Figures 1I, J). Consistent to our findings in qPCR, there was a decrease in occludin and claudin-4 expressions but an increase in claudin-2 expressions in FTY720-treated mice compared to control mice, as found in the western blot and immunofluorescence analyses. Tight junctions, which are intricate signaling hubs in a constantly changing environment that serve as an impermeable barrier to impede the free transit of solutes through the intercellular gap, make up the majority of proteins linked to gut permeability (Forster (2008) and Fasano (2012)). Paracellular permeability is largely regulated by tight junctional proteins; damage to their expression, assembly, or integrity causes an increase in epithelial permeability (Liang and Weber, 2014). Claudins form TJ strands with the cytoplasmic scaffold ZO and are essential for regulating the paracellular permeability (Furuse, 2010). In addition to claudins, TJs are the home of immunoglobulin superfamily proteins, including JAMs, and occludin, a tetra-spanning membrane protein (Furuse, 2010). The paracellular permeability is one of the main functions regulated by TJs. Occludin, with its coiled domain, functions to arrange the structural and functional components of TJs (Nusrat et al., 2000). As occludin is a crucial component of tight junctions,

permeability increases when its expression or function is reduced. Increased intestinal permeability can lead to both local and systemic inflammatory pathways when luminal components translocate into the host (Mu et al., 2017). The largest interface the body has with the outside world is the gastrointestinal epithelium (Groschwitz and Hogan, 2009). The passage of luminal toxins, as well as the antigens, through the mucosa is selectively limited by the gut epithelium (Suzuki, 2013). The concept that mucosal inflammation results from a breach in the mucosal barrier is maintained by the physical positioning of the intestinal epithelial layer, which wedges between the mucosal surface and the luminal contents (Ahmad et al., 2017). Studies using TJ protein knockout mice showed that the gastrointestinal epithelium became inflamed (Ahmad et al., 2017) (Lu et al., 2013). Additional research confirms the critical significance of permeability, particularly with regard to its ability to support the overall function of the mucosal barrier in controlling mucosal immunological homeostasis (Ahmad et al., 2017). Histological analysis of the colon samples (Figure 2A) showed the infiltration of inflammatory cells in FTY720-treated mice compared to the control. The muscularis layer of the colon showed enlargement, and mucous-secreting goblet cells also showed hyperplasia in FTY720-treated mouse colon histological sections. The breakdown of the gut barrier and immune cell infiltration are closely related events (Lin et al., 2020). We observed a significant presence of $CD19^+$ B cells, $CD11b^+$ cells, and $CD11b^+$ $Ly6G^+$ cells (neutrophils) in the colon tissue of FTY720-treated mice compared to the control. However, there was no change in $CD3^+$ T cells in the gut of FTY720-treated mice compared to the control mice (Figures 2C, D). The infiltration of $CD19^+$ B cells, $CD11b^+$ cells, and $CD11b^+$ $Ly6G^+$ neutrophils increased significantly in FTY720-treated mice compared to the control mice. FTY720, after being phosphorylated *in vivo*, binds to S1PRs (Wang et al., 1999; Van Brocklyn and Williams, 2012; Chen et al., 2017; Santacreu et al., 2019; Weigel et al., 2023) that are present on the lymphocyte surface and sequesters all the receptors except S1PR3, hence preventing lymphocyte egress from lymphoid organs. Conversely, phosphorylated FTY720 binds to S1PR3, which is present on the surface of neutrophils, macrophages, and B cells, and causes downward signaling (Sensken et al., 2008). Therefore, it is likely to find increased neutrophils, macrophages, and B cells but not T cells in the gut of FTY720-treated mice compared to the control mice. To ensure the inflammatory response in the gut due to FTY720 treatment, we measured the expression of CXCL-1 and CXCL-2, TNF-α, and IFN-γ (Figures 2E, F). Interestingly, there was a significant increase in CXCL-1 and CXCL-2, TNF-α, and IFN-γ levels in the colon of FTY720-treated mice compared to control. With increased CXCL-1 and CXCL-2, the neutrophil chemoattractants (Sawant et al., 2021) in FTY720 mice are also indicative of inflammation. It is unknown exactly how goblet cell hyperplasia occurs. A previous study reported that goblet cell hyperplasia is induced by IL-13, the major regulator of type-2-mediated inflammation, which speeds up inflammation (Huang et al., 2020).

S1PR2 has been linked to IL-13 (Zhao et al., 2018), which could possibly lead to goblet cell hyperplasia. Increased mucin-2 expression in FTY720 mice compared to the control is indicative of increased mucous production (Figure 2G). Previous research reported that colon mucin may be directly impacted by colonic inflammation (Kang et al., 2022). Subsequent investigation into the expression of antimicrobial genes, such as cathelicidin and hepcidin, revealed a notable decrease in FTY720-treated mice compared to the control (Figure 2H). It is thought to be crucial to colonic macrophage defense mechanisms against bacterial infection (Agier et al., 2015). Reduction in cathelicidin and hepcidin in the colon of FTY720-treated mice is indicative of the risk of opportunistic infection (McHugh et al. (2019), Scheenstra et al. (2020), and Ganz (2018)).

The expression of tight junction proteins is associated with the Akt–mTOR signaling pathway. In LS174T cells, human colon epithelial cells, it was shown that occludin expression is positively regulated by the PI3K–Akt-mTOR pathway (Mao et al., 2016). The Akt–mTOR pathway also activates autophagy, and the inhibition of autophagy contributes to the increase in claudin-2 expression (Zhang et al., 2017). Here, we show that FTY720 treatment to HT-29, a human colon carcinoma cell line, inhibits phosphorylation at Ser 473 of Akt and at Ser 2448 of mTOR, which is associated with a decrease in occludin and claudin-4 expression and an increase in claudin-2 expression compared to the control, as shown by Western blot analysis (Figures 3A, B) (full blot images are provided in Supplementary Figure S2). The dose of FTY720 treatment on HT-29 cells was determined previously by cell viability assay (Supplementary Figure S3). For Akt–mTOR phosphorylation, we used rapamycin, an inhibitor of mTOR, and found a similar decrease in the phosphorylation of Akt, mTOR, occludin, and claudin-4 and an increase in claudin-2 expression. The dose and time of rapamycin treatment were based on a previous report (Li et al., 2021). Therefore, it is tempting to speculate that FTY720 works through the inhibition of the mTOR signaling pathway to affect TJ protein expression. Further studies are warranted in this regard.

Among the latest findings, the most important one was that FTY720 impairs gut epithelial barrier regulation in mice. Moreover FTY720 caused a significantly increased intestinal barrier permeability and an elevated inflammatory response in the colon. These findings indicate that FTY720 causes deleterious effects in modulating the integrity of the intestinal barrier.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Ethics statement

All the protocol for the study was approved by the Institutional Animal Ethics Committee of ICMR-NICED, Kolkata, India (PRO/151/July 2018–June 2021). The experiments were carried out in accordance with the guidelines laid down by the committee for the purpose of control and supervision of experiments on animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi, India. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SS: data curation, investigation, methodology, software, writing–original draft, and writing–review and editing. DM: data curation, methodology, software, and writing–review and editing. OD: data curation, methodology, and writing–review and editing. MB: conceptualization, formal analysis, funding acquisition, investigation, project administration, resources, supervision, validation, visualization, writing–original draft, and writing–review and editing. SD: formal analysis, resources, supervision, and writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The study was funded by DST-SERB (CRG 2020 002525). (This fund does not include any publication fees).

Acknowledgments

The authors acknowledge the support of the Director, ICMR-NICED, Kolkata, for carrying out the study. The authors thank Dr. Mainak Chakraborty for his valuable insights. The authors thank Narayan Chandra Mondal for maintaining the good health of the mice. The authors thank Animesh Gope, Dr. Dipanjan Ghosh, and Bireswar Bhattacharya for confocal microscopy. The authors thank Ankita Dutta and Aaheli Masid for their support in addressing immune parameters. OD was the recipient of fellowship from the DST. SS was the recipient of fellowship from CSIR.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1407228/full#supplementary-material

References

Agier, J., Efenberger, M., and Brzezinska-Blaszczyk, E. (2015). Cathelicidin impact on inflammatory cells. *Cent. Eur. J. Immunol.* 40 (2), 225–235. doi:10.5114/ceji.2015.51359

Ahmad, R., Sorrell, M. F., Batra, S. K., Dhawan, P., and Singh, A. B. (2017). Gut permeability and mucosal inflammation: bad, good or context dependent. *Mucosal Immunol.* 10 (2), 307–317. doi:10.1038/mi.2016.128

Alemany, R., van Koppen, C. J., Danneberg, K., Ter Braak, M., and Meyer Zu Heringdorf, D. (2007). Regulation and functional roles of sphingosine kinases. *Naunyn Schmiedeb. Arch. Pharmacol.* 374 (5- 6), 413–428. doi:10.1007/s00210-007-0132-3

Bazzoni, G., and Dejana, E. (2004). Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis. *Physiol. Rev.* 84 (3), 869–901. doi:10.1152/physrev.00035.2003

Blanc, C. A., Grist, J. J., Rosen, H., Sears-Kraxberger, I., Steward, O., and Lane, T. E. (2015). Sphingosine-1- phosphate receptor antagonism enhances proliferation and migration of engrafted neural progenitor cells in a model of viral-induced demyelination. *Am. J. Pathol.* 185 (10), 2819–2832. doi:10.1016/j.ajpath.2015.06.009

Bryan, A. M., and Del Poeta, M. (2018). Sphingosine-1-phosphate receptors and innate immunity. *Cell Microbiol.* 20 (5), e12836. doi:10.1111/cmi.12836

Chakraborty, M., and Bhaumik, M. (2020). Prenatal arsenic exposure interferes in postnatal immunocompetence despite an absence of ongoing arsenic exposure. *J. Immunotoxicol.* 17 (1), 135–143. doi:10.1080/1547691X.2020.1767238

Chakraborty, M., Gautam, A., Das, O., Masid, A., and Bhaumik, M. (2023). Prenatal arsenic exposure stymies gut butyrate production and enhances gut permeability in post natal life even in absence of arsenic deftly through miR122-Occludin pathway. *Toxicol. Lett.* 374, 19–30. doi:10.1016/j.toxlet.2022.11.011

Chen, T., Huang, Z., Liu, R., Yang, J., Hylemon, P. B., and Zhou, H. (2017). Sphingosine-1 phosphate promotes intestinal epithelial cell proliferation via S1PR2. *Front. Biosci. Landmark Ed.* 22 (4), 596–608. doi:10.2741/4505

Chiba, K. (2005). FTY720, a new class of immunomodulator, inhibits lymphocyte egress from secondary lymphoid tissues and thymus by agonistic activity at sphingosine 1-phosphate receptors. *Pharmacol. Ther.* 108 (3), 308–319. doi:10.1016/j.pharmthera.2005.05.002

Choi, J. W., Gardell, S. E., Herr, D. R., Rivera, R., Lee, C. W., Noguchi, K., et al. (2011). FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc. Natl. Acad. Sci. U. S. A.* 108 (2), 751–756. doi:10.1073/pnas.1014154108

Chun, J., Goetzl, E. J., Hla, T., Igarashi, Y., Lynch, K. R., Moolenaar, W., et al. (2002). International union of pharmacology. XXXIV. Lysophospholipid receptor nomenclature. *Pharmacol. Rev.* 54 (2), 265–269. doi:10.1124/pr.54.2.265

Cohen, J. A., Barkhof, F., Comi, G., Hartung, H. P., Khatri, B. O., Montalban, X., et al. (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 362 (5), 402–415. doi:10.1056/NEJMoa0907839

Danese, S., Furfaro, F., and Vetrano, S. (2018). Targeting S1P in inflammatory bowel disease: new avenues for modulating intestinal leukocyte migration. *J. Crohns Colitis* 12 (Suppl. l_2), S678–S686. doi:10.1093/ecco-jcc/jjx107

Daniel, C., Sartory, N., Zahn, N., Geisslinger, G., Radeke, H. H., and Stein, J. M. (2007b). FTY720 ameliorates Th1- mediated colitis in mice by directly affecting the functional activity of CD4+CD25+ regulatory T cells. *J. Immunol.* 178 (4), 2458–2468. doi:10.4049/jimmunol.178.4.2458

Daniel, C., Sartory, N. A., Zahn, N., Schmidt, R., Geisslinger, G., Radeke, H. H., et al. (2007a). FTY720 ameliorates oxazolone colitis in mice by directly affecting T helper type 2 functions. *Mol. Immunol.* 44 (13), 3305–3316. doi:10.1016/j.molimm.2007.02.026

Deguchi, Y., Andoh, A., Yagi, Y., Bamba, S., Inatomi, O., Tsujikawa, T., et al. (2006). The S1P receptor modulator FTY720 prevents the development of experimental colitis in mice. *Oncol. Rep.* 16 (4), 699–703. doi:10.3892/or.16.4.699

Fasano, A. (2012). Zonulin, regulation of tight junctions, and autoimmune diseases. *Ann. N. Y. Acad. Sci.* 1258 (1), 25–33. doi:10.1111/j.1749-6632.2012.06538.x

Forster, C. (2008). Tight junctions and the modulation of barrier function in disease. *Histochem Cell Biol.* 130 (1), 55–70. doi:10.1007/s00418-008-0424-9

Fujii, T., Tomita, T., Kanai, T., Nemoto, Y., Totsuka, T., Sakamoto, N., et al. (2008). FTY720 suppresses the development of colitis in lymphoid-null mice by modulating the trafficking of colitogenic CD4+ T cells in bone marrow. *Eur. J. Immunol.* 38 (12), 3290–3303. doi:10.1002/eji.200838359

Furuse, M. (2010). Molecular basis of the core structure of tight junctions. *Cold Spring Harb. Perspect. Biol.* 2 (1), a002907. doi:10.1101/cshperspect.a002907

Ganz, T. (2018). Iron and infection. *Int. J. Hematol.* 107 (1), 7–15. doi:10.1007/s12185-017-2366-2

Gauthier, J., Vermersch, P., Chauvet, P., Varlet, P., Coiteux, V., Magro, L., et al. (2018). Successful treatment with fingolimod of graft-versus-host disease of the central nervous system. *Blood Adv.* 2 (1), 10–13. doi:10.1182/bloodadvances.2017011478

Goetzl, E. J., Kong, Y., and Voice, J. K. (2000). Cutting edge: differential constitutive expression of functional receptors for lysophosphatidic acid by human blood lymphocytes. *J. Immunol.* 164 (10), 4996–4999. doi:10.4049/jimmunol.164.10.4996

Greenspon, J., Li, R., Xiao, L., Rao, J. N., Sun, R., Strauch, E. D., et al. (2011). Sphingosine-1-phosphate regulates the expression of adherens junction protein E-cadherin and enhances intestinal epithelial cell barrier function. *Dig. Dis. Sci.* 56 (5), 1342–1353. doi:10.1007/s10620-010-1421-0

Groschwitz, K. R., and Hogan, S. P. (2009). Intestinal barrier function: molecular regulation and disease pathogenesis. *J. Allergy Clin. Immunol.* 124 (1), 3–22. quiz 1-2. doi:10.1016/j.jaci.2009.05.038

Gumber, S., Nusrat, A., and Villinger, F. (2014). Immunohistological characterization of intercellular junction proteins in rhesus macaque intestine. *Exp. Toxicol. Pathol.* 66 (9-10), 437–444. doi:10.1016/j.etp.2014.07.004

Han, Y., Li, X., Zhou, Q., Jie, H., Lao, X., Han, J., et al. (2015). FTY720 abrogates collagen-induced arthritis by hindering dendritic cell migration to local lymph nodes. *J. Immunol.* 195 (9), 4126–4135. doi:10.4049/jimmunol.1401842

Hatoum, D., Haddadi, N., Lin, Y., Nassif, N. T., and McGowan, E. M. (2017). Mammalian sphingosine kinase (SphK) isoenzymes and isoform expression: challenges for SphK as an oncotarget. *Oncotarget* 8 (22), 36898–36929. doi:10.18632/oncotarget.16370

Heinemann, U., and Schuetz, A. (2019). Structural features of tight-junction proteins. *Int. J. Mol. Sci.* 20 (23), 6020. doi:10.3390/ijms20236020

Hla, T., Lee, M. J., Ancellin, N., Paik, J. H., and Kluk, M. J. (2001). Lysophospholipids--receptor revelations. *Science* 294 (5548), 1875–1878. doi:10.1126/science.1065323

Huang, Z. Q., Liu, J., Ong, H. H., Yuan, T., Zhou, X. M., Wang, J., et al. (2020). Interleukin-13 alters tight junction proteins expression thereby compromising barrier function and dampens rhinovirus induced immune responses in nasal epithelium. *Front. Cell Dev. Biol.* 8, 572749. doi:10.3389/fcell.2020.572749

Imamura, T., Ohgane, J., Ito, S., Ogawa, T., Hattori, N., Tanaka, S., et al. (2001). CpG island of rat sphingosine kinase-1 gene: tissue-dependent DNA methylation status and multiple alternative first exons. *Genomics* 76 (1-3), 117–125. doi:10.1006/geno.2001.6607

Kang, M., Mischel, R. A., Bhave, S., Komla, E., Cho, A., Huang, C., et al. (2017). The effect of gut microbiome on tolerance to morphine mediated antinociception in mice. *Sci. Rep.* 7, 42658. doi:10.1038/srep42658

Kang, Y., Park, H., Choe, B. H., and Kang, B. (2022). The role and function of mucins and its relationship to inflammatory bowel disease. *Front. Med. (Lausanne)* 9, 848344. doi:10.3389/fmed.2022.848344

Kappos, L., Radue, E. W., O'Connor, P., Polman, C., Hohlfeld, R., Calabresi, P., et al. (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 362 (5), 387–401. doi:10.1056/NEJMoa0909494

Kono, M., Allende, M. L., and Proia, R. L. (2008). Sphingosine-1-phosphate regulation of mammalian development. *Biochim. Biophys. Acta* 1781 (9), 435–441. doi:10.1016/j.bbalip.2008.07.001

Laksitorini, M., Prasasty, V. D., Kiptoo, P. K., and Siahaan, T. J. (2014). Pathways and progress in improving drug delivery through the intestinal mucosa and blood-brain barriers. *Ther. Deliv.* 5 (10), 1143–1163. doi:10.4155/tde.14.67

Le Stunff, H., Milstien, S., and Spiegel, S. (2004). Generation and metabolism of bioactive sphingosine-1- phosphate. *J. Cell Biochem.* 92 (5), 882–899. doi:10.1002/jcb.20097

Li, S., Sheng, J., Liu, Z., Fan, Y., Zhang, C., Lv, T., et al. (2021). Potent antitumour of the mTORC1/2 dual inhibitor AZD2014 in docetaxel-sensitive and docetaxel-resistant castration-resistant prostate cancer cells. *J. Cell Mol. Med.* 25 (5), 2436–2449. doi:10.1111/jcmm.16155

Liang, G. H., and Weber, C. R. (2014). Molecular aspects of tight junction barrier function. *Curr. Opin. Pharmacol.* 19, 84–89. doi:10.1016/j.coph.2014.07.017

Lin, E. Y., Lai, H. J., Cheng, Y. K., Leong, K. Q., Cheng, L. C., Chou, Y. C., et al. (2020). Neutrophil extracellular traps impair intestinal barrier function during experimental colitis. *Biomedicines* 8 (8), 275. doi:10.3390/biomedicines8080275

Liu, H., Sugiura, M., Nava, V. E., Edsall, L. C., Kono, K., Poulton, S., et al. (2000). Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. *J. Biol. Chem.* 275 (26), 19513–19520. doi:10.1074/jbc.M002759200

Liu, M., Xie, W., Wan, X., and Deng, T. (2020). Clostridium butyricum protects intestinal barrier function via upregulation of tight junction proteins and activation of the Akt/mTOR signaling pathway in a mouse model of dextran sodium sulfate-induced colitis. *Exp. Ther. Med.* 20 (5), 10. doi:10.3892/etm.2020.9138

Lu, Z., Ding, L., Lu, Q., and Chen, Y. H. (2013). Claudins in intestines: distribution and functional significance in health and diseases. *Tissue Barriers* 1 (3), e24978. doi:10.4161/tisb.24978

Maceyka, M., and Spiegel, S. (2014). Sphingolipid metabolites in inflammatory disease. *Nature* 510 (7503), 58–67. doi:10.1038/nature13475

Mao, X., Hu, H., Tang, J., Chen, D., and Yu, B. (2016). Leucine increases mucin 2 and occludin production in LS174T cells partially via PI3K-Akt-mTOR pathway. *Anim. Nutr.* 2 (3), 218–224. doi:10.1016/j.aninu.2016.05.004

McHugh, B. J., Wang, R., Li, H. N., Beaumont, P. E., Kells, R., Stevens, H., et al. (2019). Cathelicidin is a "fire alarm", generating protective NLRP3-dependent airway epithelial cell inflammatory responses during infection with Pseudomonas aeruginosa. *PLoS Pathog.* 15 (4), e1007694. doi:10.1371/journal.ppat.1007694

Meddings, J. (2008). The significance of the gut barrier in disease. *Gut* 57 (4), 438–440. doi:10.1136/gut.2007.143172

Miyamoto, T., Matsumori, A., Hwang, M. W., Nishio, R., Ito, H., and Sasayama, S. (2001). Therapeutic effects of FTY720, a new immunosuppressive agent, in a murine model of acute viral myocarditis. *J. Am. Coll. Cardiol.* 37 (6), 1713–1718. doi:10.1016/s0735-1097(01)01204-9

Mizushima, T., Ito, T., Kishi, D., Kai, Y., Tamagawa, H., Nezu, R., et al. (2004). Therapeutic effects of a new lymphocyte homing reagent FTY720 in interleukin-10 gene-deficient mice with colitis. *Inflamm. Bowel Dis.* 10 (3), 182–192. doi:10.1097/00054725-200405000-00002

Mu, Q., Kirby, J., Reilly, C. M., and Luo, X. M. (2017). Leaky gut as a danger signal for autoimmune diseases. *Front. Immunol.* 8, 598. doi:10.3389/fimmu.2017.00598

Murphy, C. T., Hall, L. J., Hurley, G., Quinlan, A., MacSharry, J., Shanahan, F., et al. (2012). The sphingosine-1-phosphate analogue FTY720 impairs mucosal immunity and clearance of the enteric pathogen Citrobacter rodentium. *Infect. Immun.* 80 (8), 2712–2723. doi:10.1128/IAI.06319-11

Nakano, S., Mikami, N., Miyawaki, M., Yamasaki, S., Miyamoto, S., Yamada, M., et al. (2022). Therapeutic strategy for rheumatoid arthritis by induction of myeloid-derived suppressor cells with high suppressive potential. *Biol. Pharm. Bull.* 45 (8), 1053–1060. doi:10.1248/bpb.b21-01096

Nusrat, A., Parkos, C. A., Verkade, P., Foley, C. S., Liang, T. W., Innis-Whitehouse, W., et al. (2000). Tight junctions are membrane microdomains junctions are membrane microdomains. *J. Cell Sci.* 113 (Pt 10), 1771–1781. doi:10.1242/jcs.113.10.1771

Paradis, T., Begue, H., Basmaciyan, L., Dalle, F., and Bon, F. (2021). Tight junctions as a key for pathogens invasion in intestinal epithelial cells. *Int. J. Mol. Sci.* 22 (5), 2506. doi:10.3390/ijms22052506

Pulkoski-Gross, M. J., Donaldson, J. C., and Obeid, L. M. (2015). Sphingosine-1-phosphate metabolism: a structural perspective. *Crit. Rev. Biochem. Mol. Biol.* 50 (4), 298–313. doi:10.3109/10409238.2015.1039115

Rau, C. R., Hein, K., Sattler, M. B., Kretzschmar, B., Hillgruber, C., McRae, B. L., et al. (2011). Anti-inflammatory effects of FTY720 do not prevent neuronal cell loss in a rat model of optic neuritis. *Am. 438 J. Pathol.* 178 (4), 1770–1781. doi:10.1016/j.ajpath.2011.01.003

Ryu, J., Jhun, J., Park, M. J., Baek, J. A., Kim, S. Y., Cho, K. H., et al. (2020). FTY720 ameliorates GvHD by blocking T lymphocyte migration to target organs and by skin fibrosis inhibition. *J. Transl. Med.* 18 (1), 225. doi:10.1186/s12967-020-02386-w

Santacreu, B. J., Pescio, L. G., Romero, D. J., Corradi, G. R., Sterin-Speziale, N., and Favale, N. O. (2019). Sphingosine kinase and sphingosine-1-phosphate regulate epithelial cell architecture by the modulation of *de novo* sphingolipid synthesis. *PLoS One* 14 (3), e0213917. doi:10.1371/journal.pone.0213917

Sawant, K. V., Sepuru, K. M., Lowry, E., Penaranda, B., Frevert, C. W., Garofalo, R. P., et al. (2021). Neutrophil recruitment by chemokines Cxcl1/KC and Cxcl2/MIP2: role of Cxcr2 activation and glycosaminoglycan interactions. *J. Leukoc. Biol.* 109 (4), 777–791. doi:10.1002/JLB.3A0820-207R

Scheenstra, M. R., van Harten, R. M., Veldhuizen, E. J. A., Haagsman, H. P., and Coorens, M. (2020). Cathelicidins modulate TLR-activation and inflammation. *Front. Immunol.* 11, 1137. doi:10.3389/fimmu.2020.01137

Schmidt, O., Weyer, Y., Baumann, V., Widerin, M. A., Eising, S., Angelova, M., et al. (2019). Endosome and Golgi-associated degradation (EGAD) of membrane proteins regulates sphingolipid metabolism. *EMBO J.* 38 (15), e101433. doi:10.15252/embj.2018101433

Sensken, S. C., Staubert, C., Keul, P., Levkau, B., Schoneberg, T., and Graler, M. H. (2008). Selective activation of G alpha i mediated signalling of S1P3 by FTY720-phosphate. *Cell Signal* 20 (6), 1125–1133. doi:10.1016/j.cellsig.2008.01.019

Sharma, S., Mathur, A. G., Pradhan, S., Singh, D. B., and Gupta, S. (2011). Fingolimod (FTY720): first approved oral therapy for multiple sclerosis. *J. Pharmacol. Pharmacother.* 2 (1), 49–51. doi:10.4103/0976-500X.77118

Suzuki, T. (2013). Regulation of intestinal epithelial permeability by tight junctions. *Cell Mol. Life Sci.* 70 (4), 631–659. doi:10.1007/s00018-012-1070-x

Sykes, D. A., Riddy, D. M., Stamp, C., Bradley, M. E., McGuiness, N., Sattikar, A., et al. (2014). Investigating the molecular mechanisms through which FTY720-P causes persistent S1P1 receptor internalization. *Br. J. Pharmacol.* 171 (21), 4797–4807. doi:10.1111/bph.12620

Tsunemi, S., Iwasaki, T., Kitano, S., Imado, T., Miyazawa, K., and Sano, H. (2010). Effects of the novel immunosuppressant FTY720 in a murine rheumatoid arthritis model. *Clin. Immunol.* 136 (2), 197–204. doi:10.1016/j.clim.2010.03.428

Van Brocklyn, J. R., and Williams, J. B. (2012). The control of the balance between ceramide and sphingosine-1-phosphate by sphingosine kinase: oxidative stress and the seesaw of cell survival and death. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 163 (1), 26–36. doi:10.1016/j.cbpb.2012.05.006

Wang, F., Van Brocklyn, J. R., Hobson, J. P., Movafagh, S., Zukowska-Grojec, Z., Milstien, S., et al. (1999). Sphingosine 1-phosphate stimulates cell migration through a G(i)-coupled cell surface receptor. Potential involvement in angiogenesis. *J. Biol. Chem.* 274 (50), 35343–35350. doi:10.1074/jbc.274.50.35343

Weigel, C., Bellaci, J., and Spiegel, S. (2023). Sphingosine-1-phosphate and its receptors in vascular endothelial and lymphatic barrier function. *J. Biol. Chem.* 299 (6), 104775. doi:10.1016/j.jbc.2023.104775

Wolf, A. M., Eller, K., Zeiser, R., Durr, C., Gerlach, U. V., Sixt, M., et al. (2009). The sphingosine 1-phosphate receptor agonist FTY720 potently inhibits regulatory T cell proliferation *in vitro* and *in vivo*. *J. Immunol.* 183 (6), 3751–3760. doi:10.4049/jimmunol.0901011

Yu, L. C., Wang, J. T., Wei, S. C., and Ni, Y. H. (2012). Host-microbial interactions and regulation of intestinal epithelial barrier function: from physiology to pathology. *World J. Gastrointest. Pathophysiol.* 3 (1), 27–43. doi:10.4291/wjgp.v3.i1.27

Zeng, X., Wang, T., Zhu, C., Xing, X., Ye, Y., Lai, X., et al. (2012). Topographical and biological evidence revealed FTY720-mediated anergy-polarization of mouse bone marrow-derived dendritic cells *in vitro*. *PLoS One* 7 (5), e34830. doi:10.1371/journal.pone.0034830

Zhang, C., Yan, J., Xiao, Y., Shen, Y., Wang, J., Ge, W., et al. (2017). Inhibition of autophagic degradation process contributes to claudin-2 expression increase and epithelial tight junction dysfunction in TNF-α treated cell monolayers. *Int. J. Mol. Sci.* 18 (1), 157. doi:10.3390/ijms18010157

Zhao, J., Okamoto, Y., Asano, Y., Ishimaru, K., Aki, S., Yoshioka, K., et al. (2018). Sphingosine-1-phosphate receptor-2 facilitates pulmonary fibrosis through potentiating IL-13 pathway in macrophages. *PLoS One* 13 (5), e0197604. doi:10.1371/journal.pone.0197604

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 04 September 2024
DOI 10.3389/fphar.2024.1455212

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Valentina Oana Buda,
Victor Babes University of Medicine and Pharmacy, Romania
Oliviu Vostinaru,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania

*CORRESPONDENCE
Xianying Wang,
wxylby@sina.com
Xiuqing Zhu,
2018760376@gzhmu.edu.cn

RECEIVED 26 June 2024
ACCEPTED 22 August 2024
PUBLISHED 04 September 2024

CITATION
Liang S, Wang X and Zhu X (2024) Insights from pharmacovigilance and pharmacodynamics on cardiovascular safety signals of NSAIDs.
Front. Pharmacol. 15:1455212.
doi: 10.3389/fphar.2024.1455212

Insights from pharmacovigilance and pharmacodynamics on cardiovascular safety signals of NSAIDs

Shuang Liang[1], Xianying Wang[1]* and Xiuqing Zhu[2,3]*

[1]Department of Pharmacy, Hebei Medical University Third Hospital, Shijiazhuang, China, [2]Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Guangzhou Medical University, Guangzhou, China, [3]Department of Pharmacy, The Affiliated Brain Hospital, Guangzhou Medical University, Guangzhou, China

Background and Aim: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat fever, pain, and inflammation. Concerns regarding their cardiovascular safety have been raised. However, the underlying mechanism behind these events remains unknown. We aim to investigate the cardiovascular safety signals and receptor mechanisms of NSAIDs, employing a comprehensive approach that integrates pharmacovigilance and pharmacodynamics.

Methods: This study utilized a pharmacovigilance-pharmacodynamic approach to evaluate the cardiovascular safety of NSAIDs and explore potential receptor mechanisms involved. Data were analyzed using the OpenVigil 2.1 web application, which grants access to the FDA Adverse Event Reporting System (FAERS) database, in conjunction with the BindingDB database, which provides target information on the pharmacodynamic properties of NSAIDs. Disproportionality analysis employing the Empirical Bayes Geometric Mean (EBGM) and Reporting Odds Ratio (ROR) methods was conducted to identify signals for reporting cardiovascular-related adverse drug events (ADEs) associated with 13 NSAIDs. This analysis encompassed three System Organ Classes (SOCs) associated with the cardiovascular system: blood and lymphatic system disorders, cardiac disorders, and vascular disorders. The primary targets were identified through the receptor-NSAID interaction network. Ordinary least squares (OLS) regression models explored the relationship between pharmacovigilance signals and receptor occupancy rate.

Results: A total of 201,231 reports of cardiovascular-related ADEs were identified among the 13 NSAIDs. Dizziness, anemia, and hypertension were the most frequently reported Preferred Terms (PTs). Overall, nimesulide and parecoxib exhibited the strongest signal strengths of ADEs at SOC levels related to the cardiovascular system. On the other hand, our data presented naproxen and diclofenac as drugs of comparatively low signal strength. Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) were identified as central targets. OLS regression analysis revealed that the normalized occupancy rate for either COX-1 or COX-2 was significantly inversely correlated with the log-transformed signal measures for blood and lymphatic system disorders and vascular disorders, and positively correlated with cardiac disorders and vascular disorders, respectively. This suggests that higher COX-2 receptor occupancy is associated with an increased cardiovascular risk from NSAIDs.

Conclusion: Cardiovascular safety of NSAIDs may depend on pharmacodynamic properties, specifically, the percentage of the occupied cyclooxygenase isoenzymes. More studies are needed to explore these relations and improve the prescription process.

KEYWORDS

NSAIDs, cardiovascular safety signals, FAERS, OpenVigil 2.1, pharmacovigilance, pharmacodynamics, cyclooxygenase-1, cyclooxygenase-2

1 Introduction

Non-steroidal anti-inflammatory drugs, also known as NSAIDs, are commonly used to treat conditions involving fever, pain, and inflammation (Wongrakpanich et al., 2018; Bindu et al., 2020). Given their regular prescriptions for many age groups, especially adults and the elderly, and specifically for chronic conditions, thoroughly evaluating their safety is important (Derry et al., 2016; Varrassi et al., 2020). Although NSAIDs are commonly prescribed in the short run, long-term administration isn't unusual when dealing with chronic inflammatory diseases (Marcum and Hanlon, 2010; Wehling, 2014). However, concerns have arisen regarding potential risks to cardiovascular events from NSAIDs. This incorporates an increased likelihood of cardiovascular diseases like heart failure, myocardial infarction, and stroke, as well as hypertension (Lindhardsen et al., 2014).

The US Food and Drug Administration (FDA) has emphasized the increased cardiovascular risks associated with the use of NSAIDs, necessitating continuous monitoring. In 2005, the FDA issued an advisory regarding a possible increase in cardiovascular diseases with certain NSAIDs (Castelli et al., 2017). The update further emphasized this notice, highlighting the importance of carefully prescribing NSAIDs, especially long-term in high-risk groups (Tannenbaum et al., 1996; Domper Arnal et al., 2022). Despite these cautions, NSAIDs remain widely used, underscoring the importance of continuing safety tracking (Abou Zeid et al., 2019). NSAIDs exert their effects primarily by inhibiting cyclooxygenase (COX) enzymes, that is, the COX-1 and COX-2. COX-1 is constantly produced and is involved in basic cell functions such as gastric protection and platelet aggregation. COX-2, on the other hand, is inducible and essential for inflammation and pain perception. The inhibition of these enzymes leads to both the therapeutic benefits and adverse effects of NSAIDs. Non-selective NSAIDs act on both the COX-1 and the COX-2 enzymes thus producing undesirable effects on the gastrointestinal as well as the cardiovascular systems; on the other hand, there is a probability that with the use of selective COX-2 inhibitors gastrointestinal effects might be avoided but at the price of having somewhat more cardiovascular manifestations (Grosser et al., 2006).

Substantial monitoring of cardiovascular risks linked with NSAIDs remains necessary. Several past studies have linked NSAID use to an increased risk of cardiovascular diseases (García Rodríguez et al., 2011; Martín Arias et al., 2019; Schjerning et al., 2020). García Rodríguez et al. (2011) have reviewed both randomized controlled trials (RCTs) and observational studies. They found NSAIDs may raise the chances of having a non-fatal heart attack. One large study combined data from multiple observational studies. It reported higher risks of myocardial infarction, abnormal heart rhythms, and heart failure with NSAID use (Schjerning et al., 2020). Another meta-analysis specifically looked at two selective COX-2 inhibitors, celecoxib and etoricoxib. It connected them to an increased risk of cardiovascular diseases (Martín Arias et al., 2019). However, most past research grouped all NSAIDs without analyzing individual drugs or dosage levels (Wu et al., 2018; Ahmed et al., 2019). Studies also mostly focused on just a few types of cardiovascular outcomes. Compared to our research, past studies generally had smaller sample sizes from real-world settings (Kohli et al., 2014; Lin et al., 2017). Some evidence links certain NSAID effects, like how their COX selectivity impacts blood pressure and kidney function, to cardiovascular risks (Harris, 2006; Minhas et al., 2023). However, little data exists on the cardiovascular safety of individual NSAIDs, especially related to these pharmacodynamic properties (Pepine and Gurbel, 2017). Our study included relevant pharmacodynamic data and thus filled this gap in the literature.

The goal of our study was to improve understanding of each NSAID's cardiovascular safety by employing a pharmacovigilance-pharmacodynamic approach. We analyzed the pharmacovigilance data on cardiovascular systems from the FDA Adverse Event Reporting System (FAERS). We also collected the pharmacodynamic data on the receptors of NSAIDs from the BindingDB database. Our objectives were: 1) To see if certain NSAIDs may be linked to safety signals for cardiovascular adverse events; 2) To explore the relationship between reported cardiovascular risk and receptor occupancy rate of NSAIDs. These findings could help clinicians make more informed choices about NSAID use in patient care. Our methods are outlined in Figure 1.

2 Materials and methods

2.1 Data source

The study used the FDA's public database of FAERS (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) to gather information on suspected adverse drug events (ADEs) related to cardiovascular diseases from use of NSAIDs. This database, which primarily includes reports from the United States but also globally, was accessed through OpenVigil 2.1 (http://h2876314.stratoserver.net:8080/OV2/search/). This platform operated and obtained the cleaned FAERS data, which included verified and normalized drug names. Additionally, it incorporated standard medical terminology for adverse events (AEs) (Sakaeda et al., 2013). The analysis included reports submitted from January 2010 through June 2023. The study

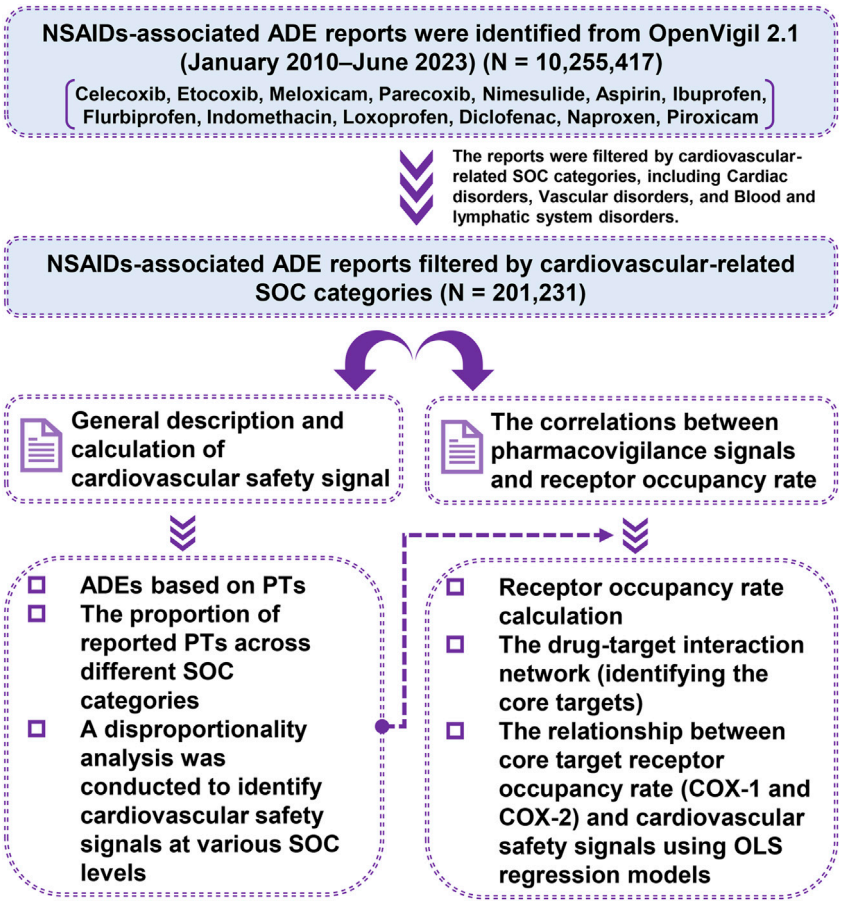


FIGURE 1
Flow diagram illustrating the sequence of studies conducted.

focused on clinically used NSAIDs. An NSAID was included in the analysis if it had at least 100 unique reports in the database and at least one report related to cardiovascular events. Ultimately, 13 NSAIDs (aspirin, celecoxib, diclofenac, etoricoxib, flurbiprofen, ibuprofen, indomethacin, loxoprofen, meloxicam, naproxen, nimesulide, parecoxib, and piroxicam) were included in the study and were listed in Table 1. The human receptor information for these NSAIDs, including the inhibitory constants (K_i), was obtained from the BindingDB database (https://www.bindingdb.org/rwd/bind/index.jsp).

2.2 Detection of cardiovascular risk-related signals

The pharmacovigilance data underwent a process of summarization and sorting based on the number of reported cases for Preferred Terms (PTs) and their corresponding System Organ Classes (SOCs) related to cardiovascular diseases. Three levels of SOCs were identified: heart disease, vascular disease, and blood and lymphatic system diseases. Adverse cardiovascular events were reported for all 13 drugs across all three SOCs, except for parecoxib, which had no reported cases in the category of blood and lymphatic system disorders.

To conduct the disproportionality analysis and explore the association between NSAID use and cardiovascular events, we utilized the ratio imbalance method using a four-square table (refer to Table 2). We employed two algorithms for disproportionate measurement: the Reporting Odds Ratio (ROR) algorithm and the Empirical Bayes Geometric Mean (EBGM) algorithm (Yang et al., 2023). ROR is a simple and highly sensitive method but lacks specificity and is not suitable when the number of target adverse event reports is less than 3 (Jiao et al., 2024). While the method known as EBGM considers the number of reports. This helps provide more stable estimates, especially when report numbers are low (Hunt et al., 2014). Therefore, we combined this method with another one called ROR to create a fuller picture. The calculation formula and the criteria for positive safety signal detection are presented in Table 3.

2.3 Correlations between cardiovascular safety signals and receptor occupancy rate

To quantify the receptor-mediated mechanisms, we selected the receptor occupancy rate, which was computed using the pharmacological receptor theory: Occupancy (%) = $100 \times C_U/(K_i + C_U)$. The variable C_U (nM) refers to the concentration of the

TABLE 1 Non-steroidal anti-inflammatory drugs (NSAIDs) and their classifications.

Drug name	Structure	Categorization	Cyclooxygenase (COX) targets of inhibition
Aspirin		Non-selective COX inhibitors	COX-1, COX-2
Ibuprofen		Non-selective COX inhibitors	COX-1, COX-2
Flurbiprofen		Non-selective COX inhibitors	COX-1, COX-2
Indomethacin		Non-selective COX inhibitors	COX-1, COX-2
Loxoprofen		Non-selective COX inhibitors	COX-1, COX-2
Diclofenac		Non-selective COX inhibitors	COX-1, COX-2
Naproxen		Non-selective COX inhibitors	COX-1, COX-2
Piroxicam		Non-selective COX inhibitors	COX-1, COX-2
Celecoxib		Selective COX-2 inhibitors	COX-2
Parecoxib		Selective COX-2 inhibitors	COX-2
Meloxicam		Selective COX-2 inhibitors	COX-2
Etoricoxib		Selective COX-2 inhibitors	COX-2
Nimesulide		Selective COX-2 inhibitors	COX-2

TABLE 2 Disproportionality analysis in pharmacovigilance using a 2 × 2 contingency table.

Drug name	Number of target adverse event reports	Number of other adverse event reports	Total
Target drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

Note: "a" represents the number of reports containing both the target drug and target adverse events (AEs). "b" represents the number of reports containing other AEs of the target drug. "c" represents the number of reports containing the target AEs of other drugs. "d" represents the number of reports containing other drugs and other AEs.

unbound drug in the blood; meanwhile, K_i (nM) stands for the inhibitory constant of the drug under consideration (Kenakin, 2004; Montastruc et al., 2015; Cepaityte et al., 2021). In the context of the receptor-NSAID interaction analysis presented in the next section, 11 NSAIDs (aspirin, celecoxib, diclofenac, etoricoxib, flurbiprofen, ibuprofen, indomethacin, meloxicam, naproxen, nimesulide, and piroxicam) were applied to the analysis with available K_i data for each of them. The C_U was estimated using the formula: $C_U = 1000 \times F_U \times C_T/MW$, where F_U depicts the proportion of unbound drug obtained from Drugbank (Harding et al., 2018), C_T (ng/mL) signifies the concentration of the drug in the blood, while MW (g/mol) refers to the molecular weight

TABLE 3 Calculation formulas and criteria for positive safety signal detection for the EBGM and ROR algorithms.

Algorithm	Formula	Threshold
EBGM	$EBGM = \frac{(aN)}{[(a+b)(a+c)]}$ $SE = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%\,CI = e^{ln(EBGM)\pm 1.96SE}$	the lower bound of 95% CI (EBGM05) > 2
ROR	$ROR = \frac{ad}{bc}$ $SE = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%\,CI = e^{ln(ROR)\pm 1.96SE}$	a ≥ 3 and the lower bound of 95% CI (ROR05) > 1

Note: EBGM and ROR refer to the Empirical Bayes Geometric Mean algorithm and the Reporting Odds Ratio algorithm, respectively. "a" represents the number of reports containing both the target drug and target adverse events (AEs). "b" represents the number of reports containing other AEs of the target drug. "c" represents the number of reports containing the target AEs of other drugs. "d" represents the number of reports containing other drugs and other AEs. "N" represents the total number of reports, calculated as a + b + c + d. "SE" represents the standard error. "95% CI" represents the 95% confidence interval. "EBGM05" and "ROR05" denote the lower limit of the 95% confidence interval of EBGM for the EBGM algorithm and the lower limit of the 95% confidence interval of ROR for the ROR algorithm, respectively.

obtained from the drug label (Cepaityte et al., 2021). In this analysis, the total drug concentration in the blood (C_T) was estimated using the upper limit of the therapeutic reference range of individual NSAIDs, as documented on the drug label (Hiemke et al., 2018). If there were two or more figures available for the target occupancy of the drug to one receptor, the mean receptor occupancy rate was used.

To explore whether cardiovascular safety signals relate to varying receptor occupancy rates, we examined the extent to which there is a connection between the receptor and NSAID network. In this network, the nodes of the network were the receptors and NSAIDs whilst the width of edges in the network represented the average receptor occupancy rate. The target which contained the largest number of degrees in the interaction networks was chosen as a central target and further analyzed. The following OLS regression model was developed to test the hypothesis: the receptor occupancy rate of the core target of NSAIDs had a relationship with the level of cardiovascular pharmacovigilance signal intensity, using normalized receptor occupancy rates and log-transformed signal measures [log (EBGM05) and log (ROR05)] across three cardiovascular SOCs. As long as the *P*-value for either algorithm is less than 0.05, the correlation is considered statistically significant. Last but not least, a scatter plot was utilized to visually illustrate the significant association between the normalized receptor occupancy rate and the log-transformed number of pharmacovigilance signal intensity.

All statistical analyses were performed using Python (3.8.13) and packages, including pandas (1.5.3), numpy (1.23.0), scipy (1.8.1), scikit-learn (1.3.2), statsmodels (0.14.0), network (3.1), matplotlib (3.4.3), seaborn (0.12.2), and proplot (0.9.7).

3 Results

3.1 Data overview

A total of 10,255,417 ADE reports for 13 NSAIDs were obtained from OpenVigil 2.1 (Please refer to Supplementary Table S1 for more details). These reports encompassed 27 different SOCs and 12,165 PTs. Following filtration based on cardiovascular-related SOC categories, a total of 201,231 ADE reports were ultimately screened (Figure 1). This subset included 93,453 PTs related to cardiac disorders, 76,766 PTs related to vascular disorders, and 31,012 PTs related to blood and lymphatic system disorders. We compiled the reported cases of adverse cardiovascular events across the different NSAIDs and ranked the PTs based on case numbers. Figure 2 displays the top ten PTs associated with cardiovascular events among the 13 NSAIDs. Among these, dizziness was the most frequently reported PT (16,316 cases), followed by anemia (8,163 cases), hypotension (6,973 cases), hypertension (6,605 cases), chest pain (6,582 cases), myocardial infarction (6,579 cases), hemorrhage (4,223 cases), syncope (4,217 cases), oedema peripheral (4,168 cases), and contusion (4,125 cases) (Figure 2). The distribution of reported cases for PTs under the three cardiovascular-related SOCs is illustrated in the pie charts (Figure 3). For cardiac disorders, the top three reported PTs were dizziness (17.5%), chest pain (7.0%), and myocardial infarction (7.0%). In the case of vascular disorders, the leading PTs were hypotension (9.1%), hypertension (8.6%), and hemorrhage (5.5%). Regarding blood and lymphatic system disorders, the most prevalent PTs were anemia (26.3%), thrombocytopenia (8.1%), and neutropenia (6.2%).

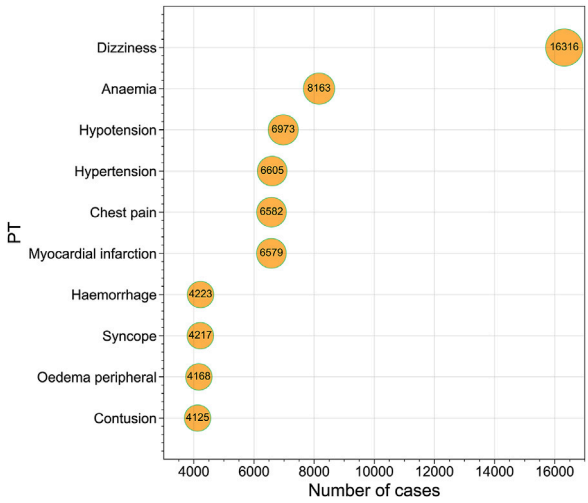


FIGURE 2
Bubble chart presenting the top 10 Preferred Terms (PTs) ranked by the number of reported cases.

FIGURE 3
Pie chart displaying the distribution of reported Preferred Terms (PTs) across different System Organ Classes (SOCs).

3.2 Signal detection at SOC level for cardiovascular safety

Significant safety signals were identified through signal detection analysis using the EBGM and ROR algorithms across the three cardiovascular-related SOCs. Figure 4 illustrates the ranking of detected signals at different SOC levels using the EBGM and ROR algorithms. Consistent disproportionality signals were identified by integrating the discriminative criteria of positive safety alert signals based on the EBGM and ROR algorithms. Specifically, this included the lower limit of the 95% confidence interval of EBGM above 2 (EBGM05 > 2) for the EBGM algorithm, or the lower limit of the 95% confidence interval of ROR above 1 (ROR05 > 1) for the ROR algorithm, along with the count of reports that include both the target drug and target AEs with a frequency equal to or greater than 3 ($a \geq 3$) (Table 3). Significant disproportionality signals were found for blood and lymphatic system disorders: nimesulide (a = 68, EBGM05 = 5.967, ROR05 = 6.395), celecoxib (a = 171, EBGM05 = 4.094, ROR05 = 4.181), etoricoxib (a = 194, EBGM05 = 4.016, ROR05 = 4.240), meloxicam (a = 102, EBGM05 = 3.638, ROR05 = 3.680), and loxoprofen (a = 508, EBGM05 = 3.162, ROR05 = 3.504). Significant disproportionality signals also emerged for six NSAIDs on cardiac disorders: parecoxib (a = 19, EBGM05 = 14.695, ROR05 = 17.349), nimesulide (a = 35, EBGM05 = 6.822, ROR05 = 7.074), etoricoxib (a = 237, EBGM05 = 4.380, ROR05 = 4.687), celecoxib (a = 1763, EBGM05 = 3.983, ROR05 = 4.160), meloxicam (a = 17, EBGM05 = 2.543, ROR05 = 2.564), and aspirin (a = 53,659, EBGM05 = 2.310, ROR05 = 2.851). The aforementioned six NSAIDs also showed consistent disproportionality signals for vascular disorders: parecoxib (a = 27, EBGM05 = 14.964, ROR05 = 19.124), nimesulide (a = 35, EBGM05 = 5.571, ROR05 = 5.771), etoricoxib (a = 69, EBGM05 = 4.857, ROR05 = 4.961), meloxicam (a = 133, EBGM05 = 3.881, ROR05 = 3.932), celecoxib (a = 520, EBGM05 = 3.521, ROR05 = 3.598), and

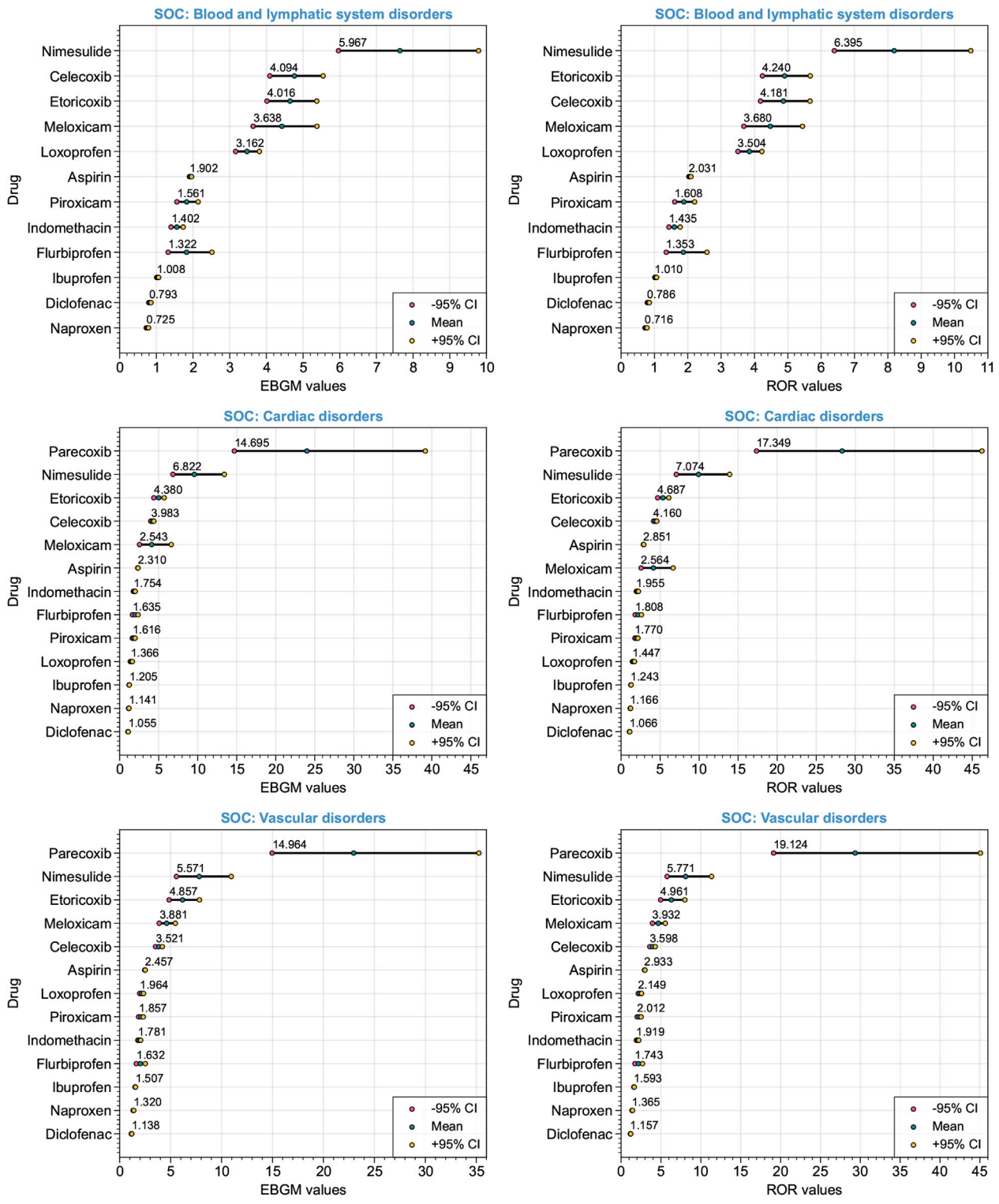


FIGURE 4
Forest plot depicting the ranking of detected signals at various System Organ Classes (SOCs) levels associated with the cardiovascular system. The Empirical Bayes Geometric Mean (EBGM) algorithm and the Reporting Odds Ratio (ROR) algorithm were utilized. Red and yellow dots represent the −95% and +95% confidence intervals, respectively. The mean EBGM or ROR values are indicated by green dots.

aspirin (a = 42,990, EBGM05 = 2.457, ROR05 = 2.933). Overall, nimesulide and parecoxib exhibited the strongest signal strengths of ADEs at SOC levels related to the cardiovascular system, reaching statistical significance. Conversely, naproxen and diclofenac showed weak signal strengths of ADEs, without any observed disproportionality.

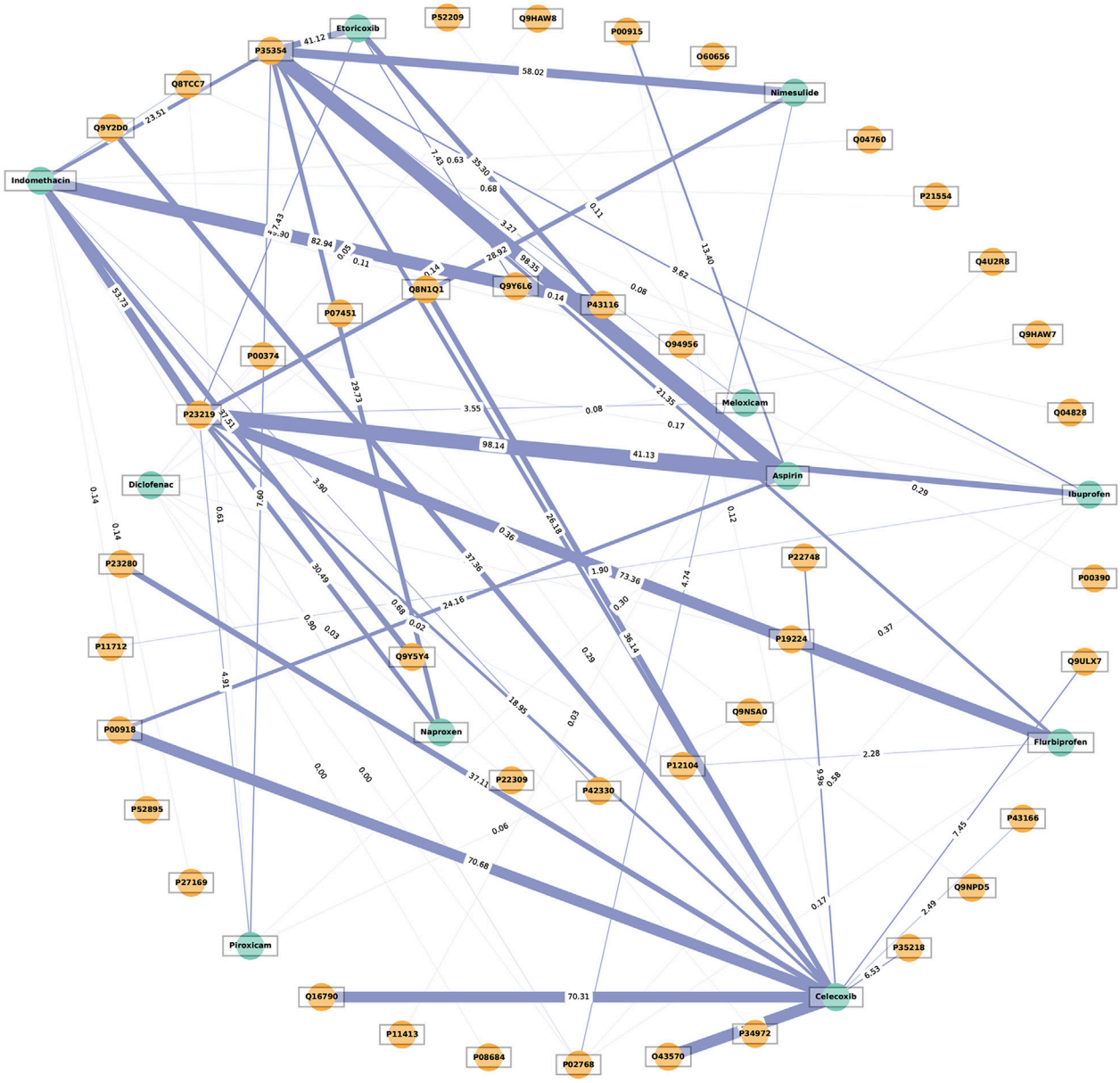


FIGURE 5
The network illustrates the interaction between receptors and non-steroidal anti-inflammatory drugs (NSAIDs). The thickness of the blue lines represents the average receptor occupancy rate. The green circles represent the NSAIDs, while the orange circles represent the targets.

3.3 Relationship between core target receptor occupancy rate and cardiovascular safety signals

A network graph was constructed to illustrate the interactions between NSAIDs (green circles) and their targets (orange circles), highlighting the significance of these interactions. The thickness of the connecting blue lines corresponds to the average occupancy rate of the targets (Figure 5). Cyclooxygenase-1 (COX-1, UniProt protein ID: P23219) and cyclooxygenase-2 (COX-2, UniProt protein ID: P35354) have emerged as central targets in the receptor-NSAID interaction network, each with a degree of 10. It is noteworthy that for COX-1, aspirin displayed the highest average occupancy rate at 98.14%, followed by flurbiprofen at 73.36%, and indomethacin at 53.73%. On the other hand, for COX-2, aspirin showed the highest average occupancy rate at 98.35%, followed by nimesulide at 58.02%, and etoricoxib at 41.12%. The UniProt protein ID numbers and their corresponding meanings were provided in Supplementary Table S2.

OLS regression models were utilized to examine the correlation between core target receptor occupancy rates and cardiovascular safety signals. Table 4 demonstrates a weak negative correlation between the normalized COX-1 receptor occupancy rate for NSAIDs and the log (EBGM05) and log (ROR05) for blood and lymphatic system disorders, as well as the log (EBGM05) for vascular disorders, with statistical significance. Conversely, a weak positive correlation was observed between the normalized

TABLE 4 Ordinary least squares (OLS) regression analysis: Normalized receptor occupancy rate of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) for non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular safety signals [log (EBGM05) and log (ROR05)] across various System Organ Classes (SOCs).

COX	SOC	EBGM algorithm				ROR algorithm			
		Coefficient [2.5% CI, 97.5% CI]	t-value	*P*-value	R^2 (%)	Coefficient [2.5% CI, 97.5% CI]	t-value	*P*-value	R^2 (%)
COX-1	Blood and lymphatic system disorders	−0.2492 [−0.475, −0.023]	−2.255	**0.032**	14.5	−0.2454 [−0.478, −0.013]	−2.154	**0.039**	13.4
	Cardiac disorders	−0.1585 [−0.362, 0.045]	−1.594	0.121	7.8	−0.1227 [−0.327, 0.082]	−1.226	0.230	4.8
	Vascular disorders	−0.1991 [−0.371, −0.027]	−2.366	**0.025**	15.7	−0.1671 [−0.337, 0.002]	−2.013	0.053	11.9
COX-2	Blood and lymphatic system disorders	0.1233 [−0.066, 0.312]	1.316	0.195	3.9	0.1378 [−0.055, 0.330]	1.443	0.156	4.6
	Cardiac disorders	0.1716 [0.017, 0.326]	2.242	**0.030**	10.5	0.1996 [0.050, 0.349]	2.699	**0.010**	14.5
	Vascular disorders	0.1159 [−0.025, 0.256]	1.664	0.103	6	0.1377 [0.004, 0.271]	2.078	**0.044**	9.1

Note: EBGM and ROR refer to the Empirical Bayes Geometric Mean and the Reporting Odds Ratio algorithms, respectively. "EBGM05" and "ROR05" denote the lower limit of the 95% confidence interval of EBGM for the EBGM algorithm and the lower limit of the 95% confidence interval of ROR for the ROR algorithm, respectively. Bold *P*-values indicate statistical significance. CI represents confidence interval.

COX-2 receptor occupancy rate for NSAIDs and the log (EBGM05) and log (ROR05) for cardiac disorders, along with the log (ROR05) for vascular disorders, with statistical significance. No significant associations were found between the COX-1 occupancy rate and log-transformed signal measures for cardiac disorders, nor between the COX-2 occupancy rate and log-transformed signal measures for blood and lymphatic system disorders. Figure 6 presents scatter plots illustrating the log (EBGM05) or log (ROR05) for these significantly correlated SOCs among 10 NSAIDs interacting with COX-1 or COX-2 in the receptor-NSAID interaction network, alongside their corresponding normalized COX-1 or COX-2 occupancy rates. NSAIDs such as aspirin, nimesulide, etoricoxib, naproxen, celecoxib, indomethacin, flurbiprofen, ibuprofen, piroxicam, and meloxicam are depicted by colored dots. This suggests that higher COX-2 receptor occupancy is associated with an increased cardiovascular risk from NSAIDs, while higher COX-1 receptor occupancy is linked to a reduced cardiovascular risk from NSAIDs.

4 Discussion

This study aimed to assess the cardiovascular safety of NSAIDs by integrating pharmacovigilance and pharmacodynamics approaches. Using the OpenVigil 2.1 platform, a comprehensive pharmacovigilance analysis was conducted on a substantial number of real-world AE reports obtained from the FAERS database, which provided data on the use of 13 NSAIDs. Additionally, a pharmacodynamics analysis was performed utilizing the BindingDB database, which offered valuable target information on drug-target interactions. The study initially provided an overview of the AEs associated with NSAIDs, including the ordering of PTs related to cardiovascular events and the proportional distribution of cardiovascular-related PTs within different SOCs. Consequently, the disproportionality analysis to search for cardiovascular safety signals at different SOC levels was performed. Therefore, for the current study, the possible pharmacological receptor mechanisms through which cardiovascular safety signals were found were investigated. This entailed determining the receptor occupancy rate and pinpointing the core targets through the drug-target interaction network. Last of all, given the hypotheses that the receptor occupancy rate of the core target, COX-1 and/or COX-2 correlated with cardiovascular safety signaling, an OLS regression model examined this relationship. Thus, combining the findings of pharmacovigilance and pharmacodynamics, this study provides significant information about the cardiovascular safety signals of NSAIDs. In summary, the study adds to the body of knowledge and evaluation of the cardiovascular risks of these commonly used NSAIDs.

Whereas earlier studies have focused on showing a risk for cardiovascular events connected with NSAID exposure determined by meta-analyses of RCTs and observational studies, there is still limited and inconclusive data available regarding individual NSAIDs (Bally et al., 2017; Schjerning et al., 2020). Multiple studies have indicated that naproxen carries the lowest cardiovascular risk among NSAIDs. In contrast, the utilization of COX-2 inhibitors or diclofenac in high-risk patients is linked to a greater occurrence of cardiovascular events (McGettigan and Henry, 2011). However, a meta-analysis revealed that all NSAIDs, including naproxen, are linked to an augmented risk of acute myocardial infarction. Conversely, the risk associated with celecoxib does not seem to surpass that of traditional NSAIDs (Bally et al., 2017). One of the objectives of our investigation was to elucidate the correlation between specific NSAIDs and the augmented risk of cardiovascular events founded upon real-world evidence.

In our analysis, we focused on the top 10 PTs associated with cardiovascular events, and the results revealed that dizziness was the most commonly reported AE. A study conducted on the adverse effects of analgesics, including 11 NSAIDs, among elderly individuals yielded consistent findings with our study,

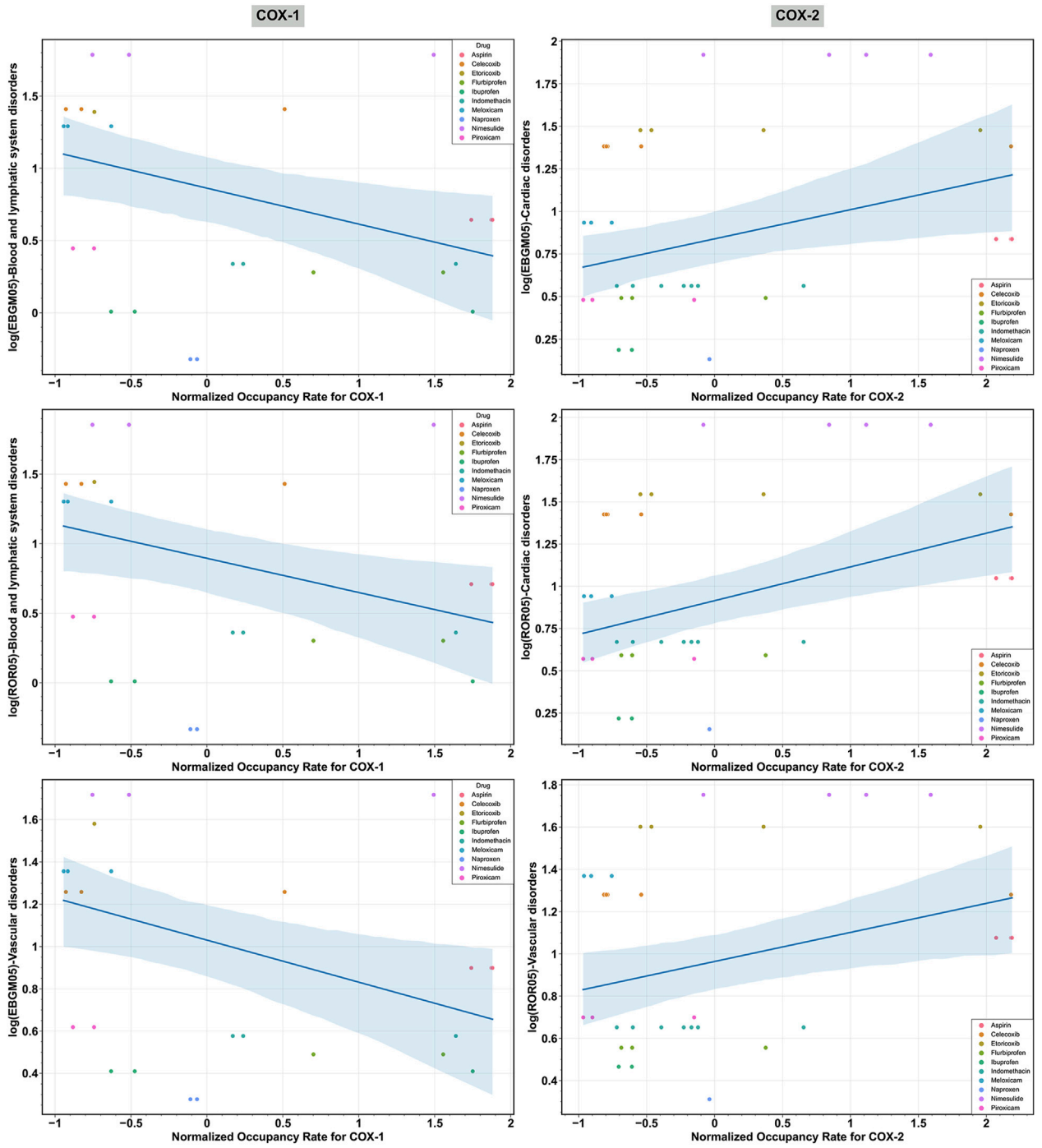


FIGURE 6
Scatter plot illustrating the significant relationships between the log-transformed signal measures [log (EBGM05) and log (ROR05)] across various System Organ Classes (SOCs) and the normalized receptor occupancy rates of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) for non-steroidal anti-inflammatory drugs (NSAIDs). "EBGM05" and "ROR05" represent the lower limit of the 95% confidence interval for EBGM using the EBGM algorithm and ROR using the ROR algorithm, respectively.

highlighting dizziness as the most frequently reported AE, except for gastrointestinal reactions (McDonald et al., 2018). However, the prevalence of these AEs varied across different categories of cardiovascular-related SOCs. Cardiac disorders were predominantly associated with dizziness as the most reported PT, whereas vascular disorders were primarily linked to hypotension as the leading PT. In the case of blood and lymphatic system disorders, anemia was the most prevalent AE.

Disproportionality analysis revealed significant safety signals associated with the reporting of cardiovascular-related AEs. Among blood and lymphatic system disorders, nimesulide demonstrated the strongest signal, while naproxen exhibited the

weakest signal. In both the cardiac disorders and vascular disorders systems, parecoxib manifested the strongest signal, whereas diclofenac evinced the weakest signal. Recent reports on the cardiovascular risk profile of NSAIDs suggest that the risk of adverse cardiovascular events varies among different NSAIDs. Naproxen appears to carry a relatively lower cardiovascular risk compared to other NSAIDs (Minhas et al., 2023). Research conducted in Denmark also indicates that naproxen exhibits a more favorable cardiovascular risk profile (Bech-Drewes et al., 2024). A systematic review and meta-analysis indicated that postoperative administration of parecoxib may elevate the risk of cardiovascular complications (Aldington et al., 2005). Our real-world research findings from the FAERS database align with the aforementioned conclusions.

Several receptor mechanisms have been proposed to elucidate the occurrence of NSAID-related cardiovascular events. Following the obtained outcomes of the present research, it is possible to assume that the factors that are related to the pharmacodynamics of NSAIDs, particularly their ability to cause COX-1 and COX-2 occupancy, may influence cardiovascular safety levels. A study also gives evidence that affords the hypothesis stating that the degree of specificity of the NSAID to COX-2 in comparison with COX-1 plays a significant role in the cardiovascular hazard (Schjerning et al., 2020). Also, it is shown that the network analysis of the target-NSAID interactions underscores the importance of these interactions. The actual analysis of the estimator obtained by the OLS regression models points towards a statistically significant, albeit relatively weak, negative correlation between the normalized occupancy rate of the COX-1 receptor and the log-transformed signal measures for blood and lymphatic system disorders and vascular disorders, as well as a positive correlation between the normalized occupancy rate of the COX-2 receptor and the log-transformed signal measures for cardiac disorders and vascular disorders. Thus, these divergent cardiovascular risks that are attributed to NSAIDs are believed to be linked to their mechanism of action that inhibits the COX enzymes, which in turn affect the synthesis of prostaglandins (PG) (Funk and FitzGerald, 2007). These enzymes, COX-1 and COX-2, play many important roles in the cardiovascular system, though some of their effects oppose each other (Khan et al., 2019). Any changes that affect the vascular function and platelet aggregation will raise the risk of thrombus formation. As illustrated in Figure 7, COX-1 is found throughout the cardiovascular system, especially in blood vessels and platelets. In healthy blood vessels, COX-1 is mainly located in the endothelial layer where it works with prostacyclin synthase (PGIS) to mostly produce prostacyclin (PGI2). Within platelets, COX-1 combines with thromboxane synthase (TXAS), leading to the primary production of thromboxane A2 (TXA2). This causes platelet aggregation, vasoconstriction, and smooth muscle hypertrophy. Conversely, the COX-1-mediated synthesis of PGI2 in vascular endothelial cells can hinder platelet aggregation, promote vasodilation, inhibit smooth muscle proliferation, and play a significant protective role in the cardiovascular system (Mitchell et al., 2021). Moreover, PGI2 has been found to modulate various prothrombotic stimuli, such as adenosine diphosphate (ADP), epinephrine, collagen, serotonin, thrombin, and TXA2 (Varga et al., 2017; Schjerning et al., 2020). A healthy cardiovascular system typically exhibits higher protective PGI2 activity than TXA2 activity (Mitchell et al., 2021). Consequently, COX-1 inhibitors like aspirin, ibuprofen, and diclofenac suppress

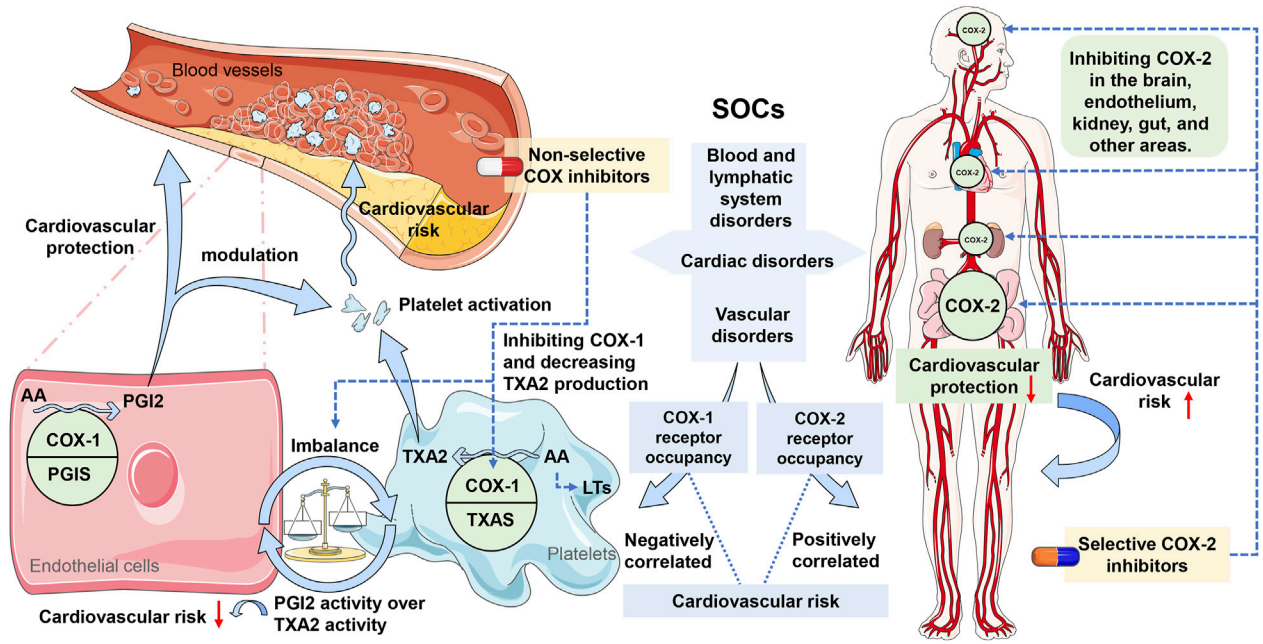


FIGURE 7
Potential molecular mechanisms of non-steroidal anti-inflammatory drugs (NSAIDs) associated with cardiovascular safety signals. Note: COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; SOCs, System Organ Classes; AA, arachidonic acid; PGIS, prostacyclin synthase; TXAS, thromboxane synthase; PGI2, prostacyclin; TXA2, thromboxane A2; LTs, leukotrienes.

TXA2 production more than PGI2 when used. This disrupts the balance between TXA2 and PGI2, resulting in elevated PGI2 activity over TXA2 activity, which offers a degree of protection. It could help to explain the relationship between the increasing COX-1 receptor occupancy with reduced cardiovascular risk from NSAIDs. On the other hand, while COX-2 is expressed in regions of vascular inflammation and disease, it is minimally expressed in most blood vessels and is largely absent from platelets. However, it plays a role in maintaining cardiovascular health in distant areas such as the kidney and endothelium. Evidence suggests that NSAIDs are associated with an increased risk of hypertension and renal impairment that can share their connection with cardiovascular diseases (Schafer, 1995; Braun et al., 2020). The results of the pharmacodynamic analysis indicate that the specific drug-receptor interactions may be some of the factors that cause this. For instance, COX-2 in the kidney safeguards the cardiovascular system by reducing blood pressure and controlling the levels of hypertensive mediators like asymmetric dimethylarginine. Inhibiting renal COX-2 with selective COX-2 inhibitors can elevate blood pressure. Endothelial COX-2 fosters the production of the antithrombotic hormone PGI2, and hindering COX-2 with selective inhibitors raises the risk of cardiac thrombosis (Mitchell et al., 2021). Therefore, this scenario may partially elucidate why selective COX-2 inhibitors show a heightened cardiovascular risk signal, where a greater COX-2 receptor occupancy correlates with an increased likelihood of adverse cardiovascular events, primarily cardiac disorders and vascular disorders.

However, the strength of the correlations mentioned above was found to be weaker for both COX-1 and COX-2, and all NSAIDs have been associated with cardiovascular risks according to systematic reviews and meta-analyses (Bally et al., 2017). Incidental COX-1 blockade by traditional NSAIDs does not reduce the likelihood of cardiovascular side effects (Mitchell et al., 2021). One possible explanation is that non-selective NSAIDs inhibit COX-1 without specificity, while also non-selectively inhibiting COX-2, potentially elevating the risk of cardiovascular events. Another hypothesis is that the inhibition of COX enzymes by NSAIDs could redirect arachidonic acid (AA) to alternative enzymatic pathways, like 5-lipoxygenase (5-LOX) and leukotrienes (LTs), which play roles in atherosclerosis and inflammation processes. NSAIDs' COX blockade might shift AA towards leukotriene C4 (LTC4) in immune cells and other LTs in endothelial cells, potentially contributing to the observed cardiovascular side effects associated with NSAIDs (Mitchell et al., 2021) (see Figure 7). These weak correlations might also be due to the opinion that cardiovascular events depend on various receptors and mechanisms (Schjerning et al., 2020). For instance, referring to Figure 5, the targets for cardiovascular adverse events tied to etoricoxib and nimesulide involve COX and two other entities, namely albumin (P02768) and prostaglandin E2 (P43116). The approval of the hypotheses of our OLS regression model moreover supports the hypothesis that adverse cardiovascular events caused by NSAIDs are due to the operations of several receptors simultaneously. In addition, it was discovered that drugs with greater selectivity for COX-2 had a higher risk of cardiovascular occurrences, which proves the concept of pharmacodynamic selectivity crucial in assessing drug safety (Bonnesen and Schmidt, 2021; Stiller and Hjemdahl, 2022). In summary, certain drugs may impact cardiovascular function through their interactions with various receptors, particularly those with distinct pharmacodynamic characteristics (Su, 2006; Soslau, 2022). The inhibition of COX-2 by NSAIDs is beneficial for pain relief and inflammation; however, it may disrupt the delicate balance between prothrombotic and antithrombotic factors, thereby increasing the risk of cardiovascular events (Graham, 2006; Rahme and Nedjar, 2007; Marsico et al., 2017; Stiller and Hjemdahl, 2022).

It is vital to notice that both the spontaneous reporting system and the disproportionality analysis are necessary tools in the field of safety monitoring. Our approach of integrating pharmacovigilance data with pharmacodynamic insights aligns with recent strategies employed in studying AEs associated with drugs within the same pharmacological class. It has been useful in explaining the receptor mechanisms underlying AEs reported in safety databases such as in cases of metabolic disturbances or pneumonia by antipsychotics and cardiovascular toxicity of drugs (Reynolds and McGowan, 2017; Cepaityte et al., 2021; Chen et al., 2023). Applying the same to NSAIDs, the given work intends to explore the receptor-based mechanisms that are associated with the observed cardiovascular risks; thereby, enhancing the understanding of the safety aspects of NSAIDs. Also, classification studies of the SOCs associated with the cardiovascular system were carried out and target-pharmacovigilance signals' interactions were also analyzed to understand possible receptor mechanisms. In summary, the key strength of our study lies in the integration of pharmacovigilance data with pharmacodynamic insights, following the previously described strategies used in investigating AEs associated with the drugs of the same pharmacological class. This has the advantage of providing a comprehensive exploration of receptor-based mechanisms underlying cardiovascular risks of NSAIDs within different cardiovascular-related SOCs, which helps to add to the knowledge base of the safety of these products.

However, it is essential to understand the limitations of the present research. Firstly, the nature of the database used for self-reporting, namely FAERS, may lead to the problem of imprecision in the analysis. For instance, there is a possibility of missing data in the early paper-based records within FAERS. Besides, the spontaneous reporting system is susceptible to various factors that can result in underreporting, omission, and overall underestimation (Hazell and Shakir, 2006). Due to the unavailability of the reports, sometimes data can be imprecise in terms of weight and onset time, which could distort the results. Secondly, it is always a limitation in all the pharmacovigilance and other observational cohort studies not to establish a causal relationship between reported AEs and drug exposure (Liu et al., 2024). Despite these limitations, disproportionality analysis remains a valuable method for identifying rare signals and monitoring drug safety. Most of the signals that have initially indicated the unsafety of certain drugs have stemmed from disproportionality observed in FAERS. Furthermore, the exact mechanisms of action of drugs that interact with specific receptors and the relation of such interactions to cardiovascular incidents are still partly unknown. The lack of sufficient samples and data on the occupancy of other receptors represents a limitation in the current study. The utilization of multiple NSAIDs was linked to a heightened risk of reporting cardiovascular events, indicating a multifactorial mechanism and synergistic effects that necessitate additional investigation.

5 Conclusion

Through the use of pharmacovigilance and pharmacodynamics, this study underlines the significance of continuous monitoring of the cardiovascular risk associated with NSAIDs. In conclusion, our findings, particularly the results of disproportionality analysis, offer significant information on the cardiovascular safety of these generally used NSAIDs. The direct correlation between receptor occupancy levels and the risk of cardiovascular adverse events underscores the significance of considering pharmacodynamic properties in drug safety assessment. The selectivity of NSAIDs for COX-2 and COX-1 can have a significant impact on their cardiovascular safety. Higher COX-2 receptor occupancy is associated with an increased cardiovascular risk from NSAIDs, while higher COX-1 receptor occupancy is linked to a reduced cardiovascular risk from NSAIDs. By integrating pharmacovigilance and pharmacodynamic analyses in our study, we were able not only to relate the detailed receptor mechanisms of NSAIDs on COX isozymes with broader safety signals of SOCs. This detailed consideration provides further clarity on the safety of NSAIDs stressing how maintaining an appropriate balance between COX-1 and COX-2 inhibition reduces cardiovascular events. Continuous post-marketing surveillance and further long-term investigations are imperative to gain a deeper understanding of the potential risks associated with NSAIDs, particularly given their widespread use for pain and inflammation management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

SL: Writing–original draft, Writing–review and editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition. XW: Funding acquisition, Resources, Supervision, Writing–review and editing. XZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Validation, Writing–original draft, Writing–review and editing.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Guangdong Provincial Hospital Association Pharmaceutical Research Special Foundation (2022YXKY11), Guangzhou Research-oriented Hospital, and Hebei Medical University Clinical Pharmacy Young Scholars Support Program-Spark Plan (XHJH202303).

Acknowledgments

We would like to thank all the authors who made outstanding contributions to this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1455212/full#supplementary-material

References

Abou Zeid, H., Kallab, R., Najm, M. A., Jabbour, H., Noun, R., Sleilati, F., et al. (2019). Safety and efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) used for analgesia after bariatric surgery: a retrospective case-control study. *Obes. Surg.* 29 (3), 911–916. doi:10.1007/s11695-018-3608-y

Ahmed, S. A., Al-Lawati, H., and Jamali, F. (2019). Dose-dependency of the cardiovascular risks of non-steroidal anti-inflammatory drugs. *Inflammopharmacology* 27 (5), 903–910. doi:10.1007/s10787-019-00621-5

Aldington, S., Shirtcliffe, P., Weatherall, M., and Beasley, R. (2005). Increased risk of cardiovascular events with parecoxib/valdecoxib: a systematic review and meta-analysis. *N. Z. Med. J.* 118 (1226), U1755. Available at: https://pubmed.ncbi.nlm.nih.gov/16311613/.

Bally, M., Dendukuri, N., Rich, B., Nadeau, L., Helin-Salmivaara, A., Garbe, E., et al. (2017). Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 357, j1909. doi:10.1136/bmj.j1909

Bech-Drewes, A., Bonnesen, K., Hauge, E. M., and Schmidt, M. (2024). Cardiovascular safety of using non-steroidal anti-inflammatory drugs for gout: a Danish nationwide case-crossover study. *Rheumatol. Int.* 44 (6), 1061–1069. doi:10.1007/s00296-024-05584-7

Bindu, S., Mazumder, S., and Bandyopadhyay, U. (2020). Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochem. Pharmacol.* 180, 114147. doi:10.1016/j.bcp.2020.114147

Bonnesen, K., and Schmidt, M. (2021). Recategorization of non-aspirin nonsteroidal anti-inflammatory drugs according to clinical relevance: abandoning the traditional NSAID terminology. *Can. J. Cardiol.* 37 (11), 1705–1707. doi:10.1016/j.cjca.2021.06.014

Braun, J., Baraliakos, X., and Westhoff, T. (2020). Nonsteroidal anti-inflammatory drugs and cardiovascular risk - a matter of indication. *Semin. Arthritis Rheum.* 50 (2), 285–288. doi:10.1016/j.semarthrit.2019.07.012

Castelli, G., Petrone, A., Xiang, J., Shrader, C., and King, D. (2017). Rates of nonsteroidal anti-inflammatory drug use in patients with established cardiovascular disease: a retrospective, cross-sectional study from NHANES 2009-2010. *Am. J. Cardiovasc. Drugs* 17 (3), 243–249. doi:10.1007/s40256-016-0212-1

Cepaityte, D., Siafis, S., Egberts, T., Leucht, S., Kouvelas, D., and Papazisis, G. (2021). Exploring a safety signal of antipsychotic-associated pneumonia: a pharmacovigilance-pharmacodynamic study. *Schizophr. Bull.* 47 (3), 672–681. doi:10.1093/schbul/sbaa163

Chen, Y., Fan, Q., Liu, Y., Shi, Y., and Luo, H. (2023). Cardiovascular toxicity induced by SSRIs: analysis of spontaneous reports submitted to FAERS. *Psychiatry Res.* 326, 115300. doi:10.1016/j.psychres.2023.115300

Derry, S., Conaghan, P., Da Silva, J. A., Wiffen, P. J., and Moore, R. A. (2016). Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst. Rev.* 4 (4), CD007400. doi:10.1002/14651858.CD007400.pub3

Domper Arnal, M. J., Hijos-Mallada, G., and Lanas, A. (2022). Gastrointestinal and cardiovascular adverse events associated with NSAIDs. *Expert Opin. Drug Saf.* 21 (3), 373–384. doi:10.1080/14740338.2021.1965988

Funk, C. D., and FitzGerald, G. A. (2007). COX-2 inhibitors and cardiovascular risk. *J. Cardiovasc. Pharmacol.* 50 (5), 470–479. doi:10.1097/FJC.0b013e318157f72d

García Rodríguez, L. A., González-Pérez, A., Bueno, H., and Hwa, J. (2011). NSAID use selectively increases the risk of non-fatal myocardial infarction: a systematic review of randomised trials and observational studies. *PLoS One* 6 (2), e16780. doi:10.1371/journal.pone.0016780

Graham, D. J. (2006). COX-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. *JAMA* 296 (13), 1653–1656. doi:10.1001/jama.296.13.jed60058

Grosser, T., Fries, S., and FitzGerald, G. A. (2006). Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J. Clin. Invest.* 116 (1), 4–15. doi:10.1172/JCI27291

Harding, S. D., Sharman, J. L., Faccenda, E., Southan, C., Pawson, A. J., Ireland, S., et al. (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res.* 46 (D1), D1091–D1106. doi:10.1093/nar/gkx1121

Harris, R. C. (2006). COX-2 and the kidney. *J. Cardiovasc. Pharmacol.* 47 (Suppl. 1), S37–S42. doi:10.1097/00005344-200605001-00007

Hazell, L., and Shakir, S. A. (2006). Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 29 (5), 385–396. doi:10.2165/00002018-200629050-00003

Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., et al. (2018). Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 51 (1-02), e1. doi:10.1055/s-0037-1600991

Hunt, C. M., Yuen, N. A., Stirnadel-Farrant, H. A., and Suzuki, A. (2014). Age-related differences in reporting of drug-associated liver injury: data-mining of WHO Safety Report Database. *Regul. Toxicol. Pharmacol.* 70 (2), 519–526. doi:10.1016/j.yrtph.2014.09.007

Jiao, X. F., Pu, L., Lan, S., Li, H., Zeng, L., Wang, H., et al. (2024). Adverse drug reaction signal detection methods in spontaneous reporting system: a systematic review. *Pharmacoepidemiol. Drug Saf.* 33 (3), e5768. doi:10.1002/pds.5768

Kenakin, T. (2004). Principles: receptor theory in pharmacology. *Trends Pharmacol. Sci.* 25 (4), 186–192. doi:10.1016/j.tips.2004.02.012

Khan, S., Andrews, K. L., and Chin-Dusting, J. P. F. (2019). Cyclo-Oxygenase (COX) inhibitors and cardiovascular risk: are non-steroidal anti-Inflammatory drugs really anti-inflammatory?. *Int. J. Mol. Sci.* 20 (17), 4262. doi:10.3390/ijms20174262

Kohli, P., Steg, P. G., Cannon, C. P., Smith, S. C., Eagle, K. A., Ohman, E. M., et al. (2014). NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. *Am. J. Med.* 127 (1), 53–60.e1. doi:10.1016/j.amjmed.2013.08.017

Lin, T. C., Solomon, D. H., Tedeschi, S. K., Yoshida, K., and Yang, Y. H. (2017). Comparative risk of cardiovascular outcomes between topical and oral nonselective NSAIDs in Taiwanese patients with rheumatoid arthritis. *J. Am. Heart Assoc.* 6 (11), e006874. doi:10.1161/JAHA.117.006874

Lindhardsen, J., Gislason, G. H., Jacobsen, S., Ahlehoff, O., Olsen, A. M., Madsen, O. R., et al. (2014). Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. *Ann. Rheum. Dis.* 73 (8), 1515–1521. doi:10.1136/annrheumdis-2012-203137

Liu, Y., Yang, R., Feng, H., Du, Y., Yang, B., Zhang, M., et al. (2024). Adverse events reporting of XPO1 inhibitor - selinexor: a real-word analysis from FAERS database. *Sci. Rep.* 14 (1), 12231. doi:10.1038/s41598-024-62852-z

Marcum, Z. A., and Hanlon, J. T. (2010). Recognizing the risks of chronic nonsteroidal anti-inflammatory drug use in older adults. *Ann. Longterm. Care* 18 (9), 24–27. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3158445/pdf/nihms-315767.pdf.

Marsico, F., Paolillo, S., and Filardi, P. P. (2017). NSAIDs and cardiovascular risk. *J. Cardiovasc. Med. Hagerst.* 18, e40–e43. doi:10.2459/JCM.0000000000000443

Martín Arias, L. H., Martín González, A., Sanz Fadrique, R., and Vazquez, E. S. (2019). Cardiovascular risk of nonsteroidal anti-inflammatory drugs and classical and selective cyclooxygenase-2 inhibitors: a meta-analysis of observational studies. *J. Clin. Pharmacol.* 59 (1), 55–73. doi:10.1002/jcph.1302

McDonald, D. D., Coughlin, S., and Jin, C. (2018). Older adults' response to analgesic adverse drug reactions: a pilot study. *Pain Manag. Nurs.* 19 (4), 333–339. doi:10.1016/j.pmn.2018.01.008

McGettigan, P., and Henry, D. (2011). Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med.* 8 (9), e1001098. doi:10.1371/journal.pmed.1001098

Minhas, D., Nidhaan, A., and Husni, M. E. (2023). Recommendations for the use of nonsteroidal anti-inflammatory drugs and cardiovascular disease risk: decades later, any new lessons learned? *Rheum. Dis. Clin. North Am.* 49 (1), 179–191. doi:10.1016/j.rdc.2022.08.006

Mitchell, J. A., Kirkby, N. S., Ahmetaj-Shala, B., Armstrong, P. C., Crescente, M., Ferreira, P., et al. (2021). Cyclooxygenases and the cardiovascular system. *Pharmacol. Ther.* 217, 107624. doi:10.1016/j.pharmthera.2020.107624

Montastruc, F., Palmaro, A., Bagheri, H., Schmitt, L., Montastruc, J. L., and Lapeyre-Mestre, M. (2015). Role of serotonin 5-HT2C and histamine H1 receptors in antipsychotic-induced diabetes: a pharmacoepidemiological-pharmacodynamic study in VigiBase. *Eur. Neuropsychopharmacol.* 25 (10), 1556–1565. doi:10.1016/j.euroneuro.2015.07.010

Pepine, C. J., and Gurbel, P. A. (2017). Cardiovascular safety of NSAIDs: additional insights after PRECISION and point of view. *Clin. Cardiol.* 40 (12), 1352–1356. doi:10.1002/clc.22814

Rahme, E., and Nedjar, H. (2007). Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. *Rheumatol. Oxf.* 46 (3), 435–438. doi:10.1093/rheumatology/kel428

Reynolds, G. P., and McGowan, O. O. (2017). Mechanisms underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *J. Psychopharmacol.* 31 (11), 1430–1436. doi:10.1177/0269881117722987

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Schafer, A. I. (1995). Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J. Clin. Pharmacol.* 35 (3), 209–219. doi:10.1002/j.1552-4604.1995.tb04050.x

Schjerning, A. M., McGettigan, P., and Gislason, G. (2020). Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat. Rev. Cardiol.* 17 (9), 574–584. doi:10.1038/s41569-020-0366-z

Soslau, G. (2022). Cardiovascular serotonergic system: evolution, receptors, transporter, and function. *J. Exp. Zool. A Ecol. Integr. Physiol.* 337 (2), 115–127. doi:10.1002/jez.2554

Stiller, C. O., and Hjemdahl, P. (2022). Lessons from 20 years with COX-2 inhibitors: importance of dose-response considerations and fair play in comparative trials. *J. Intern. Med.* 292 (4), 557–574. doi:10.1111/joim.13505

Su, J. B. (2006). Kinins and cardiovascular diseases. *Curr. Pharm. Des.* 12 (26), 3423–3435. doi:10.2174/138161206778194051

Tannenbaum, H., Davis, P., Russell, A. S., Atkinson, M. H., Maksymowych, W., Huang, S. H., et al. (1996). An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. Canadian NSAID consensus participants. *CMAJ* 155 (1), 77–88. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1487875/pdf/cmaj00097-0079.pdf.

Varga, Z., Sabzwari, S. R. A., and Vargova, V. (2017). Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus* 9 (4), e1144. doi:10.7759/cureus.1144

Varrassi, G., Pergolizzi, J. V., Dowling, P., and Paladini, A. (2020). Ibuprofen safety at the golden anniversary: are all NSAIDs the same? A narrative review. *Adv. Ther.* 37 (1), 61–82. doi:10.1007/s12325-019-01144-9

Wehling, M. (2014). Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects. *Eur. J. Clin. Pharmacol.* 70 (10), 1159–1172. doi:10.1007/s00228-014-1734-6

Wongrakpanich, S., Wongrakpanich, A., Melhado, K., and Rangaswami, J. (2018). A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging Dis.* 9 (1), 143–150. doi:10.14336/AD.2017.0306

Wu, K., Na, K., Chen, D., Wang, Y., Pan, H., and Wang, X. (2018). Effects of non-steroidal anti-inflammatory drug-activated gene-1 on Ganoderma lucidum polysaccharides-induced apoptosis of human prostate cancer PC-3 cells. *Int. J. Oncol.* 53 (6), 2356–2368. doi:10.3892/ijo.2018.4578

Yang, H., Wan, Z., Chen, M., Zhang, X., Cui, W., and Zhao, B. (2023). A real-world data analysis of topotecan in the FDA Adverse Event Reporting System (FAERS) database. *Expert Opin. Drug Metab. Toxicol.* 19 (4), 217–223. doi:10.1080/17425255.2023.2219390

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 13 September 2024
DOI 10.3389/fphar.2024.1369442

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Tianyi Zhao,
Tianjin University of Traditional Chinese Medicine, China
Yunhui Chen,
Chengdu University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Yufei Yang,
yyf93@vip.sina.com

RECEIVED 12 January 2024
ACCEPTED 02 September 2024
PUBLISHED 13 September 2024

CITATION
Ning C, Yan Y, Wang Y, Li R, Liu W, Qiu L, Sun L and Yang Y (2024) Research trends on chemotherapy induced nausea and vomiting: a bibliometric analysis.
Front. Pharmacol. 15:1369442.
doi: 10.3389/fphar.2024.1369442

Research trends on chemotherapy induced nausea and vomiting: a bibliometric analysis

Chunhui Ning[1], Yunzi Yan[2], Yansong Wang[2], Rui Li[1], Wenjie Liu[1], Linjie Qiu[1], Lingyun Sun[1] and Yufei Yang[1]*

[1]Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Graduate College, Beijing University of Traditional Chinese Medicine, Beijing, China

Background: CINV is a frequent adverse response to cancer treatment. There is still much to learn about the pathophysiology and initiating event of CINV, which necessitates continued research despite decades of effort. Identifying the current foci of the complex disease and assessing the scientific impact of pertinent study are made more difficult by the abundance of publications on CINV. Therefore, our goals in this article are to evaluate developments in this field, examine patterns in research domains, and gauge the expansion of CINV research production globally.

Methods: Articles about CINV published between 2012 and 2022 were found by searching the Web of Science Core Collection of Clarivate Analytics. The number of publications over time was visualized using Microsoft Office Excel 2019. CiteSpace and VOSviewer were utilized to create knowledge maps that analyzed collaborations between nations, organizations, and writers. They also presented the history of CINV research and highlighted its current areas of focus.

Results: In this study, 846 papers in all were assessed. Most publications (237, 28.01%) came from the United States. University of Toronto was the most productive institution (34, 4.01%). With 25 articles published, or 2.96% of the total, Aapro Matti published the most. The most frequently published journal was found to be Supportive Care (158, 18.68%). "Palonosetron," "Moderately emetogenic chemotherapy," "5-HT3 receptor antagonist," and "Neurokinin 1 receptor antagonists" were considered the hot topics. It can be seen that the research focus is on the drug treatment of chemotherapy-induced nausea and vomiting.

Conclusion: Through bibliometric analysis, we were able to gain profound insights into CINV research for the first time. Researchers looking to uncover research frontiers and comprehend important information in this discipline may find the study's findings useful.

KEYWORDS

chemotherapy induced nausea and vomiting, bibliometric analysis, research trends, hot spots, knowledge mapping analysis

1 Introduction

As one of the three main cancer treatment methods, chemotherapy is among the most often used and successful approaches, along with surgery and radiation therapy (Marx et al., 2013; Chung et al., 2021). As a systemic therapy, it inhibits the growth of cancer cells, which either spread throughout the body or are eradicated by medication. However, because it can harm normal cells while harming tumor cells, it may have adverse reactions and side effects (Pearce et al., 2017). Moreover, CINV is a frequent adverse response to cancer treatment (Lee et al., 2020). The majority of chemotherapy patients had one or more side effects; exhaustion was the most prevalent side effect, occurring in 80% of cases, followed by nausea and vomiting (48%) and pain (48%) (Henry et al., 2008). In particular, nausea and vomiting require special attention because they can worsen the patient's quality of life, have an adverse effect on food intake (Marx et al., 2016), and may result in poor adherence to chemotherapy, which can lead to dose reductions or discontinuation, all of which have a significant negative impact on the effectiveness of the treatment. Antitumor medications can typically be categorized into four categories: high, moderate, low, and mild emetic risk during antitumor therapy. According to the guidelines, the incidence of vomiting caused by highly emetogenic chemotherapy (HEC) is more than 90% among patients who do not receive prophylactic antiemetic agents within 24 h of chemotherapy; the incidence for moderately emetogenic chemotherapy (MEC) is 30%–90%; the incidence for low-emetogenic chemotherapy (LEC) is 10%–30%; and the incidence for mildly emetogenic chemotherapy is less than 10% (Herrstedt, 2018). The field of chemotherapy-induced emesis has undergone significant transformation with the introduction of novel antiemetic medicines. The most often used antiemetics for CINV prior to the use of olanzapine include dexamethasone, NK-1R antagonists, and 5-HT3R antagonists (Gupta et al., 2021). It is advised to use dexamethasone, neurokinin-1R antagonists, and 5-HT3R antagonists in conjunction for HEC. Combining 5-HT3R antagonists with neurokinin-1R antagonists is recommended for MEC. A single antiemetic medication, such as a dopamine receptor antagonist, dexamethasone, or a 5HT3 receptor antagonist, may also be taken into consideration for LEC. It is not advisable for people undergoing chemotherapy with a mild emetic regimen to regularly take antiemetic medications (Olver et al., 2017; Herrstedt, 2018). Olanzapine, a medication belonging to the benzodiazepine class, is a second-generation psychotropic used to treat bipolar disorder and schizophrenia (Navari, 2014; Yokoe et al., 2019). Olanzapine has been proposed as an effective antiemetic, and since the early 2000s, the National Comprehensive Cancer Network (NCCN) and the Multinational Association for Supportive Care in Cancer (MASCC) have advocated olanzapine for the prevention and treatment of CINV (Saudemont et al., 2020).

There are still a lot of unanswered questions about CINV despite decades of scientific research, which has drawn a lot of interest from academics. As a result, there has been a steady interest in the condition as a research topic, with numerous publications of literature occurring year. Bibliometric analysis is a method that is typically used to thoroughly expose the research status in a particular topic by measuring and visualizing the qualitative, quantitative, and chronological characteristics associated to diverse fields of research. This helps to highlight significant issues for future research (Guler et al., 2016). The current study's objective is to use knowledge maps to illustrate the state of CINV research now, as well as its knowledge components, research trends, and growing areas during the past 10 years. This article highlights recent advancements in the topic and gives a summary of the research and scholarly contributions that have been made in it.

2 Methods

2.1 Search strategy

The Web of Science Core Collection provided the data (WOSCC). The complete search strategy is demonstrated in Supplementary Table S1. On 2 April 2023, we finished all of the retrieval and extraction work to prevent bias resulting from the database's daily changes. The records that were retrieved were called download_txt and saved as plain text files.

2.2 Study selection

Figure 1 depicted the study's selection criteria and literature screening procedure. Briefly, we entered search terms for an initial search, after then, two researchers went over the papers obtained during the preliminary search and eliminated those that did not meet the specified inclusion requirements as follows: 1) "English" was the only language used for publication; 2) except for letters, comments, reviews, and conference abstracts, the categories of literature included are articles; 3) the source of the publication was the Social Sciences Citation Index (SSCI) and WoSCC Citation Index Expanded (SCI-E) databases; 4) the entire 11-year search

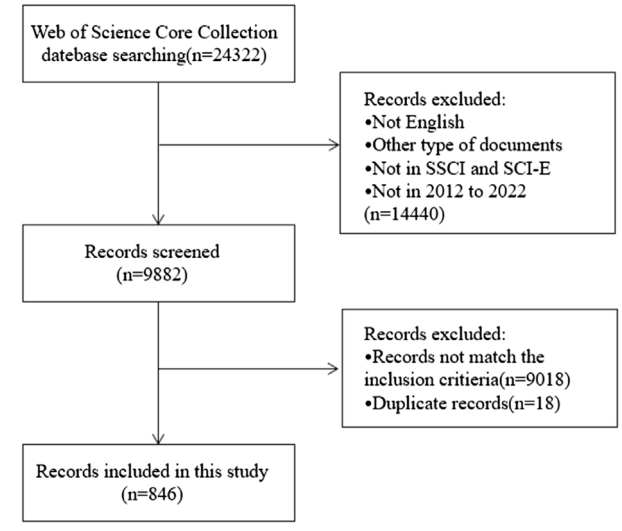


FIGURE 1
Flowchart of the literature screening process.

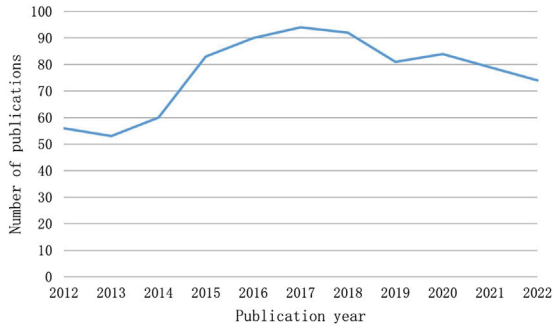


FIGURE 2
The number of articles published annually in CINV research.

period ran from 2012 (1 January 2012) to 2022 (31 December 2022); 5) the subject matter of the chosen article must be chemotherapy-induced nausea and vomiting; it cannot be related to other conditions like pregnancy, disorders of the digestive system, disorders of the nervous system, radiotherapy, etc.

2.3 Data analysis

For visualizing the knowledge structure, distribution, and evolution of a particular area, CiteSpace (Chen et al., 2009)—a publicly downloadable software program created by Drexel University professor Chaomei Chen in the USA—is highly popular. There are other resources that provide comprehensive explanations of every indicator that was computed in this study using CiteSpace and VOSviewer (Okhovati and Arshadi, 2021). CiteSpace was used in this study to: 1) create a knowledge map that visualizes collaborations between nations, institutions, and authors; 2) analyse co-citations in references; 3) create a network and cluster map of co-occurring keywords; 4) show the timeline view of co-occurring keywords; and 5) identify references and keywords with strong citation bursts. To visually examine keyword co-occurrence, VOSviewer was utilized. The temporal trends of publications were shown using Microsoft Excel.

3 Results

From 1 January 2012, to 31 December 2022, 24,322 records were found. The following factors led to the exclusion of 14,440 records: 1) the literature was not published in English; 2) it was not a research article (reviews, conference abstracts, letters, and ongoing papers); 3) it was not sourced from the WoSCC's SCI-E or SSCI databases; and 4) the literature was not published in the period of 2012–2022. By reading the complete text or abstract, the remaining 9,882 records were evaluated in more detail. Ultimately, this bibliometric analysis included 846 works that satisfied the inclusion and exclusion criteria after removing 18 duplicate publications (Figure 1). The 846 papers used in this analysis were published in 280 journals, cited 9,842 references from 3,351 publications, were written by 5,029 authors from 1,762 organizations in 61 counties.

3.1 Analysis of publications and journals

The number of publications over a given time span shows how this field's research is developing. Figure 2 illustrates the two phases of the research trends, while the quantity of publications on CINV remained relatively constant. With the exception of 2013, the first period from 2012 to 2017 saw an increase in the number of publications. In 2015, at this point, there was an outbreak in CINV research. 2017 saw a peak publishing volume of 94. With the exception of 2020, the publication output in the second stage, which ran from 2017 to 2022, exhibited a declining tendency.

Table 1 lists the top 10 journals for CINV publications published in the past 10 years. The highest production (158, 18.68%) is attributed to supportive care in cancer, with Pediatric Blood and Cancer coming in second (24, 2.84%) and Future Oncology in third (22, 2.60%). Thirty percent of all publications come from the top ten journals in terms of published articles. Annals of Oncology is the most influential journal in the field despite ranking seventh in terms of articles. Out of the 10 journals, it has the highest IF (51.769) and average number of citations (95.33).

3.2 Analysis of the cooperative relationship

Studies on CINV have been published in 61 different nations and areas. The top ten countries by prolificity are displayed in Table 2. With 237 publications, the United States published the most, followed by Japan (184), China (142), and Switzerland (62). Based on citation counts, the top three countries were the United States (5,169), Switzerland (2,133), and China (1,823). With an average citation/publication of 34.40, Switzerland was highest, followed by Germany (31.72) and England (29.71). Additionally, the United States (0.52), Switzerland (0.24), and China (0.22) were the top three nations in terms of centrality. The collaboration network between these nations is depicted in Figure 3, where each country is represented by a node, the size of which reflects the nation's publication output. The collaboration between nations is represented by the lines connecting the nodes; the thicker the line, the closer the entities are to cooperating. Different colors are used to identify cooperation groups across nations. There are 31 nations included in this network map, and each country has at least five publications in this field.

Out of all of them, China and the US are probably the two most central and closely connected nations in the network. The United States also has some connections to practically every other nation in the network, with the strongest connections being to Canada, Germany, and Switzerland. China has ties to South Korea, Australia, Canada, and other nations, although it has international links less than the United States. As a result, it is noteworthy that the United States has the largest network of collaboration, extending throughout Asia and Europe.

Table 3 displays the top 10 institutions in terms of the quantity of publications each. The most publications were contributed by the University of Toronto (34), with Clinique de Genolier (30), Helsinn Healthcare SA (25), and other institutions following closely behind. University of Toronto also held the record for the most total citations of any institution. The Mayo Clinic was the

TABLE 1 The top 10 journals involved in CINV research.

Rank	Journal	Count (%of 846)	Citation	Average citation/ Publication	IF (2021)
1	SUPPORTIVE CARE IN CANCER	158 (18.68)	2,730	17.28	3.359
2	PEDIATRIC BLOOD and CANCER	24 (2.84)	424	17.67	3.838
3	FUTURE ONCOLOGY	22 (2.60)	121	5.50	3.674
4	INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY	16 (1.89)	77	4.81	2.435
5	ANTICANCER RESEARCH	16 (1.89)	284	17.75	2.435
6	ONCOLOGIST	15 (1.77)	164	10.93	5.837
7	ANNALS OF ONCOLOGY	15 (1.77)	1,430	95.33	51.769
8	JOURNAL OF ONCOLOGY PHARMACY PRACTICE	15 (1.77)	52	3.47	1.416
9	BMC CANCER	12 (1.42)	44	3.67	4.638
10	CANCER NURSING	11 (1.30)	103	9.36	2.760

TABLE 2 The top 10 countries/regions involved in CINV research.

Rank	Country	Count	Citations	Average citation/Publication	Centrality
1	United States	237	5,169	21.81	0.52
2	Japan	184	1797	9.77	0.03
3	China	142	1823	12.84	0.22
4	Swizerland	62	2,133	34.40	0.24
5	Italy	62	1,680	27.10	0.09
6	Canada	58	1,629	28.09	0.03
7	Germany	46	1,459	31.72	0.06
8	South Korea	36	408	11.33	0.00
9	England	31	921	29.71	0.02
10	Australia	27	769	28.48	0.04

organization with the greatest average citation/publication. The University of Toronto, the Clinique de Genolier, Merck and Company, and the Fondazione IRCCS Istituto Nazionale Tumori Milan showed the highest degree of centrality (no < 0.1) out of all the institutions. As seen in Figure 4, each institution is represented by each node. A node's radius grows as it contributes more to the CINV research. The cooperation is represented by the links connecting nodes, whose thicknesses are correlated with the collaboration's strength. A purple ring indicates a node with a high betweenness centrality rating, and a red ring indicates a burst. Because of their global cooperation, Harvard University and Clinique de Genolier were named as the network's central countries. The Clinicique de Genolier, for instance, collaborated extensively with the University of Toronto, the University of Alabama System, the Hospital for Sick Children (SickKids), the Fondazione IRCCS Istituto Nazionale Tumori Milan, Harvard University, and other institutions. It was the institution with the widest scientific collaboration.

In addition, we evaluated the authors in this study who were the most prolific. With 25 articles, Professor Aapro Matti of the Genolier Cancer Centre was the most productive author. He was followed in output by Shimokawa Mototsugu (23) and Iihara Hirotoshi (20). Likewise, Table 4 shows that Navari Rudolph M had the greatest average citation count (59.29) and total citation count (830). Citespace also carried out the examination of co-authorship (Figure 5). In a similar vein, every node stands for an author, while the lines connecting the nodes show the relationships between authors. The degree of cooperation between the two writers increases with the thickness of the relationship between two nodes. As a result, Aapro Matti Hesketh Paul J, Schnadig Ian D, Rapoport Bernardo L, Clemons Mark, and Molassiotis Alexander are all working closely together. Moreover, there are also noticeable active partnerships amongst Kikkawa Fumitaka, Hayashi Toshinobu, Iihara Hirotoshi, Kitagawa Yuko, and Shimokawa Mototsugu.

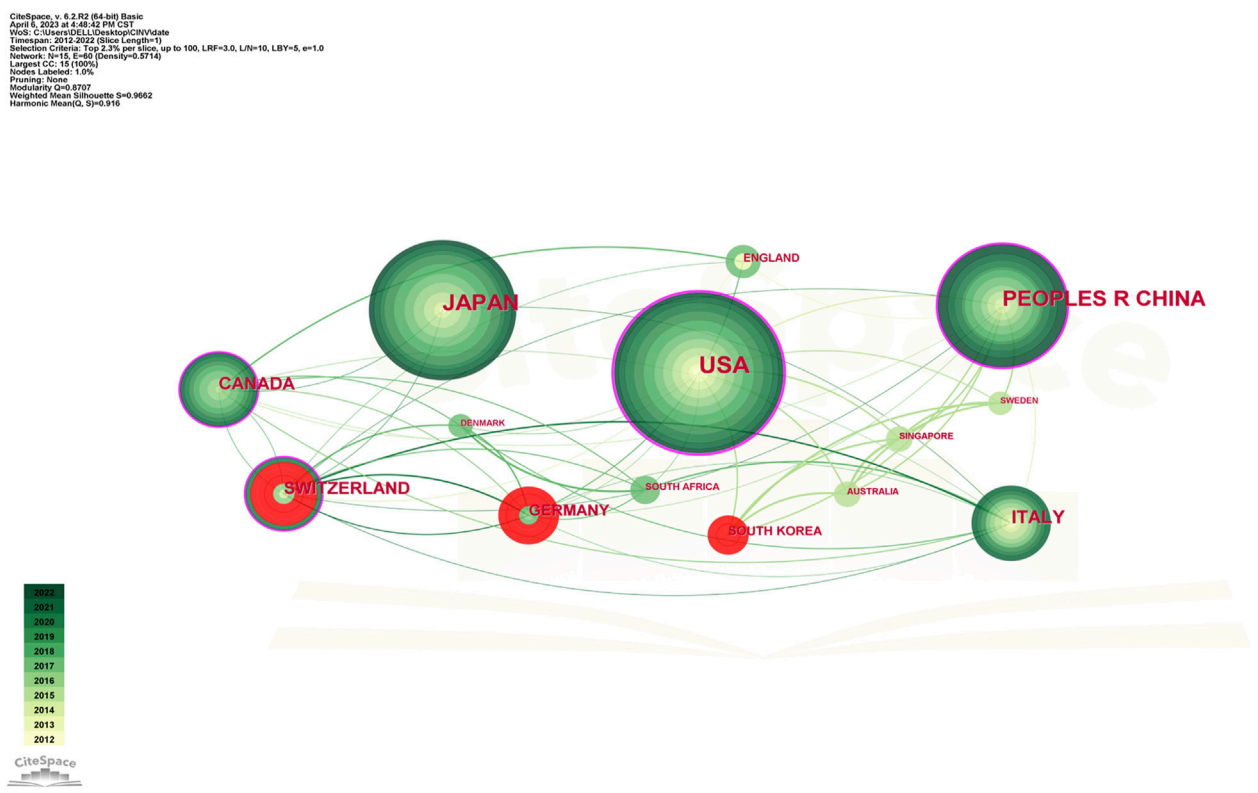


FIGURE 3
Network of countries and regions engaged in CINV research.

TABLE 3 The top 10 institutions involved in CINV research.

Rank	Institution	Count	Citations	Average Citation/Publication	Centrality
1	University of Toronto	34	838	24.65	0.20
2	Clinique de Genolier	30	661	22.03	0.42
3	Helsinn Healthcare SA	25	545	21.80	0.06
4	Gifu University	23	163	7.09	0.00
5	Merck and Company	22	199	9.05	0.19
6	Hospital for Sick Children (SickKids)	21	471	22.43	0.03
7	Kyushu Cancer Center	19	138	7.26	0.05
8	Fondazione IRCCS Istituto Nazionale Tumori Milan	17	177	10.41	0.21
9	Mayo Clinic	16	445	27.81	0.01
10	National Cancer Center - Japan	16	415	25.94	0.00

3.3 Keyword analysis

Co-citation and citation coupling are the foundations of keyword co-occurrence analysis in bibliometrics (Lee and Su, 2010; Li et al., 2016). The goal is to look at the relationships between keywords that occur frequently in a set of publications that represent popular themes. The more times a phrase appears together, the closer the relationship between those terms is. Keywords were taken from 846 papers for the current investigation. Using a threshold of 10, 242 keywords were found using VOSviewer after unrelated keywords were eliminated and those with similar semantic meanings were combined.

The map of keywords with high co-occurrence frequencies that CiteSpace examined is displayed in Figure 6. The keywords were divided into six clusters: the prognostic factors for CINV (light blue cluster), the drug therapy mechanism for CINV (green cluster), clinical trials related to CINV (purple cluster), drug therapy for CINV (dark blue cluster), risk factors for CINV (red cluster), and

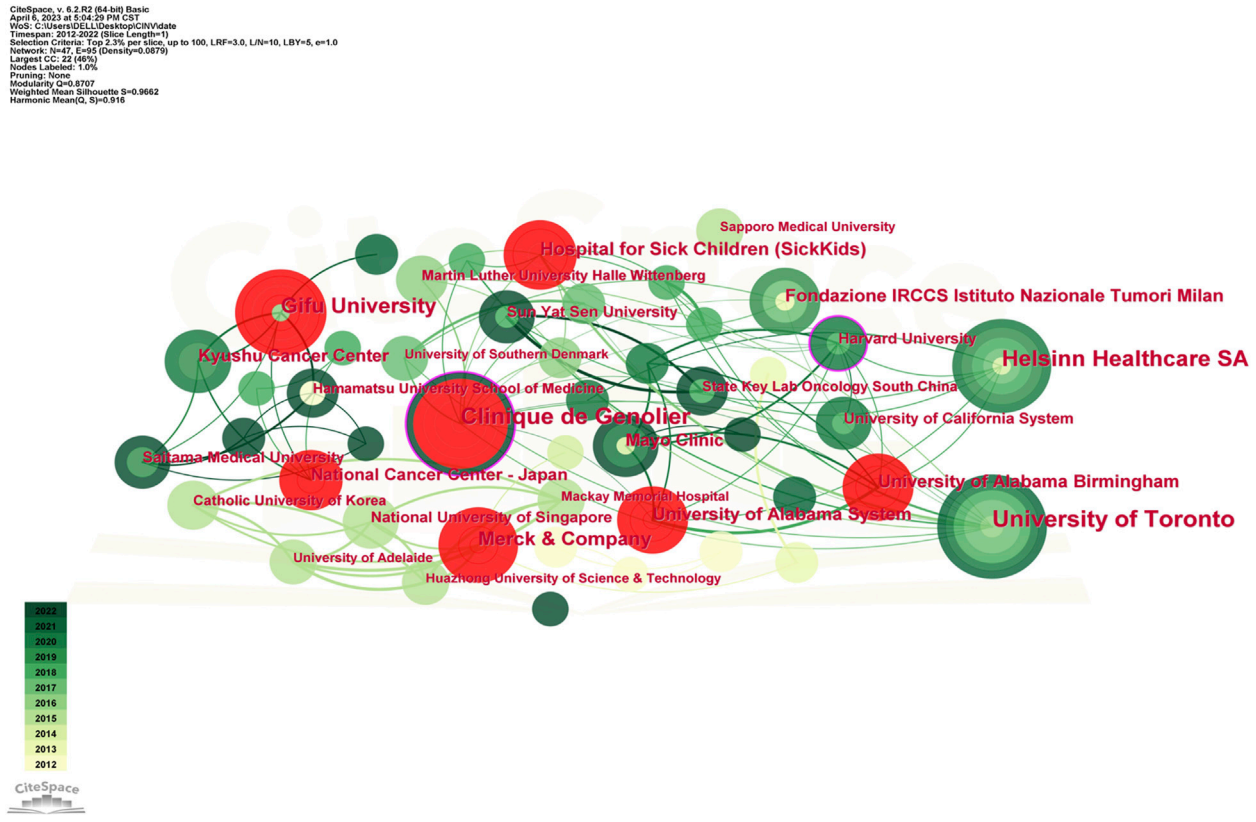


FIGURE 4
Network of institution engaged in CINV research.

TABLE 4 The top 10 authors involved in CINV research.

Rank	Author	Count	Citations	Average Citation/Publication
1	Aapro, Matti	25	514	20.56
2	Shimokawa, Mototsugu	23	271	11.78
3	Iihara, Hirotoshi	20	72	3.60
4	Dupuis, L Lee	16	451	28.19
5	Navari, Rudolph M	14	830	59.29
6	Sung, Lillian	14	410	29.29
7	Celio, Luigi	12	174	14.50
8	Schwartzberg, Lee	12	183	15.25
9	Jordan, Karin	12	305	25.42
10	Hayashi, Toshinobu	11	60	5.45

CINV prevention and support care (yellow cluster). The VOSviewer-generated keyword clustering analysis mapping is displayed in Figure 7. One or more keywords with a particular relationship to each other make create a keyword cluster. The terms "palonosetron" (Cluster 0), "moderately emetogenic chemotherapy" (Cluster 1), "5-HT3 receptor antagonist" (Cluster 2), "chemotherapy-induced nausea and vomiting" (Cluster 3), "non-inferiority trial" (Cluster 4), and "neurokinin 1 receptor antagonists" (Cluster 5) are among the total number of clustering patterns that have been identified. Additionally, these clusters have a large number of lines connecting the nodes, indicating a high co-occurrence rate for keywords.

The keyword co-occurrence timeline view is displayed in Figure 8, which allows us to track the development of research subjects over time. The map contains nodes that stand in for keywords. The links show the co-occurrences of each keyword.

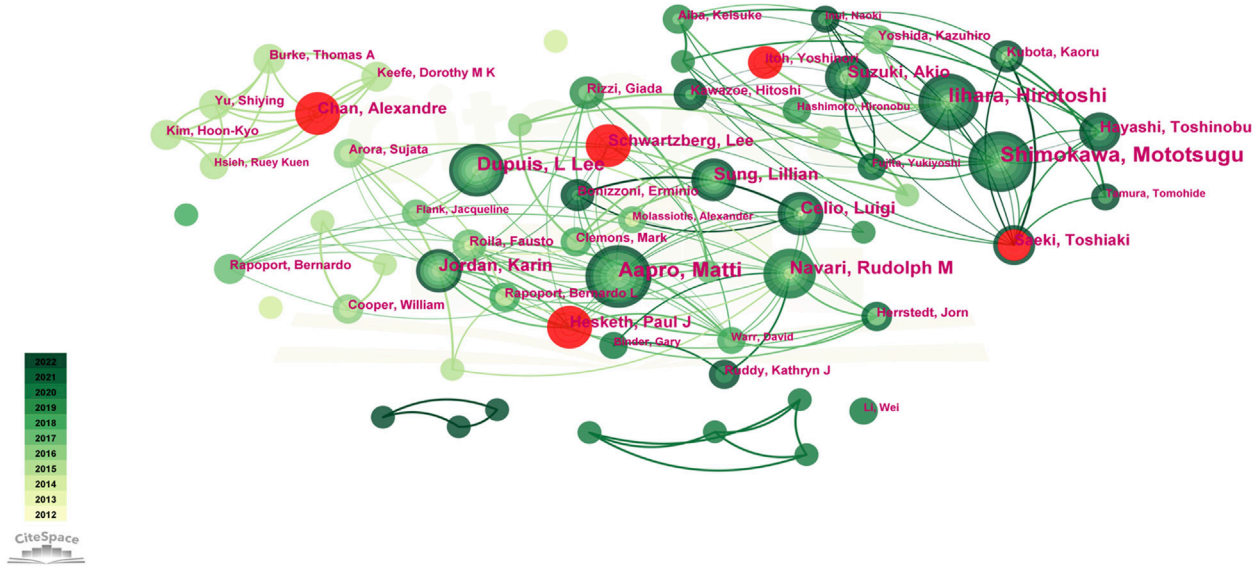


FIGURE 5
Network of authors engaged in CINV research.

The keywords' chronological sequence reflects the evolution of CINV study themes over time. Burst keywords are also seen to be early warning signs of new trends. Figure 9 displays the keywords in this field with the strongest citation bursts. Year in the figure denotes the first year the keyword appears. The burst's beginning and finish are represented by the terms begin and end, respectively. When the keywords appear frequently, they are indicated by a red bar, and when they occur infrequently, they are displayed by a blue bar. "Antiemetics American society" has the strongest citation burst out of any of these.

3.4 Co-cited references and references burst

490 co-cited references were examined, and Supplementary Table S2 presents the top ten. The main topics covered in these publications, which were thought of as the foundation for information on CINV research, are the epidemiology of CINV, consensus and guidelines for diagnosing and treating the disease, and a sizable randomized controlled placebo clinical trial. Among them, Basch et al. (2011b) published an article, entitled "Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update" in Clinical Oncology, which was the most frequently co-cited and ranked first (216), followed by "The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—The Aprepitant Protocol 052 Study Group," written by Hesketh et al. (2003) in Clinical Oncology (165), "Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment" authored by Bloechl-Daum et al. (2006) in Clinical Oncology (159), and "Drug therapy: Chemotherapy-induced nausea and vomiting" published by Hesketh Paul J. (Hesketh, 2008) in Gastroenterology (148). Two of the top ten co-cited articles were published in the esteemed peer-reviewed New England Journal of Medicine (IF 158.5), while half of the top ten were published in the Journal of Clinical Oncology (IF 37.7).

The top 5 co-cited references in Table 5 with the highest betweenness centrality score were thought to be crucial in creating the theoretical foundation of CINV. The study titled "Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting" (published in the New England Journal of Medicine) had the highest centrality (0.20, 2016). Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update (published in the Journal of Clinical Oncology, 0.16, 2017) and The Effect of Guideline-consistent Antiemetic Therapy on Chemotherapy-Induced Nausea and Vomiting (CINV): the Pan European Emesis Registry (PEER) (published in the Annals of Oncology, 0.16, 2014) were next. Top 5 co-cited references focused on 1) updating on guidelines for antiemetic drugs (Basch et al., 2011a; Hesketh et al., 2017); 2) antiemetic drug efficacy (Olanzapine, for example,) in preventing nausea and vomiting in

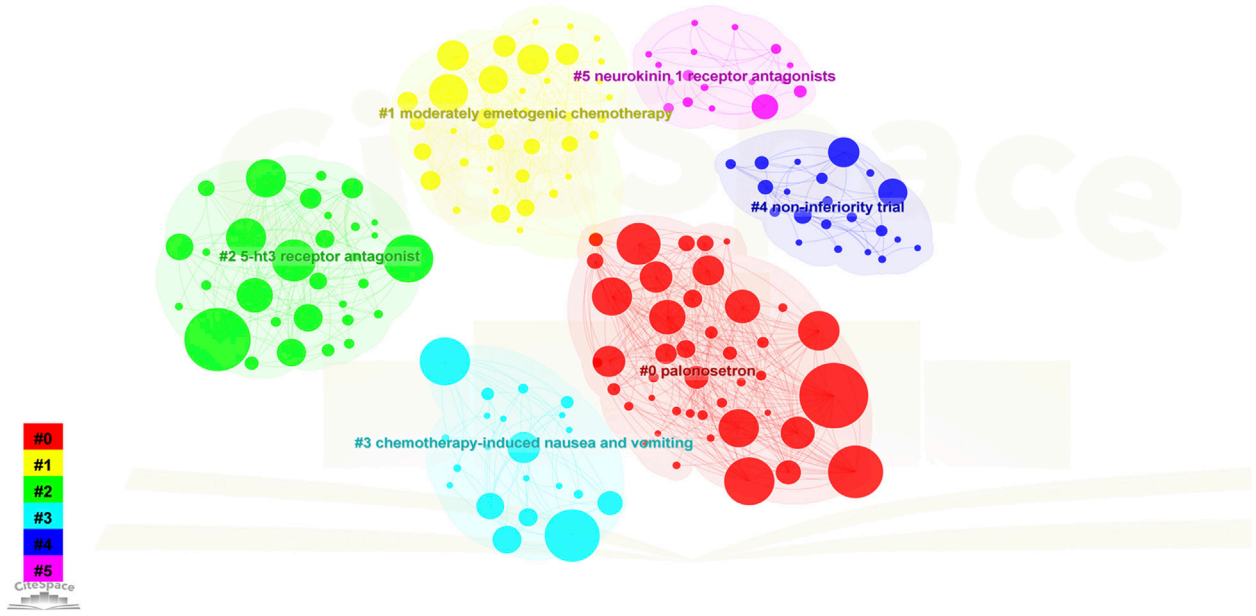


FIGURE 6
Keyword clustering analysis in CINV research.

chemotherapy patients (Hesketh et al., 2003; Poli-Bigelli et al., 2003; Warr et al., 2005; Hesketh, 2008; Saito et al., 2009; Navari et al., 2016); 3) effect of guideline-consistent CINV prophylaxis (GCCP) on patient outcomes (Aapro et al., 2012); and 4) impact of CINV on patients' quality of life (QoL) after emetogenic chemotherapy (Bloechl-Daum et al., 2006).

References with bursts of citations can show how a knowledge domain has evolved. Citation bursts are references that academics in a certain discipline pay attention to for a set amount of time. The top 25 references with the strongest citation bursts are shown in Figure 10. For publications connected to CINV, the burst lasted a minimum of 2 years and a maximum of 6 years. The timeline is represented by a blue bar, and the period of time during which a subject is discovered to have a burst is shown by a red segment that shows the beginning year, ending year, and duration of the burst. A higher citation frequency is indicated by a stronger strength. Of these references, 24% (6/25) of the bursts happened in 2016, while 20% (5/25) of the bursts happened in 2012. Remarkably, 60% (15/25) stopped in 2018 or later. The strongest burst (44.14) among the top 25 references occurred for the paper entitled "Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update" (Basch et al., 2011b), with a citation burst lasting from 2013 to 2016, followed by "Randomized, double-blind, dose-ranging trial of the oral neurokinin-1 receptor antagonist casopitant mesylate for the prevention of cisplatin-induced nausea and vomiting" (Roila et al., 2009), which was published in Annals of Oncology and exhibited a citation burst from 2012 to 2015 (42.02), and "Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update" (Hesketh et al., 2017), which was published in Journal of Clinical Oncology and saw a citation burst from 2018 to 2022 (30.58). Overall, the burst strength of the top 25 references ranged from 7.70 to 44.14, while the most frequent burst duration was 4 years.

4 Discussion

4.1 General information

CINV research was actively conducted in Europe (Italy, England, Switzerland, and Germany), Asia (China, Japan, and South Korea), North America (the United States and Canada), and Oceania (Australia), as Table 2; Figure 3 demonstrate. A node's capacity to establish connections with other nodes in the network is referred to as its betweenness centrality. Information flows are more likely to be guided by a source with a high betweenness centrality, demonstrating its versatility in cooperation and potentially revolutionary qualities (Yan and Ding, 2009). Collaboration has been shown to improve the quality of research, and the number of co-authors positively correlates with the impact of citations, particularly in cases when international collaboration is involved (Wuchty et al., 2007). As a result, the United States, Switzerland, China, and Canada played a crucial role in fostering international impact and collaboration in the CINV field.

High-yield educational institutions are primarily found in North America, Asia, and Europe, as Table 3; Figure 4 illustrate. All things

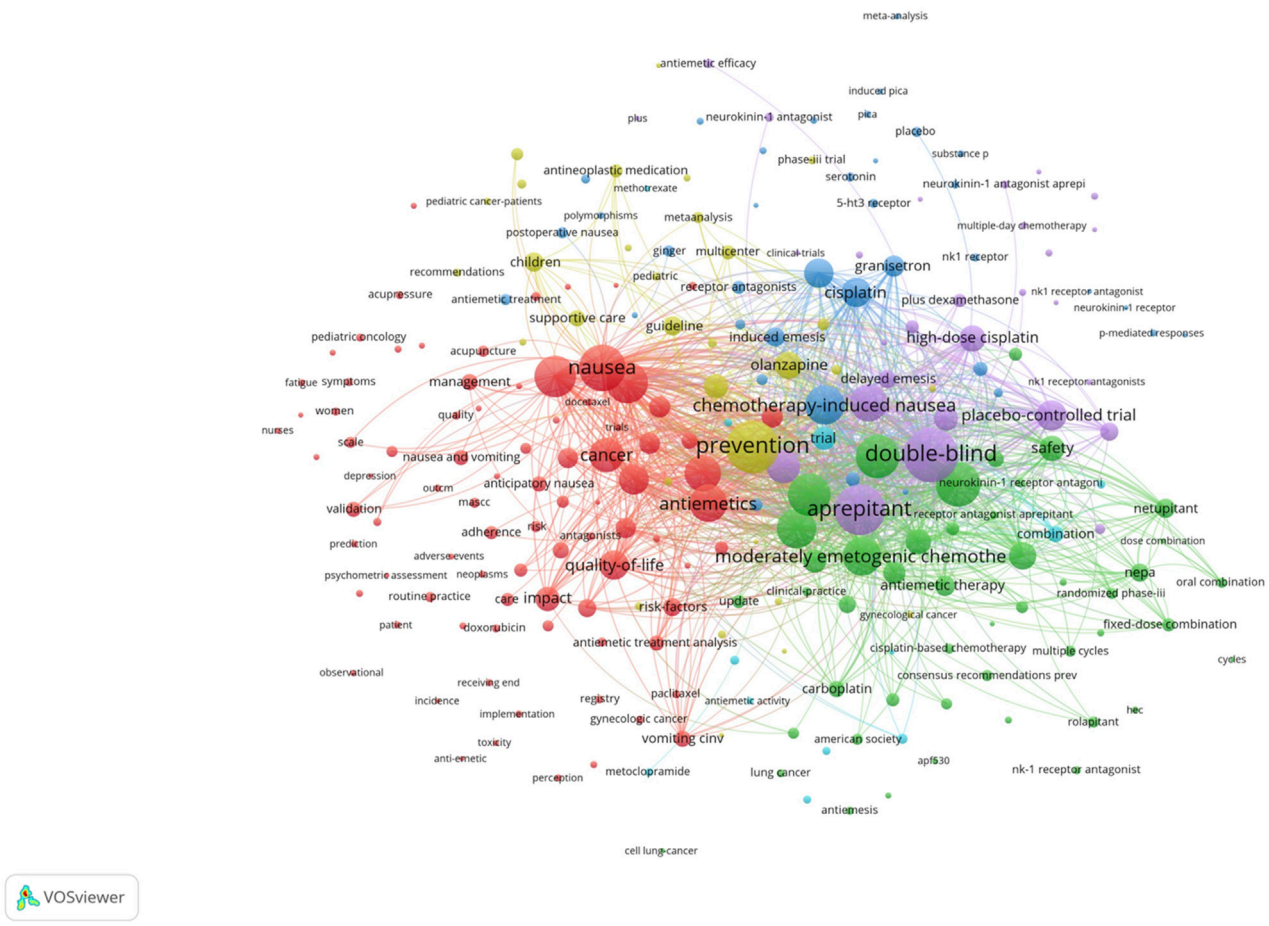


FIGURE 7
The cooperation network of keywords in CINV research.

considered, the American institutions had wide-ranging international collaboration ties. As an illustration of extensive cross-continental cooperation, the most active institution, University of Toronto, extensively partnered with National University of Singapore, University of South Australia, Ottawa Hospital Research Institute, and Akron Children's Hospital. But European institutions have few international collaboration links. As a result, the relationship between Clinique de Genolier, which ranked second in scientific output, and institutions such as Ruprecht Karls University Heidelberg, University of Milan, Odense University Hospital, and Helsinn Healthcare SA tended to be limited to be an intra-continent phenomenon.

Scholars from the United States and Japan were clearly the dominant forces, as Table 4; Figure 5 demonstrate. The high ranking of Japanese academics was accompanied by a scarcity of other Asian scholars, particularly those from China and South Korea, which resembled the top institutions' landscape devoid of any Chinese or Korean institutions. It is plausible that insufficient exchange of resources, ideas, and information hindered CINV research in China and South Korea. Asian nations, including China and South Korea, are therefore urged to pursue global scientific collaboration while raising research productivity, which is directly related to higher research quality and more research capability.

Table 1 indicates that research on CINV has mostly appeared in journals related to supportive care, pediatric hematological cancer, and cancer pharmacy practice. This suggests that CINV treatment is complex and affects patients of nearly all ages.

The quantity of co-citations was typically used to evaluate a study's impact on the scientific community and its academic success (Moed, 2009). In this domain, journals with a high co-citation rate are called mainstream journals. The majority of high co-citations were discovered in journals with high impact factor (IF), suggesting that CINV research published in prestigious journals has continuously garnered attention.

4.2 Knowledge base

Publications that have been referred collectively by other publications are known as co-cited references, and they serve as a kind of knowledge foundation for a specific field of study. The prevention and management of CINV have been covered in great length in a number of articles that were published on the subject between 2012 and 2022. The scientific community has acknowledged these references (Hesketh et al., 2003; Poli-Bigelli et al., 2003; Warr et al., 2005; Bloechl-Daum et al., 2006; Hesketh,

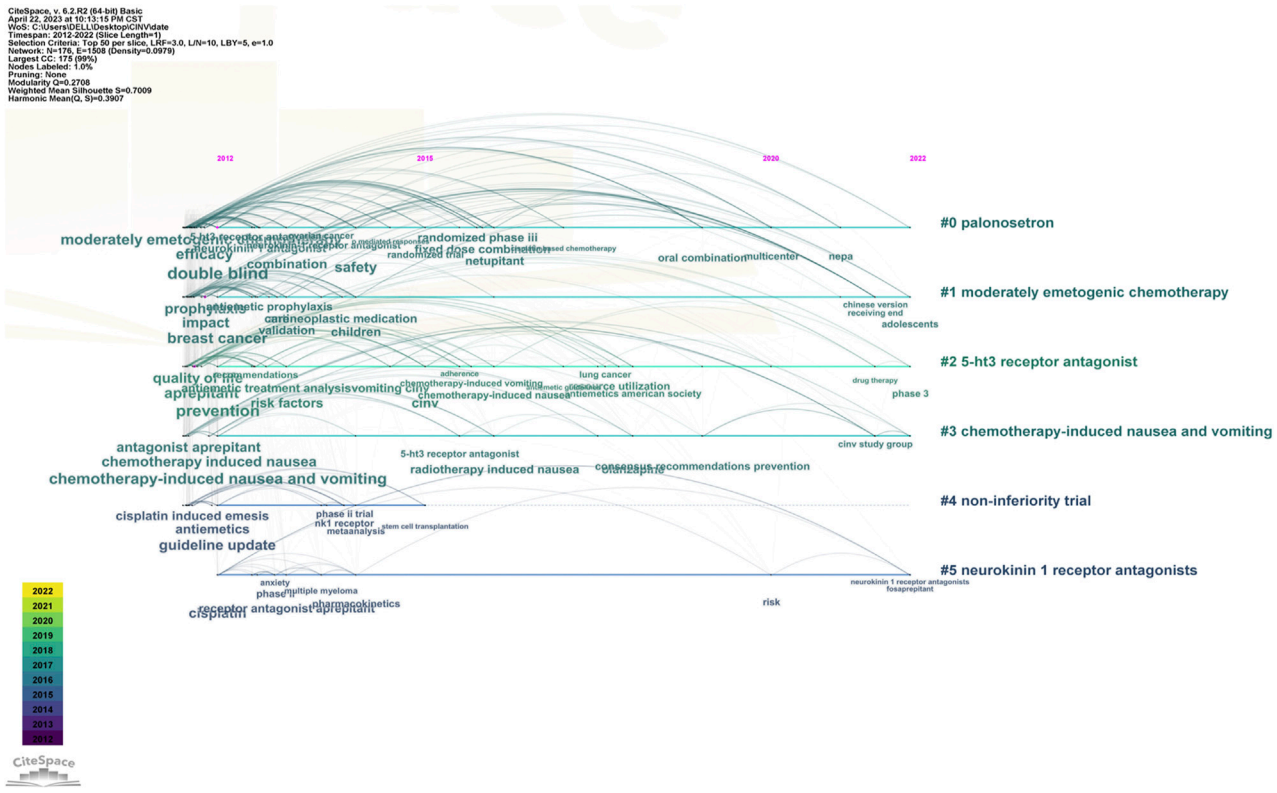


FIGURE 8
The timeline view of keywords in CINV research.

2008; Saito et al., 2009; Basch et al., 2011a; Aapro et al., 2012; Navari, 2014; Hesketh et al., 2017) included in Table 5 as knowledge carriers. This recognition provides a foundation for future research endeavors that aim to generate novel insights. Most of the studies assess the effectiveness of oral medicines as a preventative therapy through randomized controlled trials. The most thoroughly investigated of these medicines are neurokinin-1 (NK1) receptor antagonists, 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists and antipsychotic medication (aprepitant, palonosetron and olanzapine). The corroborative data from Figure 7, which demonstrate that aprepitant forms a key component of knowledge, are also indicative of this argument.

4.3 Research frontiers

The research frontiers in this discipline are shown by keywords that exhibit persistent strong citation bursts, as illustrated in Figure 9. The majority of the newly popular subjects are pharmaceuticals like olanzapine.

4.4 Medical therapy for CINV

Inhibiting the production of inflammatory mediators, dexamethasone, a corticosteroid often used in 2-, 3-, or 4-drug combinations with other agents, reduces the severity of CINV by acting directly on the solitary tract nucleus (STN), the neurotransmitter 5-HT, and receptor proteins NK1, NK2, etc., while maintaining the patients' normal physiological functions (Kageyama, 2000; Ho et al., 2004; Suzuki et al., 2004; Dewan et al., 2010). Marco Filetti et al. (2023) collected data from 53 randomized controlled trials (RCTs), which included 22,228 patients with any type of cancer receiving HEC. They then compared various antiemetic regimens to prevent CINV. In terms of complete response, 3- or 4-drug regimens comprising dexamethasone plus NK antagonists, either alone or in combination, produced the highest likelihood of being the most successful regimen. In terms of complete, acute, and delayed response, regimens that combine dexamethasone with a 5-HT3 antagonist have the lowest likelihood of being the most successful regimen (Filetti et al., 2023). When it comes to preventing both acute and delayed CINV in patients receiving HEC and/or MEC, many national guidelines recommend dexamethasone as first-line use in combination with other agents. However, a study conducted by Vardy et al. found that in the week following MEC, patients reported tolerability issues that they linked to dexamethasone, including agitation (27%), increased appetite (19%), weight gain (16%), and acne (15%) (Vardy et al., 2006; Hesketh et al., 2017). These lead us to believe that, when combined with somewhat emetogenic chemotherapy, the negative effects of dexamethasone may exceed its advantages.

In the prevention of CINV, 5-HT3 receptor antagonists (5-HT3 RAs) are essential because they prevent 5-HT3 receptors from binding to serotonin released by enterochromaffin cells in the mucosa of the gastrointestinal (GI) tract in response to

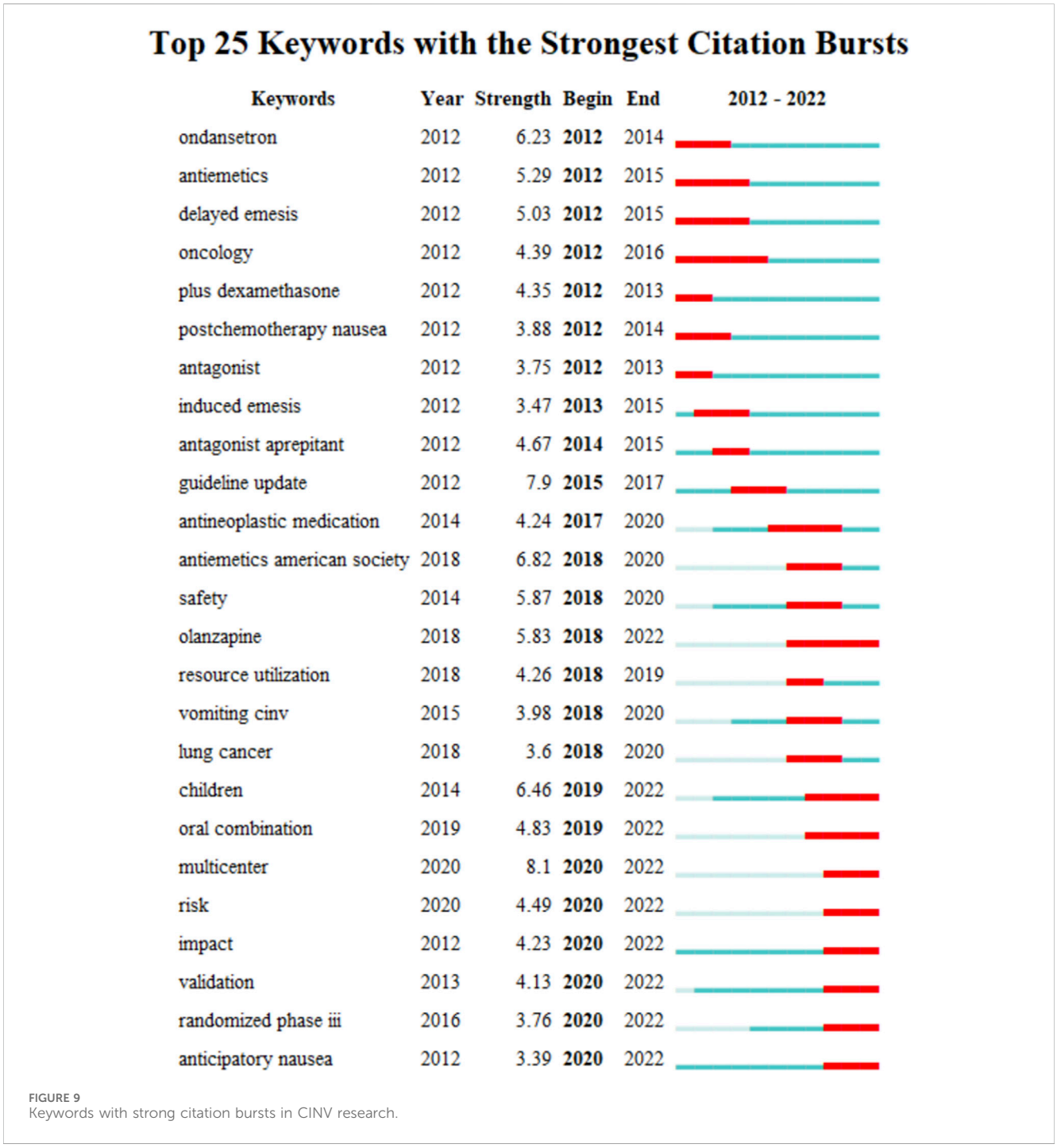


FIGURE 9
Keywords with strong citation bursts in CINV research.

chemotherapy (as well as other potentially toxic chemical or mechanical stimuli). This causes the chemoreceptor trigger zone to send a signal to areas within the medulla, which in turn causes increased salivation, respiratory rate, pharyngeal, GI, and abdominal muscle contractions, as well as emesis (Adel, 2017). The structures of the first-generation 5-HT3 RAs, such as ondansetron, dolasetron, granisetron, and tropisetron, were similar to those of serotonin (Hesketh and Gandara, 1991; Lorusso, 2016). The emergence of a second generation of this class of medications was signaled by the invention of palonosetron, a 5-HT3 RA with a structure dissimilar to serotonin. Palonosetron has a longer half-life (of 40 h) for hplasma compared to less than 10 h for old-generation drugs and a binding affinity for the 5-HT3 receptor that is at least thirty times higher *in vitro* than older 5-HT3 Ras (Lorusso, 2016). Palonosetron outperformed older 5HT3 RAs in controlling CINV during the delayed and overall postchemotherapy periods, according to a pooled analysis of four randomized, double-blind, phase III trials comparing palonosetron to ondansetron, dolasetron, and granisetron in the prevention of CINV (Schwartzberg et al., 2014). While 5-HT3 RAs are advised for the first-line prevention of CINV, the medical literature has expressed concerns regarding adverse events (AEs) such as headaches, constipation, elevated ALT,

TABLE 5 Top 5 co-cited references with the highest betweenness centrality in CINV research.

Rank	Reference	Centrality	Year
1	Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting	0.2	2016
2	Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update	0.16	2017
2	The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER)	0.16	2012
3	Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	0.13	2020
4	Risk factors of chemotherapy-induced nausea and vomiting: Index for personalized antiemetic prophylaxis	0.11	2013
4	2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following multiple-day chemotherapy, high-dose chemotherapy, and breakthrough nausea and vomiting	0.11	2017
5	Antiemetic Guideline Consistency and Incidence of Chemotherapy-Induced Nausea and Vomiting in US Community Oncology Practice: INSPIRE Study	0.09	2014

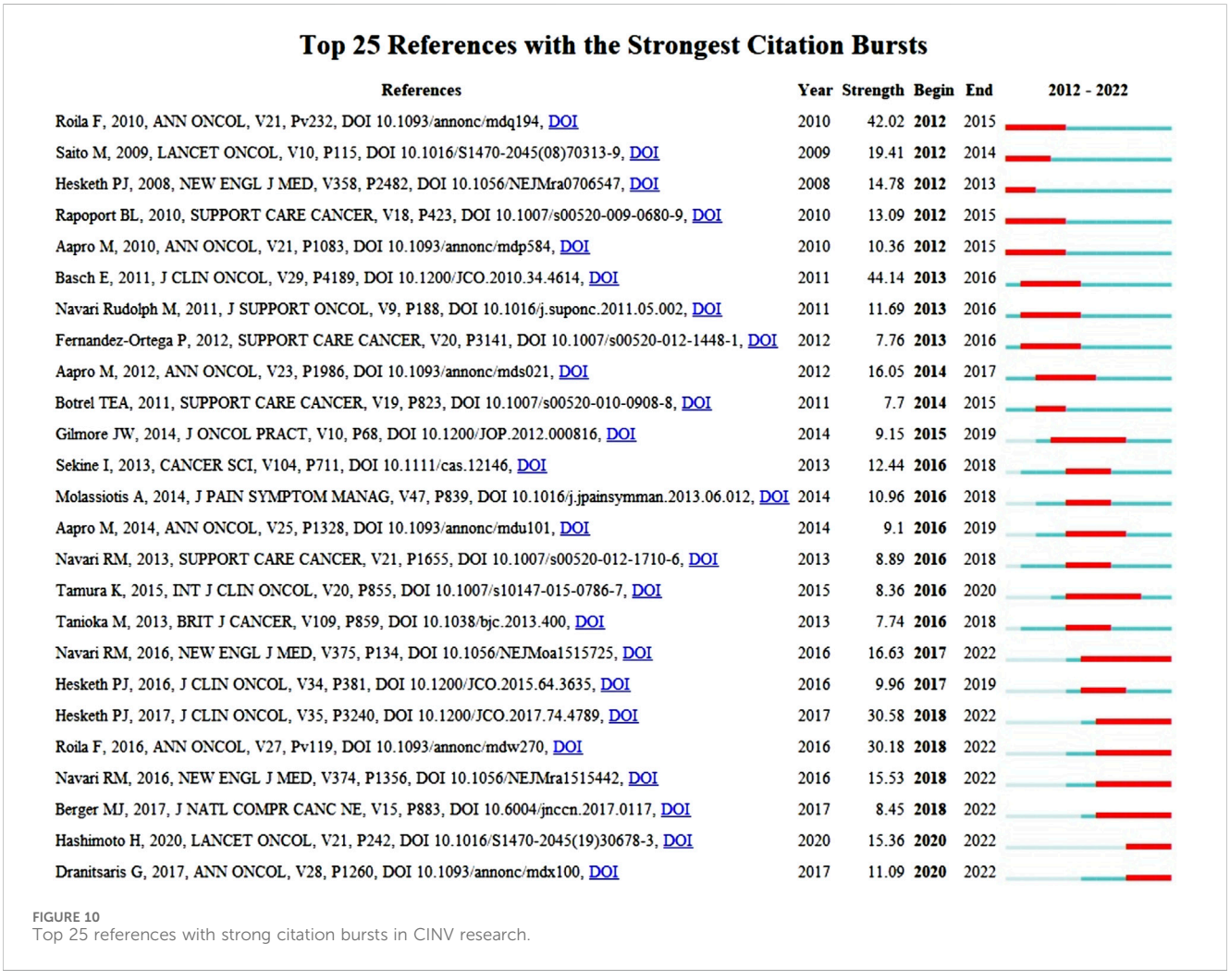


FIGURE 10
Top 25 references with strong citation bursts in CINV research.

and prolongation of the QT interval, which is linked to severe ventricular arrhythmias (Schwartzberg et al., 2014; Tricco et al., 2016).

By blocking NK1 receptors, NK1 receptor antagonists (NK1 RAs) have been demonstrated to benefit in both acute and delayed CINV by lowering substance *P* activity (Yuan et al., 2016). Findings from a double-blind, randomized, placebo-controlled study conducted in Latin America demonstrated that treatment with aprepitant, the most traditional NK1 RA, in addition to the usual ondansetron and dexamethasone regimen offered better antiemetic protection than standard therapy alone and was generally well tolerated in cancer patients undergoing high-dose

cisplatin-based chemotherapy (Poli-Bigelli et al., 2003). NK1 RA netupitant and second-generation 5-HT3 RA palonosetron are combined in a fixed-dose combination called netupitant/palonosetron (NEPA; Akynzeo), which is approved in the EU and the United States for use (in conjunction with dexamethasone) in the prevention of community-acquired pneumonia (CINV) in adults. It is available in oral and, more recently, intravenous (IV) formulations (the IV formulation uses fosnetupitant, a water-soluble prodrug of netupitant). NEPA was compared to aprepitant plus granisetron (an additional combination of an NK1 RA and a 5-HT3 RA) in a phase III non-inferiority trial that was double-blind, randomized, and conducted in Asia. A single oral dose of NEPA was found to be non-inferior to a 3 day regimen of aprepitant with granisetron in this trial. The overall CR rates (primary endpoint) were 73.8% and 72.4%, respectively (between-group difference 1.5%; 95% CI − 4.5% to 7.5%), satisfying the non-inferiority margin of −10% (Zhang et al., 2018).

A member of the benzodiazepine class of psychotropics, olanzapine is a second-generation antipsychotic that was first licensed for the treatment of depression, bipolar disorder, and schizophrenia. However, olanzapine also inhibits dopamine, 5-HT2, and 5-HT3 receptors, which has antiemetic properties (Navari, 2014; Koth and Kolesar, 2017; Filetti et al., 2023). For patients undergoing multiday chemotherapy regimens, olanzapine (5 mg) in combination with fosaprepitant, ondansetron, and dexamethasone proved to be more effective than triple antiemetic treatment alone, according to a randomized, double-blind, placebo-controlled phase 3 trial conducted in 22 hospitals (Zhao et al., 2023). Twelve papers from the database published before 18 April 2021, were eventually included in a meta-analysis by Wang et al. (2021); the study subjects were adult cancer patients receiving HEC or MEC. The purpose of this review was to examine how 10 mg and 5 mg of olanzapine affected the management and prevention of CINV. The findings indicated that individuals with HEC could benefit most from 10 mg of olanzapine, while those with MEC or those without a high risk of CINV might benefit most from 5 mg (Wang et al., 2021). Takako also recruited 153 cisplatin-treated patients for a phase II clinical study. The findings revealed that the incidence of somnolence was 45.5% and 53.3%, respectively, and that the CR for the delayed period was 78% (80% CI: 70.3 – 83.8, $p = 0.01$) in the 10 mg olanzapine group and 86% (80% CI: 79.2–90.7, $p < 0.001$) in the 5 mg olanzapine group (Slimano et al., 2018). Likewise, numerous research investigations have indicated that olanzapine at doses of 10 mg and 5 mg much enhanced delayed vomiting, markedly decreased the frequency and length of nausea in individuals at high risk, and 5 mg olanzapine resulted in reduced somnolence (Slimano et al., 2018; Clemons et al., 2020; Hashimoto et al., 2020; Molassiotis, 2020; Suehiro et al., 2021). Olanzapine is most commonly used to treat nausea and vomiting brought on by chemotherapy drugs; however, the most common side effects are drowsiness and dizziness. These adverse reactions are not immediately apparent, so there is no need to stop using Olanzapine, and there have not yet been any reports of notable extrapyramidal reactions (Tanaka et al., 2019).

Currently, for the medical treatment of nausea and vomiting induced by chemotherapy, such as ondansetron and olanzapine are widely used clinically. However, intensive research has shown that while these drugs exhibit therapeutic effects, they inevitably bring about a series of side effects, which significantly hinder the substantial improvement of patients' quality of life during chemotherapy. In view of this, future research should focus on exploring and developing complementary and alternative therapies for preventing or treating nausea and vomiting caused by chemotherapy, with the aim of reducing the occurrence of adverse reactions related to drug treatment, thereby enhancing patients' treatment experience and quality of life in a more comprehensive and safe manner.

5 Limitations

There are some restrictions on this study. First off, the study's analysis is restricted to works released between 2012 and 2022, previous works are not included. Furthermore, the analysis was limited to English-language publications, which may have missed pertinent work that was published in other languages. Additionally, the study's exclusive reliance on the SCI-E database of WOS limits the variety of literature kinds that may be taken into account. Second, there are some restrictions on the CiteSpace software used for the investigation, like a 500 network size limit, which could affect the analysis's findings. Despite these drawbacks, the study provides a thorough analysis and synopsis of the accomplishments made in the subject of CINV during the previous several decades, aiding in the comprehension of the field's current state of development by scholars.

6 Conclusion

This work is a comprehensive application of bibliometric and knowledge mapping approaches to analyze the literature on chemotherapy-induced nausea and vomiting (CINV). We used cutting-edge resources like CiteSpace and VOSviewer to improve the scope and depth of our analysis. With the aid of these technologies, we were able to extract a wider range of insightful information from the data. Setting itself apart from conventional evaluations, this work provides a fresh and impartial viewpoint on the state of CINV research. Overall, in the past 10 years, the bibliometric profile of CINV seeks to locate, assess, and illustrate publications concerning qualitative, semi-qualitative, and chronological elements. We also demonstrated that North America and Europe were at the forefront of CINV research with regard to qualitative, quantitative, and collaborative variables. In terms of institutional, regional, and national collaboration, high-yield Asian nations like China and Japan have a dismal track record. To enable future developments in this field of study, this inhibiting trend must shift, and future cooperative activities should be encouraged, supported, and carried out internationally. The publications described NK1 Ras, Olanzapine, and 5-HT3 Ras as potential areas of research for CINV treatments.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

CN: Writing–original draft, Writing–review and editing, Formal Analysis, Investigation. YnY: Data curation, Writing–review and editing. YW: Software, Writing–review and editing. RL: Methodology, Writing–review and editing. WL: Investigation, Writing–review and editing. LQ: Formal Analysis, Writing–review and editing. LS: Methodology, Supervision, Writing–review and editing. YfY: Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by Special Project of Scientific Research of Capital Health Development (Grant No. 2022-1-4171), Beijing Natural Science Foundation (J230038) and the Hospital capability enhancement project of Xiyuan Hospital, CACMS (NO. XYZX0201-19). Special Project of Scientific Research of Capital Health Development (Grant No. 2022-1-4171) provided funding for this work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1369442/full#supplementary-material

References

Aapro, M., Molassiotis, A., Dicato, M., Peláez, I., Rodríguez-Lescure, Á., Pastorelli, D., et al. (2012). The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann. Oncol.* 23 (8), 1986–1992. doi:10.1093/annonc/mds021

Adel, N. (2017). Overview of chemotherapy-induced nausea and vomiting and evidence-based therapies. *Am. J. Manag. Care.* 23 (14 Suppl. l), S259–S265.

Basch, E., Prestrud, A. A., Hesketh, P. J., Kris, M. G., Feyer, P. C., Somerfield, M. R., et al. (2011a). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* 29 (31), 4189–4198. doi:10.1200/jco.2010.34.4614

Basch, E., Prestrud, A. A., Hesketh, P. J., Kris, M. G., Feyer, P. C., Somerfield, M. R., et al. (2011b). Antiemetics: American society of clinical oncology clinical practice guideline update. *J. Clin. Oncol.* 29 (31), 4189–4198. doi:10.1200/jco.2010.34.4614

Bloechl-Daum, B., Deuson, R. R., Mavros, P., Hansen, M., and Herrstedt, J. (2006). Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J. Clin. Oncol.* 24 (27), 4472–4478. doi:10.1200/jco.2006.05.6382

Chen, C., Chen, Y., Hou, J., and Liang, Y. (2009). CiteSpace II:Detecting and visualizing emerging trends and transient patterns in scientific literature. *J. China Soc. Sci. Tech. Inf.* 28 (3), 401–421. doi:10.1002/asi.20317

Chung, C., Boterberg, T., Lucas, J., Panoff, J., Valteau-Couanet, D., Hero, B., et al. (2021). Neuroblastoma. *Pediatr. Blood Cancer* 68 (Suppl. 2), e28473. doi:10.1002/pbc.28473

Clemons, M., Dranitsaris, G., Sienkiewicz, M., Sehdev, S., Ng, T., Robinson, A., et al. (2020). A randomized trial of individualized versus standard of care antiemetic therapy for breast cancer patients at high risk for chemotherapy-induced nausea and vomiting. *Breast* 54, 278–285. doi:10.1016/j.breast.2020.11.002

Dewan, P., Singhal, S., and Harit, D. (2010). Management of chemotherapy-induced nausea and vomiting. *Indian Pediatr.* 47 (2), 149–155. doi:10.1007/s13312-010-0023-4

Filetti, M., Lombardi, P., Giusti, R., Falcone, R., Scotte, F., Giannarelli, D., et al. (2023). Efficacy and safety of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: a systematic review and network meta-analysis. *Cancer Treat. Rev.* 115, 102512. doi:10.1016/j.ctrv.2023.102512

Guler, A. T., Waaijer, C. J. F., and Palmblad, M. (2016). Scientific workflows for bibliometrics. *Scientometrics* 107 (2), 385–398. doi:10.1007/s11192-016-1885-6

Gupta, K., Walton, R., and Kataria, S. P. (2021). Chemotherapy-induced nausea and vomiting: pathogenesis, recommendations, and new trends. *Cancer Treat. Res. Commun.* 26, 100278. doi:10.1016/j.ctarc.2020.100278

Hashimoto, H., Abe, M., Tokuyama, O., Mizutani, H., Uchitomi, Y., Yamaguchi, T., et al. (2020). Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 21 (2), 242–249. doi:10.1016/s1470-2045(19)30678-3

Henry, D. H., Viswanathan, H. N., Elkin, E. P., Traina, S., Wade, S., and Cella, D. (2008). Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support. Care Cancer* 16 (7), 791–801. doi:10.1007/s00520-007-0380-2

Herrstedt, J. (2018). The latest consensus on antiemetics. *Curr. Opin. Oncol.* 30 (4), 233–239. doi:10.1097/cco.0000000000000450

Hesketh, P. J. (2008). Drug therapy: chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 358 (23), 2482–2494. doi:10.1056/NEJMra0706547

Hesketh, P. J., and Gandara, D. R. (1991). Serotonin antagonists: a new class of antiemetic agents. *J. Natl. Cancer Inst.* 83 (9), 613–620. doi:10.1093/jnci/83.9.613

Hesketh, P. J., Grunberg, S. M., Gralla, R. J., Warr, D. G., Roila, F., De Wit, R., et al. (2003). The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. *J. Clin. Oncol.* 21 (22), 4112–4119. doi:10.1200/jco.2003.01.095

Hesketh, P. J., Kris, M. G., Basch, E., Bohlke, K., Barbour, S. Y., Clark-Snow, R. A., et al. (2017). Antiemetics: American society of clinical oncology clinical practice guideline update. *J. Clin. Oncol.* 35 (28), 3240–3261. doi:10.1200/jco.2017.74.4789

Ho, C. M., Ho, S. T., Wang, J. J., Tsai, S. K., and Chai, C. Y. (2004). Dexamethasone has a central antiemetic mechanism in decerebrated cats. *Anesth. Analg.* 99 (3), 734–739. doi:10.1213/01.Ane.0000130003.68288.C7

Kageyama, Y. (2000). A case of isolated ACTH deficiency who developed autoimmune-mediated hypothyroidism and impaired water diuresis during glucocorticoid replacement therapy. *Endocr. J.* 47 (6), 667–674. doi:10.1507/endocrj.47.667

Koth, S. M., and Kolesar, J. (2017). New options and controversies in the management of chemotherapy-induced nausea and vomiting. *Am. J. Health Syst. Pharm.* 74 (11), 812–819. doi:10.2146/ajhp160227

Lee, P.-C., and Su, H.-N. (2010). Investigating the structure of regional innovation system research through keyword co-occurrence and social network analysis. *Innovation-Management Policy and Pract.* 12 (1), 26–40. doi:10.5172/impp.12.1.26

Lee, S. R., Kim, S. M., Oh, M. Y., and Lee, J. M. (2020). Efficacy of olanzapine for high and moderate emetogenic chemotherapy in children. *Child. (Basel)* 7 (9), 140. doi:10.3390/children7090140

Li, H., An, H., Wang, Y., Huang, J., and Gao, X. (2016). Evolutionary features of academic articles co-keyword network and keywords co-occurrence network: based on two-mode affiliation network. *Phys. a-Statistical Mech. Its Appl.* 450, 657–669. doi:10.1016/j.physa.2016.01.017

Lorusso, V. (2016). Management of chemotherapy-induced nausea and vomiting by risk profile: role of netupitant/palonosetron. *Ther. Clin. Risk Manag.* 12, 917–925. doi:10.2147/tcrm.S89215

Marx, W., Kiss, N., Mccarthy, A. L., Mckavanagh, D., and Isenring, L. (2016). Chemotherapy-induced nausea and vomiting: a narrative review to inform dietetics practice. *J. Acad. Nutr. Diet.* 116 (5), 819–827. doi:10.1016/j.jand.2015.10.020

Marx, W. M., Teleni, L., Mccarthy, A. L., Vitetta, L., Mckavanagh, D., Thomson, D., et al. (2013). Ginger (Zingiber officinale) and chemotherapy-induced nausea and vomiting: a systematic literature review. *Nutr. Rev.* 71 (4), 245–254. doi:10.1111/nure.12016

Moed, H. F. (2009). New developments in the use of citation analysis in research evaluation. *Arch. Immunol. Ther. Exp. (Warsz.)* 57 (1), 13–18. doi:10.1007/s00005-009-0001-5

Molassiotis, A. (2020). Time to re-think the olanzapine dose. *Lancet Oncol.* 21 (2), 189–190. doi:10.1016/s1470-2045(19)30791-0

Navari, R. M. (2014). Olanzapine for the prevention and treatment of chronic nausea and chemotherapy-induced nausea and vomiting. *Eur. J. Pharmacol.* 722, 180–186. doi:10.1016/j.ejphar.2013.08.048

Navari, R. M., Qin, R., Ruddy, K. J., Liu, H., Powell, S. F., Bajaj, M., et al. (2016). Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 375 (2), 134–142. doi:10.1056/NEJMoa1515725

Okhovati, M., and Arshadi, H. (2021). COVID-19 research progress: bibliometrics and visualization analysis. *Med. J. Islam. Repub. Iran.* 35, 20. doi:10.47176/mjiri.35.20

Olver, I., Ruhlmann, C. H., Jahn, F., Schwartzberg, L., Rapoport, B., Rittenberg, C. N., et al. (2017). 2016 Updated MASCC/ESMO Consensus Recommendations: controlling nausea and vomiting with chemotherapy of low or minimal emetic potential. *Support. Care Cancer* 25 (1), 297–301. doi:10.1007/s00520-016-3391-z

Pearce, A., Haas, M., Viney, R., Pearson, S. A., Haywood, P., Brown, C., et al. (2017). Incidence and severity of self-reported chemotherapy side effects in routine care: a prospective cohort study. *PLoS One* 12 (10), e0184360. doi:10.1371/journal.pone.0184360

Poli-Bigelli, S., Rodrigues-Pereira, J., Carides, A. D., Julie Ma, G., Eldridge, K., Hipple, A., et al. (2003). Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 97 (12), 3090–3098. doi:10.1002/cncr.11433

Roila, F., Rolski, J., Ramlau, R., Dediu, M., Russo, M. W., Bandekar, R. R., et al. (2009). Randomized, double-blind, dose-ranging trial of the oral neurokinin-1 receptor antagonist casopitant mesylate for the prevention of cisplatin-induced nausea and vomiting. *Ann. Oncol.* 20 (11), 1867–1873. doi:10.1093/annonc/mdp194

Saito, M., Aogi, K., Sekine, I., Yoshizawa, H., Yanagita, Y., Sakai, H., et al. (2009). Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol.* 10 (2), 115–124. doi:10.1016/s1470-2045(08)70313-9

Saudemont, G., Prod'homme, C., Da Silva, A., Villet, S., Reich, M., Penel, N., et al. (2020). The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. *BMC Palliat. Care.* 19 (1), 56. doi:10.1186/s12904-020-00559-4

Schwartzberg, L., Barbour, S. Y., Morrow, G. R., Ballinari, G., Thorn, M. D., and Cox, D. (2014). Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). *Support. Care Cancer.* 22 (2), 469–477. doi:10.1007/s00520-013-1999-9

Slimano, F., Netzer, F., Borget, I., Lemare, F., and Besse, B. (2018). Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. *Int. J. Clin. Pharm.* 40 (5), 1265–1271. doi:10.1007/s11096-018-0649-1

Suehiro, M., Kojima, Y., Takahashi, M., Ito, Y., Keira, T., Ikegawa, K., et al. (2021). Antiemetic efficacy of adding olanzapine 5 mg to aprepitant, palonosetron and dexamethasone-sparing after day two for cancer patients receiving anthracycline and cyclophosphamide. *Cancer Manag. Res.* 13, 1617–1624. doi:10.2147/cmar.S280995

Suzuki, T., Sugimoto, M., Koyama, H., Mashimo, T., and Uchida, I. (2004). Inhibitory effect of glucocorticoids on human-cloned 5-hydroxytryptamine3A receptor expressed in xenopus oocytes. *Anesthesiology* 101 (3), 660–665. doi:10.1097/00000542-200409000-00014

Tanaka, K., Inui, N., Karayama, M., Yasui, H., Hozumi, H., Suzuki, Y., et al. (2019). Olanzapine-containing antiemetic therapy for the prevention of carboplatin-induced nausea and vomiting. *Cancer Chemother. Pharmacol.* 84 (1), 147–153. doi:10.1007/s00280-019-03868-5

Tricco, A. C., Blondal, E., Veroniki, A. A., Soobiah, C., Vafaei, A., Ivory, J., et al. (2016). Comparative safety and effectiveness of serotonin receptor antagonists in patients undergoing chemotherapy: a systematic review and network meta-analysis. *BMC Med.* 14 (1), 216. doi:10.1186/s12916-016-0761-9

Vardy, J., Chiew, K. S., Galica, J., Pond, G. R., and Tannock, I. F. (2006). Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. *Br. J. Cancer.* 94 (7), 1011–1015. doi:10.1038/sj.bjc.6603048

Wang, D. Y., Chen, Y., Zhang, Y., and Shen, Y. Q. (2021). The balance between the effectiveness and safety for chemotherapy-induced nausea and vomiting of different doses of olanzapine (10 mg versus 5 mg): a systematic review and meta-analysis. *Front. Oncol.* 11, 705866. doi:10.3389/fonc.2021.705866

Warr, D. G., Hesketh, P. J., Gralla, R. J., Muss, H. B., Herrstedt, J., Eisenberg, P. D., et al. (2005). Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J. Clin. Oncol.* 23 (12), 2822–2830. doi:10.1200/jco.2005.09.050

Wuchty, S., Jones, B. F., and Uzzi, B. (2007). The increasing dominance of teams in production of knowledge. *Science* 316 (5827), 1036–1039. doi:10.1126/science.1136099

Yan, E., and Ding, Y. (2009). Applying centrality measures to impact analysis: a coauthorship network analysis. *J. Am. Soc. Inf. Sci. Technol.* 60 (10), 2107–2118. doi:10.1002/asi.21128

Yokoe, T., Hayashida, T., Nagayama, A., Nakashoji, A., Maeda, H., Seki, T., et al. (2019). Effectiveness of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: a systematic review and network meta-analysis. *Oncologist* 24 (6), e347–e357. doi:10.1634/theoncologist.2018-0140

Yuan, D. M., Li, Q., Zhang, Q., Xiao, X. W., Yao, Y. W., Zhang, Y., et al. (2016). Efficacy and safety of neurokinin-1 receptor antagonists for prevention of chemotherapy-induced nausea and vomiting: systematic review and meta-analysis of randomized controlled trials. *Asian pac. J. Cancer Prev.* 17 (4), 1661–1675. doi:10.7314/apjcp.2016.17.4.1661

Zhang, L., Lu, S., Feng, J., Dechaphunkul, A., Chang, J., Wang, D., et al. (2018). A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). *Ann. Oncol.* 29 (2), 452–458. doi:10.1093/annonc/mdx698

Zhao, Y., Yang, Y., Gao, F., Hu, C., Zhong, D., Lu, M., et al. (2023). A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of olanzapine plus triple antiemetic regimen for the prevention of multiday highly emetogenic chemotherapy-induced nausea and vomiting (OFFER study). *EClinicalMedicine* 55, 101771. doi:10.1016/j.eclinm.2022.101771

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 19 September 2024
DOI 10.3389/fphar.2024.1418609

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Umberto Aguglia,
University Magna Graecia, Italy
Jieying Zhang,
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, China
Zhijie Zhao,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Jian Xu,
xuj@zju.edu.cn

†These authors have contributed equally to this work

RECEIVED 16 April 2024
ACCEPTED 08 August 2024
PUBLISHED 19 September 2024

CITATION
Ge C, Jin L, Tian J-J, Yang N and Xu J (2024) Comparative safety analysis of lacosamide and perampanel in epilepsy management: insights from FAERS database.
Front. Pharmacol. 15:1418609.
doi: 10.3389/fphar.2024.1418609

Comparative safety analysis of lacosamide and perampanel in epilepsy management: insights from FAERS database

Chang Ge[1†], Liuyin Jin[2†], Jing-Jing Tian[3†], Na Yang[4] and Jian Xu[1,5*]

[1]Department of Obstetrics and Gynecology, Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, China, [2]Lishui Second People's Hospital, Zhejiang, China, [3]Department of Sports, Tsinghua University, Beijing, China, [4]Guangdong Pharmaceutical University, Guangzhou, China, [5]Department of Obstetrics and Gynecology, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Epilepsy is a chronic neurological condition requiring effective management with minimal adverse effects. Lacosamide (LCM) and Perampanel (PER), two promising treatments, have distinct profiles that merit comparative analysis to guide clinical decision-making.

Methods: This study utilizes a pharmacovigilance analysis of adverse events reported in the FDA Adverse Event Reporting System database from Q1 2009 to Q3 2023. Employing disproportionality and Bayesian analyses, we assessed and compared the AE signals associated with LCM and PER to elucidate their safety profiles in epilepsy treatment.

Results: The analysis included 12,576 AE reports for LCM and 2,703 for PER, highlighting a higher incidence of psychiatric disorders, including aggression with LCM, and a notable association of PER with psychiatric disorders such as psychotic disorders and dizziness. LCM showed a relatively safe profile during pregnancy, whereas PER's data suggested caution due to reported cases of suicidal ideation and attempts.

Conclusion: This comprehensive evaluation underscores the importance of understanding the distinct AE profiles of LCM and PER in clinical practice, providing valuable insights for personalized epilepsy management. Future research with rigorous prospective designs is recommended to validate these findings and explore the mechanisms underlying the reported adverse events.

KEYWORDS

epilepsy, lacosamide, perampanel, pharmacovigilance, FAERS, adverse events

1 Introduction

Epilepsy affects over 50 million people globally, making it one of the most common neurological disorders (Kanner and Bicchi, 2022). The disorder is characterized by the occurrence of spontaneous seizures, which are manifestations of excessive and abnormal neural activity in the brain (Thijs et al., 2019). The management of epilepsy primarily relies on anti-seizure drugs (ASDs), which aim to reduce the frequency and severity of these seizures, thus improving the quality of life for those affected (Charalambous et al., 2014). Among the

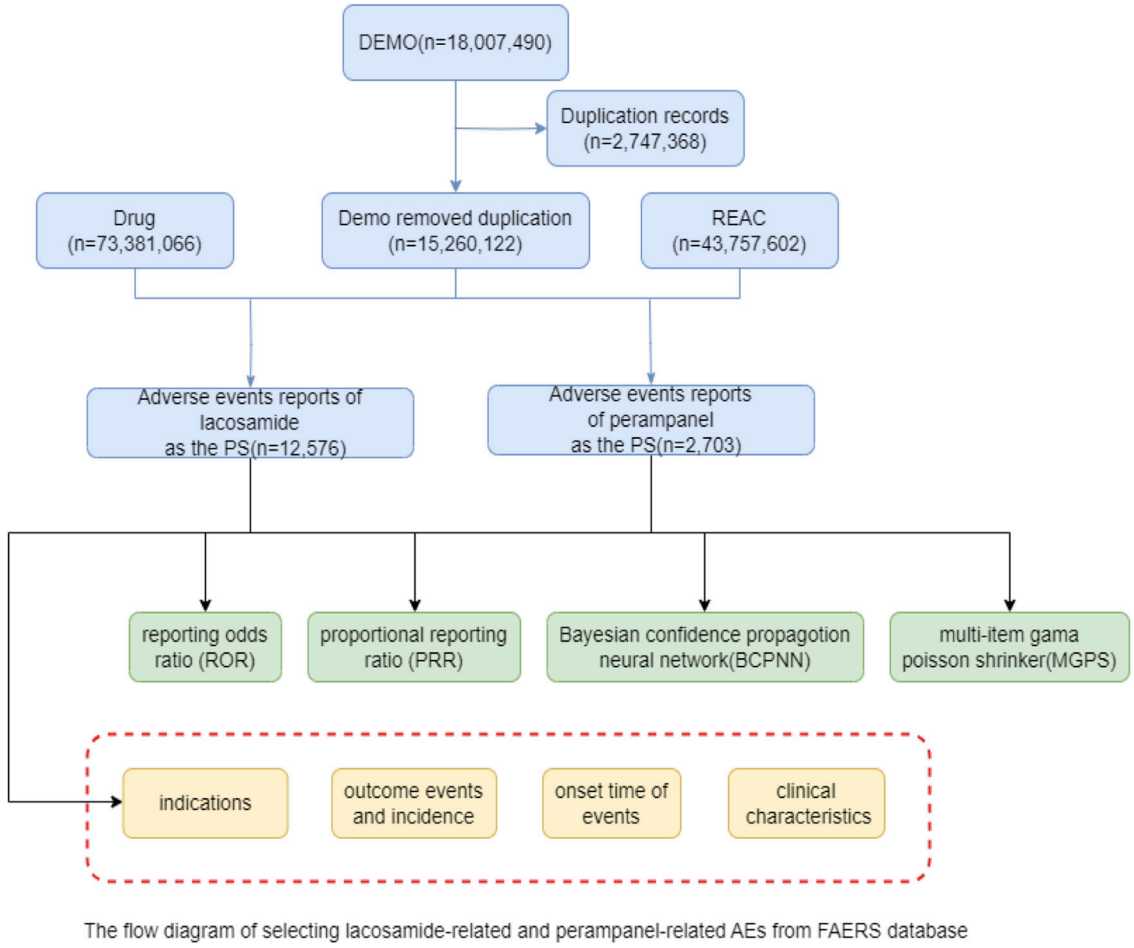


FIGURE 1
The flow diagram of selecting LCM-related and PER-related AEs from FAERS database.

newer therapeutic options, Lacosamide (LCM) and Perampanel (PER) have emerged as significant additions to the pharmacological arsenal against epilepsy (Li et al., 2020; Yamamoto et al., 2022). LCM, by modulating sodium channels, offers a novel approach to stabilizing neuronal activity and has been incorporated into treatment protocols following its FDA approval in 2008 (Harris and Murphy, 2011). PER, distinct in its mechanism, selectively inhibits AMPA-type glutamate receptors, addressing overexcitation in the brain, a key factor in seizure occurrences (Bresnahan et al., 2023).

However, the introduction of new medications brings forth the challenge of understanding their safety profiles comprehensively. While LCM and PER have been heralded for their efficacy, the spectrum of adverse events (AEs) associated with these drugs raises concerns that warrant careful consideration (Zaccara et al., 2013). For LCM, reports have surfaced indicating potential risks such as dizziness, vision disturbances, and even more serious conditions like cardiac and hematologic anomalies (Roberti et al., 2024). PER's side effects, including behavioral changes and dizziness, have similarly prompted discussions about its suitability for all patient demographics, especially given the drug's effectiveness across a broad range of seizure types (Rohracher et al., 2016). Such adverse reactions not only affect patient compliance but also pose a dilemma for clinicians striving to balance therapeutic effectiveness with patient safety (Gaitatzis and Sander, 2013).

Addressing this critical gap, our study harnesses the vast repository of the FDA Adverse Event Reporting System (FAERS) database to undertake a detailed examination of the AEs linked to LCM and PER (Liu et al., 2023). This pharmacovigilance analysis aims to distill crucial data on the nature and frequency of AEs, offering a granular view of the safety landscape surrounding these ASDs. By providing a comparative insight into the adverse profiles of LCM and PER, this research endeavors to equip healthcare providers with the knowledge needed to make informed decisions in epilepsy management. Ultimately, our objective is to contribute to the optimization of epilepsy care, ensuring that treatment decisions are informed by a thorough understanding of the benefits and risks associated with these advanced therapeutic options.

2 Methods

2.1 Study design and data acquisition

This investigation was conducted as a retrospective pharmacovigilance study, systematically analyzing AE reports derived from the FAERS database spanning from Q1 2009 to Q3 2023. The FAERS database, as a pivotal tool for post-marketing

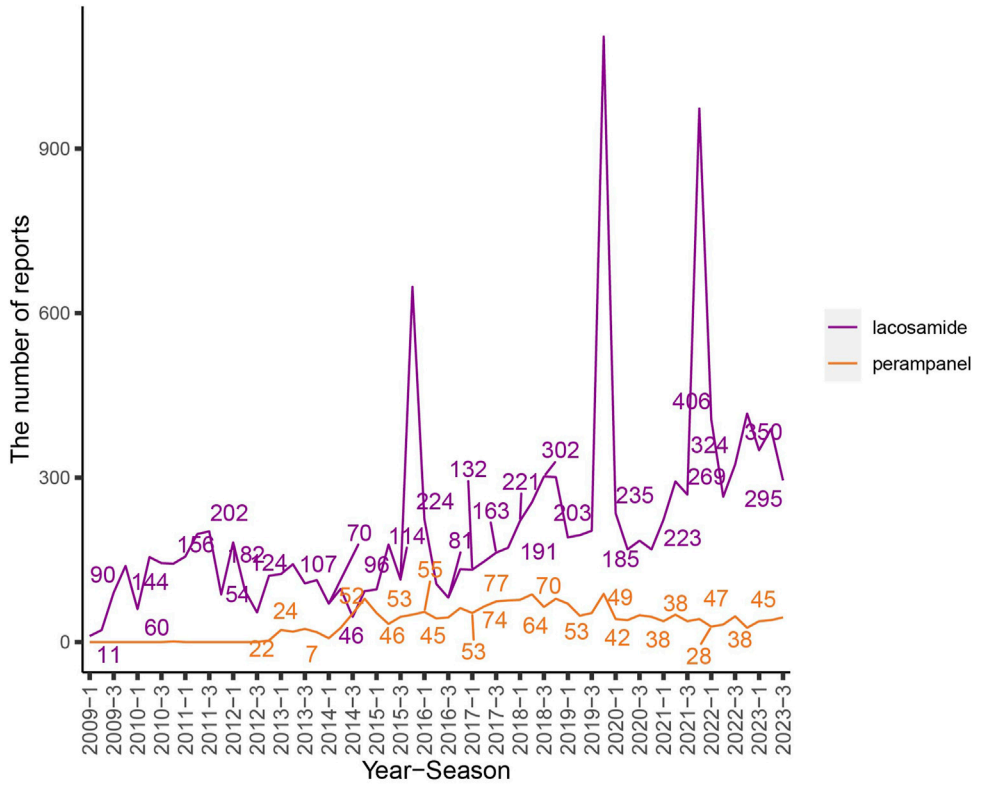


FIGURE 2
The flow chart and the number of adverse events reported quarterly after the marketing of LCM and PER. Note: The purple line represents the reports of LCM while the orange line represents the reports of PER. *X*-axis shows the timeline when the drug was used, and *Y*-axis displays the number of reports per quarter.

surveillance, compiles AE reports submitted by a diverse cohort including healthcare professionals, consumers, and pharmaceutical entities, thereby facilitating a comprehensive monitoring of drug safety in real-world scenarios. Our analytical focus centered on discerning and contrasting the AE signals attributable to LCM and PER, leveraging their divergent pharmacodynamic profiles.

2.2 Data extraction and processing

AE reports pertinent to LCM and PER were meticulously extracted utilizing their generic denominations as search keys. Rigorous scrutiny was applied to each report to ascertain its relevance, followed by the elimination of redundant entries to uphold data integrity. Essential data parameters extracted encompassed demographic details (age and gender), AE narratives, outcomes of the events, and the reporter's affiliation (healthcare professionals or consumers). The R 4.3.2 and Open Vigil were deployed for the extraction and management of data, enabling an efficient sifting through voluminous datasets and the identification of duplicate records with enhanced accuracy.

2.3 Adverse event codification

The codification of AEs was aligned with the terminologies prescribed by the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. MedDRA's hierarchical structure facilitates the uniform categorization of AE information, thereby ensuring consistency in reporting across various pharmacovigilance studies. AEs were classified according to the primary System Organ Classes (SOCs) and Preferred Terms (PTs), as delineated in MedDRA, to furnish a granular analysis of the AE profiles associated with both drugs.

2.4 Statistical methodology

Signals were coded, classified, and located using preferred terms (PT) and System Organ classes (SOCs) in MedDRA26.1 software to analyze specific SOCs and PTSS involved in adverse event signals. Here we included PT reporting counts ≥3 in our subsequent analysis. In this study, we used four methods: Report Odds Ratio (ROR), Proportional Report Ratio (PRR), Bayesian Neural Network (BCPNN), Multinomial Gamma Poisson (MGPS) for signal recognition and disproportionality analysis. The purpose is to use the advantages of each to expand the detection range, verify the results from multiple perspectives, and make reasonable use of the characteristics of different algorithms to detect more comprehensive and reliable safety signals. The combination of multiple algorithms can be cross-validated to reduce false positives, and more potential rare adverse reactions can be detected by adjusting the threshold and variance. ROR is used to identify the disproportionality of drug-

TABLE 1 Data of reports associated with LCM and PER from Q1 of 2009 to Q3 of 2023.

	LCM	PER
Number of events	12576	2073
Year		
2009	262 (2.08)	
2010	502 (3.99)	1 (0.05)
2011	642 (5.10)	
2012	450 (3.58)	3 (0.14)
2013	486 (3.86)	83 (4.00)
2014	306 (2.43)	164 (7.91)
2015	1036 (8.24)	182 (8.78)
2016	544 (4.33)	205 (9.89)
2017	614 (4.88)	268 (12.93)
2018	1079 (8.58)	307 (14.81)
2019	1693 (13.46)	259 (12.49)
2020	758 (6.03)	177 (8.54)
2021	1758 (13.98)	168 (8.10)
2022	1412 (11.23)	133 (6.42)
2023	1034 (8.22)	123 (5.93)

event reporting compared to all other events, and a higher ROR indicates that there may be an underlying signal. The PRR measures the ratio of drug reports to all other drug reports in a given event, and a PRR significantly greater than 1 indicates the presence of a signal. BCPNN computes information component (IC) values using Bayesian logic, with a positive IC indicating a strong correlation. MGPS is a Bayesian data mining method that calculates empirical Bayesian geometric average (EBGM) to assess the strength of the association, with higher EBGM indicating the presence of a stronger signal. When the signal conforms to 1. ROR ≥3 and 95%CI (lower limit) > 1; 2. PRR ≥2 and 95%CI (lower limit) > 1; 3. IC025 > 0; 4. When EBGM05 > 2, we considered the adverse reaction to be significant. See Appendix file. docx for detailed algorithms and formulas.

3 Results

3.1 Descriptive analysis

3.1.1 Comprehensive analysis of adverse event reporting statistics

The extensive dataset compiled by FAERS is depicted in Figure 1, showcasing a total of 18,007,490 AE reports collected from the first quarter of 2009 to the third quarter of 2023. After cleaning the data, FAERS collected a total of 15,260,122 AE reports, of which 12,576 were related to LCM and 2,703 were related to PER. LCM has an average of 838 AE reports annually. In contrast, PER is a new drug approved for a shorter period of time, whose AE reports do not exist every year, but have been accumulated to 2073 in the past decade, averaging approximately 200 cases per year. Notably, the temporal distribution of these reports reveals a peak in AE reporting for PER in the years 2018 and 2019, with 307 and 259 reports respectively, as detailed in Figure 2 and Table 1. Meanwhile, as shown in Figure 3 and Table 2, the majority of these reports come from the United States, followed by Japan, as well as other countries like Germany and France. This trend suggests a potential increase in the drug's utilization or possibly an enhanced vigilance in reporting AEs.

3.1.2 Demographic distribution and reporting sources: an insightful overview

Table 3 presents a detailed demographic breakdown of AE reports related to the treatment of epilepsy with LCM and PER, highlighting a slight predominance of female reporters, constituting approximately 48% of the total reports. Males reported 39.73% and 45.44% of AE reports for LCM and PER, respectively, indicating a nuanced gender distribution in the reporting pattern. The age demographics, primarily concentrated in the 18-45 age group, underline the significance of this cohort in AE reporting, although a considerable fraction of reports did not specify age details. Furthermore, the sources of these AE reports vary significantly between the two drugs. For LCM, consumer reports lead, followed by healthcare professionals, indicating a proactive involvement of patients in reporting AEs. In contrast, for PER, healthcare professionals are the primary reporters, which may reflect a difference in the perceived severity or clinical identification of AEs. This variance in reporting sources is crucial for understanding the pharmacovigilance landscape and is vividly illustrated in Table 3.

3.1.3 Delving into drug indications and the temporal dynamics of adverse events

The specific uses of LCM and PER, primarily for epilepsy and seizures, are substantiated by the data in Table 4, showcasing that these conditions account for over three-quarters of all AE reports. The presence of a considerable percentage of reports with unknown indications suggests a gap in documentation or possible off-label use, adding a layer of complexity to drug safety monitoring. The AE profiles for both drugs, as elaborated in Table 5, reveal distinct patterns of side effects. LCM's AEs are led by overdose (612 case reports), somnolence (405 case reports), and intentional product misuse (291 case reports), indicating specific areas of concern. For PER, aggression (297 case reports), dizziness (152 case reports), and irritability (126 case reports) stand out, suggesting a different set of challenges for patients and healthcare providers. These detailed statistics, presented in Table 5, are pivotal for understanding the risk profiles of these medications. The Time-to-Onset (TTO) analysis, depicted in Table 6, provides an invaluable perspective on the temporal distribution of AEs. LCM exhibits a higher proportion of immediate adverse reactions within 7 days of initiation, whereas PER shows a tendency towards longer-term effects, evident in the significantly higher reports of AEs occurring after 60 days. This temporal aspect of AE reporting, as detailed in Table 6, offers crucial insights into the onset patterns of adverse reactions, enabling more informed clinical decisions and patient management strategies.

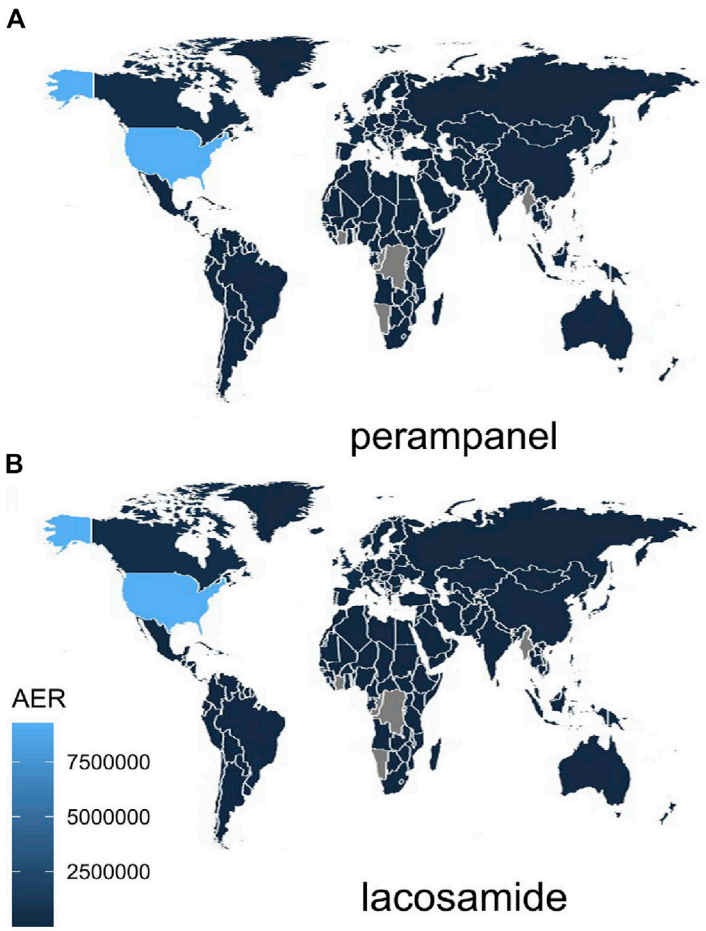


FIGURE 3
Global Distribution of Adverse Event Reports for LCM and PER note:The varying shades of blue in the map indicate the distribution of adverse event reports for the drug across different countries. Lighter shades correspond to higher report numbers, while grey signifies the absence of AE reports in that particular region. AER, adverse event reports.

3.2 Disproportionality analysis

3.2.1 Analysis of adverse events of LCM and PER

The comprehensive disproportionality analysis of AE reports for LCM and PER, extracted from the FDA's FAERS) database, reveals significant insights into the safety profiles of these antiepileptic drugs (ASDs). This analysis, grounded in a robust statistical framework, identified 173 and 117 strong signals with an Information Component (IC) of 2 Standard Deviations (SD) ≥ 1.0 for LCM and PER, respectively. As shown in Table 7, these signals, indicative of a statistically significant disproportionality between the observed and expected number of AE reports, highlight potential areas of concern and necessitate a deeper examination of the drugs' safety profiles. For LCM, the analysis delineates a range of AEs specific to its clinical use. Among the notable findings in the System Organ Classes (SOCs) related to injury, poisoning, and procedural complications, overdose incidents stand out with a $\chi2$ value of 1637.98 and a 95% confidence interval (CI) lower limit of 4.16, reflecting an IC-2SD of 3.69. This is closely followed by intentional product misuse ($\chi2$ = 943.49, 95% CI lower limit = 4.53, IC-2SD = 2.33), and maternal exposure during pregnancy ($\chi2$ = 708.86, 95% CI lower limit = 4.15, IC-2SD = 4.67), underscoring critical areas for clinical vigilance. Additionally, LCM is uniquely associated with memory impairment ($\chi2$ = 404.28, 95% CI lower limit = 2.81, IC-2SD = 1.65) and bradycardia ($\chi2$ = 833.92, 95% CI lower limit = 5.37, IC-2SD = 2.62) within the nervous and cardiac disorder SOCs, respectively. Other specific AEs such as amnesia, diplopia, and head injury further highlight the drug's diverse impact on patients.

Conversely, PER exhibits a distinct set of AEs, particularly concentrated within psychiatric disorders. Strong signals were identified for suicidal ideation, suicide attempt, and a spectrum of behavioral disturbances including anger, agitation, confusional state, and homicidal ideation, signifying the drug's pronounced effects on mental health. The presence of dizziness ($\chi2$ = 310.88, 95% CI lower limit = 3.28, IC-2SD = 1.91) and intentional overdose ($\chi2$ = 665.32, 95% CI lower limit = 9.85, IC-2SD = 3.64) as significant AE signals within the SOC of intentional overdose adds to the safety concerns associated with PER. Moreover, neurological impacts, as evidenced by ataxia ($\chi2$ = 1423.88, 95% CI lower limit = 28.99, IC-2SD = 5.3) and altered state of consciousness ($\chi2$ = 649.5, 95% CI lower limit = 14.83, IC-2SD = 4.36), were exclusively linked to PER, underscoring its potential neurological implications. This analysis not only reinforces the importance of ongoing safety monitoring and evaluation of ASDs but also emphasizes the need for healthcare professionals to be acutely aware of these potential risks when

TABLE 2 Global distribution of adverse event reports for LCM and PER.

	LCM	PER
Reporter country		
United States	6575 (52.28)	589 (28.41)
Japan	994 (7.90)	506 (24.41)
France	489 (3.89)	175 (8.44)
Germany	658 (5.23)	124 (5.98)
United Kingdom	147 (1.17)	101 (4.87)
Spain	198 (1.57)	86 (4.15)
Italy	251 (2.00)	53 (2.56)
Colombia	276 (2.19)	
Canada	176 (1.40)	
Brazil	152 (1.21)	
Mexico	125 (0.99)	
Australia	54 (0.43)	
Austria	50 (0.40)	
China	50 (0.40)	
other	2381 (18.93)	439 (21.18)

prescribing LCM and PER. Understanding the specific AE profiles of these drugs enables clinicians to devise more informed and individualized treatment plans, enhancing patient safety and therapeutic outcomes in the management of epilepsy.

3.2.2 System disorders analysis of adverse events

LCM's AEs predominantly affect the nervous system, with a substantial number of reports (n = 9737), showcasing a ROR of 3.97 (95% CI: 3.88-4.07). This is indicative of LCM's significant neurological effects. Following this, injury, poisoning, and procedural complications also emerge as areas of concern (n = 5630, ROR 1.76, 95% CI: 1.71-1.81), alongside general disorders and administration site conditions (n = 4569, ROR 0.66, 95% CI: 0.64-0.68), psychiatric disorders (n = 3396, ROR 1.7, 95% CI: 1.64-1.76), and gastrointestinal disorders (n = 1624, ROR 0.49, 95% CI: 0.47-0.52). Each of these areas presents a distinct facet of LCM's impact on patient wellbeing, underscoring the need for comprehensive monitoring and management strategies to mitigate these risks. Conversely, PER exhibits a markedly different AE distribution, most notably in psychiatric disorders, where it presents a significantly higher ROR of 8.76 (95% CI: 8.26-9.3) with 1667 reports. This stark contrast emphasizes the substantial psychiatric risk associated with PER, necessitating vigilant mental health assessments for patients under treatment. Additionally, nervous system disorders (n = 1118, ROR 3.25, 95% CI: 3.04-3.48), general disorders and administration site conditions (n = 427, ROR 0.42, 95% CI: 0.38-0.47), injury, poisoning and procedural complications (n = 419, ROR 0.83, 95% CI: 0.75-0.91), and gastrointestinal disorders (n = 178, ROR 0.4, 95% CI: 0.34-0.46) further delineate PER's broad spectrum of AEs. This distribution provides essential insights into the drug's varied effects beyond its primary use, highlighting the complexities of managing its side effects, which can be found in Table 8.

In the examination of psychiatric disorders of Supplementary Table S1, both LCM and PER exhibited notable signals for aggression. In the realm of nervous system disorders of Supplementary Table S2, a comparative assessment showed that PER had a higher rate of reported drop attacks Contrastingly, in Supplementary Table S3, LCM was found to have a higher risk of causing general disorders and conditions related to administration site.

3.3 Time scans of safety signals

To elucidate the evolution of safety signals over time, this study conducted time scans across several keyAEs including aggression, psychotic disorder, somnolence, dizziness, ataxia, and confusional state for both LCM and PER. The graphical analysis revealed a steady or increasing trend in the incidence of these AEs, with the confidence intervals narrowing over time. This pattern indicates a consistent and strong correlation between the occurrence of these AEs and the administration of each drug. Notably, as demonstrated in Figure 4, LCM exhibited a significant correlation with aggression, psychotic disorder, and ataxia, highlighted by an increase in reports and corresponding Information Component (IC) values over time. Somnolence, particularly, saw a rapid increase in IC values to at least 2 within a 6-year period or less, marking the quickest escalation observed in this study.

Conversely, PER's relationship with these AEs showcased a potentially higher correlation, although the impact of its market release year on this correlation remains to be fully understood. Specifically, dizziness presented a distinct aspect of PER's AE profile, differing markedly from LCM's steady trend. This suggests that, despite LCM's consistent association with the selected AEs, the strength of association for these adverse effects is particularly pronounced with PER.

3.4 Comparison of safety signals in four system organ classes

An in-depth comparison of AE signals across four major system organ classes unveiled distinct characteristics for each drug, as detailed in Figure 5. PER emerged with aggression in psychiatric disorders as its most prominent signal, underscoring a significant concern in its usage. On the other hand, LCM was closely associated with hepatic arteriovenous malformation within congenital, familial, and genetic disorders, reflecting its unique safety signal based on ROR and Chi-square analyses.

Furthermore, LCM was notably linked to off-label use and overdose within the injury, poisoning, and procedural complications SOC, accumulating 1436 and 612 reports, respectively. These findings suggest a critical area of concern for LCM regarding its administration and usage parameters. Additionally, LCM exhibited the strongest signal for multi-drug resistance across the study, achieving the highest ROR, which highlights significant implications for its clinical management and efficacy. Sudden unexplained death in epilepsy represented another crucial signal for LCM, distinguishing its risk profile from PER. Despite this, the general disorders category for both drugs displayed similar report volumes and minimal differences in ROR and Chi-square, indicating some overlap in their AE spectrums within this SOC.

TABLE 3 Population Information associated with LCM and PER from Q1 of 2004 to Q3 of 2023.

	LCM	PER
Gender		
female	6136 (48.79)	999 (48.19)
male	4996 (39.73)	942 (45.44)
unkown	1444 (11.48)	132 (6.37)
weight	68.00 (54.00,83.46)	62.90 (48.00,75.00)
Age	48.00 (28.00,65.00)	34.00 (19.00,52.00)
age_yrQ		
<18	925 (7.36)	336 (16.21)
18–45	2378 (18.91)	655 (31.60)
45–65	2013 (16.01)	346 (16.69)
65–75	984 (7.82)	102 (4.92)
≥75	916 (7.28)	67 (3.23)
unknow	5360 (42.62)	567 (27.35)
Reporter		
Physician	4580 (36.42)	1450 (69.95)
Pharmacist	1133 (9.01)	213 (10.27)
Consumer	5696 (45.29)	171 (8.25)
Other health-professional	888 (7.06)	212 (10.23)
route		
oral	4619 (36.73)	2000 (96.48)
other	7311 (58.13)	54 (2.60)
Outcomes		
hospitalization	3590 (30.32)	887 (49.50)
other serious	6258 (52.85)	599 (33.43)
death	1271 (10.73)	126 (7.03)
life threatening	366 (3.09)	110 (6.14)
disability	216 (1.82)	55 (3.07)
congenital anomaly	126 (1.06)	10 (0.56)
required intervention to Prevent Permanent Impairment/Damage	15 (0.13)	5 (0.28)

4 Discussion

The escalation in reported AEs for LCM and PER, as observed from 2014 to 2019, underscores the complex landscape of epilepsy management and the vital role of ASDs in this domain (Palleria et al., 2017). This significant increase, highlighted by nearly fivefold growth in annual reports by 2019, reflects not only the expanded indications and enhanced utilization of these medications but also underscores the critical importance of rigorous post-marketing surveillance to safeguard patient health (Abou-Khalil, 2019).

Our comprehensive and systematic analysis, leveraging the vast repository of the FAERS, marks a pivotal stride in understanding the real-world safety profiles of LCM and PER (Hu et al., 2018). By transcending the limitations inherent in clinical trial settings or narrower AE-focused studies, our work provides a panoramic view of the safety issues potentially associated with these drugs. The introduction of innovative time scans scoring in our methodology represents a forward-thinking approach to pharmacovigilance, aiming to preemptively identify and mitigate future safety signals and thus refine the predictive accuracy of AE reporting (Kang et al., 2014).

Epilepsy's pronounced incidence among young adults and its onset during formative years, influenced by a myriad of factors, is reflected in the age demographics of AE reports analyzed in our study (Manford, 2017). The predominance of reports within the 18-45 age range aligns with the epidemiological understanding of epilepsy, offering a validation of our data's relevance (Perucca et al., 2018). The slight female preponderance in AE reporting, while not indicative of a significant gender disparity, highlights the necessity for gender-aware management strategies in epilepsy care (Hophing et al., 2022). The disproportionality analysis conducted as part of our investigation reveals nuanced insights into the AE profiles of LCM and PER (Hu et al., 2022). With nervous system disorders and psychiatric disorders emerging as significant concerns, our findings align with and expand upon the safety data available from clinical trials and drug labels (Beghi et al., 2015). This detailed examination not only corroborates known safety profiles but also unveils specific areas requiring vigilant monitoring, such as the heightened incidence of aggression and irritability associated with these ASDs (Kamitaki et al., 2021).

4.1 Comparative analysis

Our findings align with and extend the results of previous clinical studies on Lacosamide LCM and PER. Villanueva et al. (Villanueva et al., 2015) reported that LCM has a relatively favorable safety profile with manageable adverse events, which is consistent with our data showing a lower incidence of psychiatric disorders compared to PER. However, our study highlights a significant association of LCM with dizziness and cardiac anomalies, warranting attention during clinical use. On the other hand, Pascarella et al. (Pascarella et al., 2020) and Gasparini et al. (Gasparini et al., 2022) noted that PER is often linked with severe psychiatric disorders including aggression, irritability, and suicidal ideation. Our analysis corroborates these findings and emphasizes the pronounced psychiatric effects of PER, which were observed to have a higher reporting odds ratio and information component values compared to LCM. This comparative insight underscores the need for clinicians to carefully weigh the benefits and risks when selecting these ASDs for epilepsy management.

4.2 Age-related analysis

The occurrence of AEs according to patient age reveaed distinct patterns for LCM and PER, which are critical for personalized treatment strategies. Sarkis et al. (Sarkis et al., 2017) documented that older patients treated with LCM exhibited higher incidences of dizziness and ataxia. Our study supports these observations, showing a notable

TABLE 4 Top ten indications in adverse events reports of LCM and PER.

Indications	LCM	n (%)	PER	n (%)
1	seizures	9112 (77.94)	seizures	1576 (76.41)
2	product used for unknown indication	2290 (19.58)	product used for unknown indication	382 (18.52)
3	trigeminalneuralgia	30 (0.26)	syndrome	25 (1.21)
4	syndrome	24 (0.21)	foetal exposure during pregnancy	17 (0.82)
5	migraine	13 (0.11)	accidental exposure to product by child	9 (0.44)
6	neuralgia	9 (0.08)	amyotrophic lateral sclerosis	9 (0.44)
7	pain	8 (0.07)	essential tremor	3 (0.15)
8	prophylaxis	8 (0.07)	infantile spasms	3 (0.15)
9	neuropathy peripheral	8 (0.07)	drop attacks	2 (0.1)
10	off label use	6 (0.05)	dentatorubral-pallidoluysian atrophy	2 (0.1)

TABLE 5 Top ten in the number of adverse events reports of LCM and PER.

AE	LCM	n	PER	n
1	overdose	612	aggression	297
2	somnolence	405	dizziness	152
3	intentional product misuse	291	irritability	126
4	memory impairment	277	somnolence	115
5	maternal exposure during pregnancy	245	suicidal ideation	113
6	balance disorder	213	suicide attempt	108
7	bradycardia	194	psychotic disorder	87
8	amnesia	191	anger	78
9	diplopia	185	agitation	76
10	aggression	161	intentional overdose	63

TABLE 6 The Time-to-onset (TTO) of adverse events reports of LCM and PER.

	LCM	PER
tto	16.00 (0.00,133.00)	34.00 (9.00,124.25)
ttoQ		
<7	957 (17.16)	154 (10.34)
7–28	348 (6.24)	177 (11.89)
28–60	197 (3.53)	138 (9.27)
≥60	801 (14.36)	291 (19.54)
unknown	3275 (58.71)	729 (48.96)

prevalence of these AEs among patients aged 65 and above. In contrast, younger patients, particularly those below 45, reported higher instances of somnolence and memory impairment with LCM.

For PER, Wheless et al. (Wheless et al., 2023) and Pascarella et al. (Pascarella et al., 2023) identified significant age-related differences in AE profiles, with younger patients (under 18) experiencing more behavioral issues and aggression. Our data similarly indicate a higher frequency of psychiatric AEs in younger populations treated with PER. These age-related findings are pivotal for clinicians to consider, as they highlight the differential risk profiles of LCM and PER across various age groups, informing safer and more effective epilepsy management tailored to individual patient needs.

4.3 Pregnancy safety profile

The safety of LCM and PER during pregnancy is a crucial consideration, given the potential risks to both the mother and the fetus. Our study found that LCM exhibited a relatively safe profile during pregnancy, with fewer reports of severe AEs compared to PER. Specifically, the data showed 245 AE reports related to maternal exposure during pregnancy for LCM, with an ROR of 4.71 (95% CI: 4.15-5.34) and an IC of 2.22, indicating a strong but manageable risk. These findings are in line with previous studies that suggest LCM can be used with caution during pregnancy due to its lower teratogenic potential.

In contrast, PER's safety profile during pregnancy raises more concerns. There were 21 reports of AEs related to maternal exposure, with a significant association with severe psychiatric disorders such as suicidal ideation and attempts, as well as aggression. The ROR for PER-related maternal exposure was 1.02 (95% CI: 0.67-1.57), with an IC of 0.03, suggesting a less pronounced but still notable risk profile. These findings align with clinical recommendations to exercise caution when prescribing PER to pregnant women due to its potential adverse effects on mental health.

4.4 Potential biases

Our study, while comprehensive, is not without limitations. The reliance on spontaneous reporting to the FAERS database

TABLE 7 Comparison of single adverse events of LCM and PER from different SOCs.

soc	pt	lacosamide					perampanel				
		Case Reports	ROR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)	Case Reports	ROR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)
psychiatric disorders	aggression	161	5.56 (4.76, 6.49)	596.23	2.46 (2.24)	5.52 (4.84)	297	90.7 (80.61, 102.06)	24465.27	6.4 (6.23)	84.29 (76.37)
nervous system disorders	dizziness						152	3.85 (3.28, 4.53)	310.88	1.91 (1.68)	3.76 (3.29)
nervous system disorders	seizure	2466	38.58 (37.01, 40.21)	81584.73	5.13 (5.07)	34.96 (33.77)	138	13.12 (11.07, 15.54)	1498.04	3.67 (3.43)	12.75 (11.07)
psychiatric disorders	irritability	129	3.48 (2.92, 4.13)	225.99	1.79 (1.54)	3.46 (2.99)	126	26.63 (22.3, 31.79)	3016.66	4.69 (4.44)	25.88 (22.31)
nervous system disorders	somnolence	405	3.4 (3.08, 3.75)	676.1	1.75 (1.61)	3.37 (3.1)	115	7.24 (6.02, 8.72)	603.68	2.83 (2.56)	7.09 (6.07)
psychiatric disorders	suicidal ideation						113	17.31 (14.36, 20.87)	1692.64	4.08 (3.81)	16.9 (14.45)
psychiatric disorders	suicide attempt						108	25.29 (20.89, 30.61)	2455.3	4.62 (4.35)	24.67 (21.03)
psychiatric disorders	psychotic disorder						87	42.02 (33.98, 51.98)	3403.86	5.36 (5.06)	41.08 (34.38)
psychiatric disorders	anger						78	30.12 (24.07, 37.69)	2152.39	4.88 (4.56)	29.54 (24.49)
psychiatric disorders	agitation						76	13.98 (11.14, 17.54)	899.78	3.78 (3.46)	13.75 (11.37)
injury, poisoning and procedural complications	intentional overdose						63	12.64 (9.85, 16.21)	665.32	3.64 (3.28)	12.47 (10.13)
general disorders and administration site conditions	gait disturbance						60	3.61 (2.8, 4.65)	111.55	1.84 (1.47)	3.57 (2.89)
nervous system disorders	status epilepticus	361	57.86 (52.04, 64.33)	19083.63	5.78 (5.62)	54.79 (50.14)	55	64.1 (49.08, 83.7)	3350.87	5.97 (5.59)	62.89 (50.31)
general disorders and administration site conditions	drug interaction						54	4.39 (3.35, 5.73)	139.46	2.12 (1.74)	4.35 (3.47)
psychiatric disorders	confusional state						50	3.94 (2.98, 5.21)	108.59	1.97 (1.57)	3.91 (3.1)
psychiatric disorders	abnormal behaviour						48	17.26 (12.99, 22.94)	726.46	4.09 (3.69)	17.07 (13.45)
psychiatric disorders	homicidal ideation						46	200.53 (149.47, 269.04)	8828.92	7.6 (7.18)	193.89 (151.63)
nervous system disorders	ataxia						38	39.93 (28.99, 54.99)	1423.88	5.3 (4.85)	39.43 (30.17)

(Continued on following page)

10.3389/fphar.2024.1418609

TABLE 7 (*Continued*) Comparison of single adverse events of LCM and PER from different SOCs.

soc	pt	lacosamide					perampanel				
		Case Reports	ROR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)	Case Reports	ROR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)
nervous system disorders	epilepsy	454	26.61 (24.23, 29.22)	10817.33	4.69 (4.55)	25.76 (23.82)	36	15.27 (11, 21.2)	475.48	3.92 (3.45)	15.13 (11.5)
nervous system disorders	balance disorder	213	3.91 (3.41, 4.47)	456.42	1.96 (1.76)	3.88 (3.47)	36	4.94 (3.56, 6.86)	112.22	2.3 (1.83)	4.91 (3.73)
nervous system disorders	altered state of consciousness						35	20.69 (14.83, 28.87)	649.5	4.36 (3.88)	20.5 (15.52)
injury, poisoning and procedural complications	overdose	612	4.51 (4.16, 4.89)	1637.98	2.15 (2.03)	4.44 (4.15)					
nervous system disorders	generalised tonic-clonic seizure	421	43.75 (39.67, 48.24)	16789.8	5.39 (5.25)	41.81 (38.53)					
injury, poisoning and procedural complications	intentional product misuse	291	5.09 (4.53, 5.71)	943.49	2.33 (2.17)	5.04 (4.57)					
nervous system disorders	memory impairment	277	3.16 (2.81, 3.56)	404.28	1.65 (1.48)	3.14 (2.84)					
injury, poisoning and procedural complications	maternal exposure during pregnancy	245	4.71(4.15, 5.34)	708.86	2.22(2.04)	4.67(4.21)					
nervous system disorders	partial seizures	199	70.39 (61, 81.23)	12814.03	6.05 (5.85)	66.32 (58.83)					
cardiac disorders	bradycardia	194	6.18 (5.37, 7.12)	833.92	2.62 (2.41)	6.13 (5.44)					
nervous system disorders	amnesia	191	4.92 (4.26, 5.67)	590.41	2.29 (2.08)	4.88 (4.33)					
eye disorders	diplopia	185	12.53 (10.83, 14.48)	1932.23	3.63 (3.42)	12.35 (10.94)					
nervous system disorders	petit mal epilepsy	166	62.24 (53.24, 72.77)	9482.94	5.88 (5.66)	59.06 (51.82)					
injury, poisoning and procedural complications	head injury	141	7.48 (6.34, 8.83)	784.14	2.89 (2.65)	7.42 (6.46)					
pregnancy, puerperium and perinatal conditions	pregnancy	137	12.94 (10.93, 15.32)	1488.53	3.68 (3.43)	12.77 (11.09)					
general disorders and administration site conditions	multiple-drug resistance	135	86.14 (72.33, 102.59)	10585.65	6.33 (6.08)	80.33 (69.41)					

10.3389/fphar.2024.1418609

TABLE 8 Comparison of system disorders of adverse event signals between LCM and PER.

soc	lacosamide						perampanel					
	Case Reports	ROR (95% CI)	PRR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)	Case Reports	ROR (95% CI)	PRR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)
psychiatric disorders	3396	1.7 (1.64, 1.76)	1.63 (1.57, 1.7)	888.09	0.71 (0.66)	1.63 (1.59)	1667	8.76 (8.26, 9.3)	6.07 (5.84, 6.31)	7487.34	2.6 (2.52)	6.07 (5.78)
nervous system disorders	9737	3.97 (3.88, 4.07)	3.15 (3.09, 3.21)	15620.95	1.65 (1.62)	3.14 (3.08)	1118	3.25 (3.04, 3.48)	2.73 (2.57, 2.9)	1338.39	1.45 (1.35)	2.73 (2.58)
congenital, familial and genetic disorders	216	1.92 (1.68, 2.19)	1.91 (1.67, 2.19)	94.21	0.93 (0.74)	1.91 (1.71)	20	1.34 (0.86, 2.08)	1.34 (0.87, 2.06)	1.74	0.42 (-0.2)	1.34 (0.93)
ear and labyrinth disorders	207	1.31 (1.14, 1.5)	1.31 (1.14, 1.5)	14.86	0.38 (0.19)	1.31 (1.16)	29	1.33 (0.92, 1.92)	1.33 (0.92, 1.93)	2.39	0.41 (-0.11)	1.33 (0.98)
pregnancy, puerperium and perinatal conditions	470	3.06 (2.8, 3.36)	3.04 (2.76, 3.35)	642.76	1.6 (1.47)	3.03 (2.81)	21	1.02 (0.67, 1.57)	1.02 (0.66, 1.57)	0.01	0.03 (-0.57)	1.02 (0.72)
hepatobiliary disorders	197	0.61 (0.53, 0.7)	0.61 (0.53, 0.7)	49.56	-0.71 (-0.91)	0.61 (0.54)	38	0.92 (0.67, 1.26)	0.92 (0.67, 1.26)	0.29	-0.13 (-0.58)	0.92(0.7)
injury, poisoning and procedural complications	5630	1.76 (1.71, 1.81)	1.64 (1.61, 1.67)	1553.2	0.71 (0.67)	1.64 (1.6)	419	0.83 (0.75, 0.91)	0.84 (0.76, 0.93)	14.2	-0.25 (-0.39)	0.84 (0.77)
metabolism and nutrition disorders	526	0.67 (0.61, 0.73)	0.67 (0.62, 0.72)	85.26	-0.57 (-0.69)	0.67 (0.63)	84	0.8 (0.65, 1)	0.81 (0.65, 1)	4.01	-0.31 (-0.62)	0.81 (0.67)
eye disorders	720	0.98(0.91, 1.05)	0.98(0.91, 1.06)	0.31	-0.03(-0.14)	0.98(0.92)	67	0.67 (0.53, 0.85)	0.68 (0.54, 0.86)	10.7	-0.57 (-0.91)	0.68 (0.55)
renal and urinary disorders	323	0.46 (0.41, 0.52)	0.47 (0.42, 0.53)	200.75	-1.1 (-1.26)	0.47 (0.43)	50	0.52 (0.39, 0.68)	0.52 (0.4, 0.68)	22.45	-0.94 (-1.34)	0.52 (0.41)
general disorders and administration site conditions	4569	0.66 (0.64, 0.68)	0.7 (0.69, 0.71)	699.68	-0.51 (-0.55)	0.7 (0.69)	427	0.42 (0.38, 0.47)	0.47 (0.43, 0.52)	307.58	-1.08 (-1.22)	0.47 (0.44)
reproductive system and breast disorders	109	0.35 (0.29, 0.42)	0.35 (0.29, 0.43)	130.14	-1.5 (-1.77)	0.35 (0.3)	19	0.47 (0.3, 0.74)	0.47 (0.3, 0.74)	11.29	-1.08 (-1.72)	0.47 (0.32)
investigations	1311	0.59(0.55, 0.62)	0.6(0.57, 0.64)	368.26	-0.73(-0.81)	0.6(0.57)	138	0.45 (0.38, 0.54)	0.47 (0.4, 0.55)	87.6	-1.09 (-1.33)	0.47 (0.41)
skin and subcutaneous tissue disorders	939	0.46(0.43, 0.49)	0.47(0.44, 0.5)	595.44	-1.09(-1.18)	0.47(0.45)	128	0.44 (0.37, 0.53)	0.46 (0.39, 0.55)	86.3	-1.12 (-1.37)	0.46 (0.4)
gastrointestinal disorders	1624	0.49 (0.47, 0.52)	0.52 (0.5, 0.54)	800.12	-0.95 (-1.02)	0.52 (0.5)	178	0.4 (0.34, 0.46)	0.42 (0.37, 0.48)	156.85	-1.25 (-1.47)	0.42 (0.37)
respiratory, thoracic and mediastinal disorders	661	0.37 (0.34, 0.4)	0.38 (0.35, 0.41)	708.39	-1.4 (-1.51)	0.38 (0.36)	97	0.4 (0.33, 0.49)	0.41 (0.34, 0.5)	86.11	-1.28 (-1.57)	0.41 (0.35)

(Continued on following page)

10.3389/fphar.2024.1418609

TABLE 8 (*Continued*) Comparison of system disorders of adverse event signals between LCM and PER.

soc	lacosamide						perampanel					
	Case Reports	ROR (95% CI)	PRR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)	Case Reports	ROR (95% CI)	PRR (95% CI)	chisq	IC(IC025)	EBGM(EBGM05)
cardiac disorders	1497	1.64 (1.56, 1.73)	1.62 (1.53, 1.72)	360.88	0.69 (0.62)	1.62 (1.55)	46	0.38 (0.29, 0.51)	0.39 (0.29, 0.52)	44.82	-1.36 (-1.77)	0.39 (0.31)
infections and infestations	1086	0.55 (0.51, 0.58)	0.56 (0.53, 0.59)	399.01	-0.84 (-0.92)	0.56 (0.53)	103	0.37 (0.3, 0.45)	0.38 (0.31, 0.46)	108.16	-1.38 (-1.66)	0.38 (0.33)
blood and lymphatic system disorders	330	0.54 (0.48, 0.6)	0.54 (0.49, 0.6)	130.12	-0.88 (-1.04)	0.54 (0.49)	30	0.36 (0.25, 0.52)	0.36 (0.25, 0.51)	33.81	-1.46 (-1.97)	0.36 (0.27)
vascular disorders	387	0.49 (0.44, 0.54)	0.49 (0.44, 0.54)	205.37	-1.02 (-1.16)	0.49 (0.45)	32	0.31 (0.22, 0.43)	0.31 (0.22, 0.44)	50.05	-1.69 (-2.18)	0.31 (0.23)
musculoskeletal and connective tissue disorders	583	0.28 (0.26, 0.31)	0.3 (0.28, 0.32)	1039.02	-1.76 (-1.88)	0.3 (0.28)	67	0.24 (0.19, 0.3)	0.25 (0.2, 0.32)	160.77	-2.01 (-2.35)	0.25 (0.2)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	477	0.45 (0.41, 0.5)	0.46 (0.42, 0.51)	311.47	-1.12 (-1.25)	0.46 (0.43)	24	0.16 (0.11, 0.24)	0.16 (0.11, 0.24)	106.28	-2.62 (-3.18)	0.16 (0.12)
immune system disorders	161	0.39 (0.33, 0.45)	0.39 (0.33, 0.46)	155.59	-1.36 (-1.58)	0.39 (0.34)	9	0.15 (0.08, 0.29)	0.15 (0.08, 0.29)	42.23	-2.7 (-3.59)	0.15 (0.09)
endocrine disorders	45	0.49 (0.37, 0.66)	0.49 (0.37, 0.66)	23.82	-1.03 (-1.44)	0.49 (0.38)						

10.3389/fphar.2024.1418609

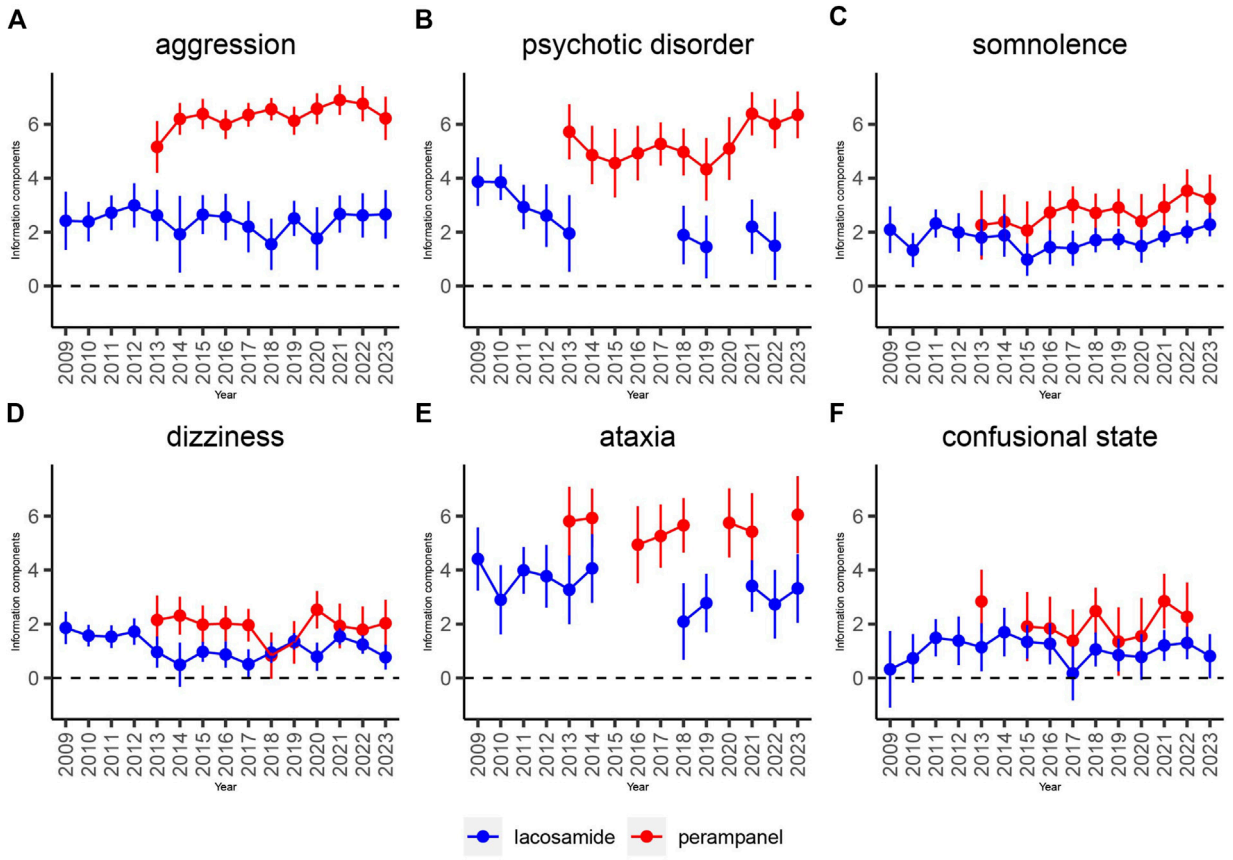


FIGURE 4
Information component and its 95% credibility interval over time for LCM and PER -associated adverse events. Note: Abbreviations: The blue line represents the reports of LCM while the red line represents the reports of PER; IC, information component; CI, credibility interval. The error bars show the 95% credibility interval (CI) of the information component (IC), when the IC curve is in a steady upward trend and the 95% CI narrowed, the signal is stable and the association is strong. Shrinkage of CI of IC over time with increasing data means that confidence interval gets smaller. Once the value 0 is not included in the CI, a signal is flagged.

introduces potential biases, including underreporting and variability in report quality. Additionally, the observational nature of our analysis does not allow for causality establishment between drug exposure and AEs, and the absence of a denominator in spontaneous reports limits the ability to calculate precise incidence rates (Kamel et al., 2013). These factors necessitate cautious interpretation of our findings and underscore the need for continuous and multifaceted pharmacovigilance efforts. Despite these limitations, our study significantly contributes to the pharmacovigilance landscape by providing a broad and detailed exploration of the safety profiles of LCM and PER.

4.5 Clinical implications

The distinct safety profiles of LCM and PER have significant implications for clinical practice. For instance, the lower incidence of psychiatric AEs with LCM makes it a preferable choice for patients with a history of mental health issues. Moreover, the age-related AE patterns suggest that LCM might be more suitable for older adults, while PER might require careful monitoring in younger patients due to its higher association with behavioral disturbances.

The pregnancy safety profile further influences treatment decisions. LCM's relatively safer profile during pregnancy could make it a more suitable option for women of childbearing age or those planning to conceive. On the other hand, the heightened psychiatric risks associated with PER necessitate a thorough risk-benefit analysis and close monitoring when prescribed to pregnant patients.

4.6 Novelty and future directions

Our study's novelty lies in its extensive use of the FAERS database to provide a real-world comparative safety analysis of LCM and PER. This approach offers a broader and more detailed view of the AE profiles than clinical trials alone. Future research should focus on prospective studies to validate these findings and explore the underlying mechanisms of the reported AEs. Additionally, integrating genetic and biomarker data could further refine the personalization of ASD therapy, enhancing both efficacy and safety. Our work underscores the dynamic

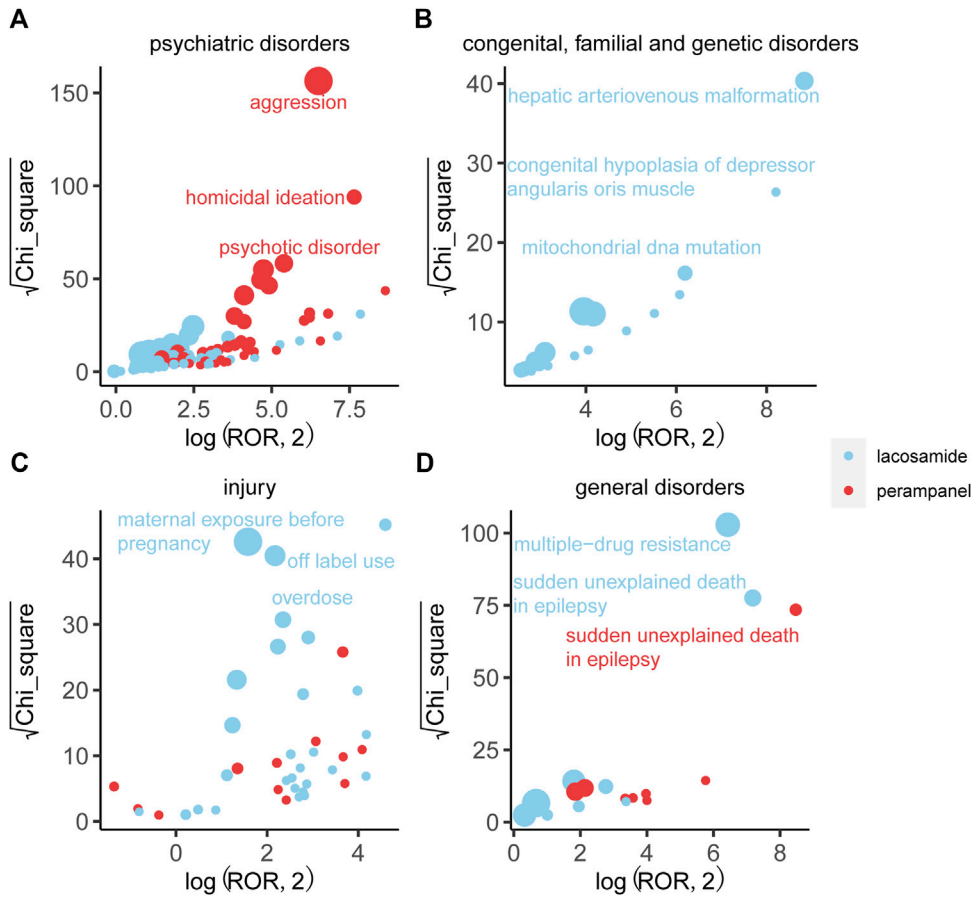


FIGURE 5
Comparison of four system organ classes safety signals between LCM and PER. Note: **(A)** Blood and lymphatic system disorders; **(B)** Hepatobiliary disorders; **(C)** Respiratory, thoracic and mediastinal disorders; **(D)** Cardiac disorders. Figure 3 respectively shows the mining results of adverse event signals of T-DM1 and T-DXd in four system organ classes. The x-axis is log2ROR, and the y-axis is the square root of the $\chi 2$ value. All points in the figure represent the mined adverse reaction signals, and the size of points represents the number of reported adverse reactions. ROR and PRR methods were used to determine the location of each adverse event in the figure. When the position of the point in the graph is higher and further, both algorithms prove that the signal of the adverse event is strong.

nature of drug safety, highlighting the critical need for ongoing monitoring and evaluation in the post-marketing phase. By elucidating the specific AEs associated with these ASDs and their potential impacts on patient care, we offer valuable insights for healthcare providers (Mesraoua et al., 2020). This knowledge empowers clinicians to make more informed decisions in the management of epilepsy, balancing therapeutic efficacy with patient safety. Furthermore, our findings stress the importance of personalized treatment strategies that consider individual patient factors and potential AE risks. The enhanced understanding of AE profiles provided by our study can guide clinicians in optimizing treatment plans, ultimately improving patient outcomes in epilepsy care.

5 In conclusion

Our comprehensive analysis emphasizes the indispensable role of pharmacovigilance in optimizing epilepsy management. As LCM and PER continue to play crucial roles in treating this challenging condition, our study contributes to a deeper understanding of their safety profiles, facilitating informed clinical decision-making and enhancing patient care. Future research, armed with more robust pharmacovigilance methods, will continue to build upon our findings, further advancing the goal of safe and effective epilepsy treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

CG: Writing–original draft, Writing–review and editing. LJ: Conceptualization, Investigation, Writing–review and editing. J-JT: Supervision, Writing–review and editing. JX: Formal Analysis, Writing–review and editing. NY: Funding acquisition, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1418609/full#supplementary-material

SUPPLEMENTARY TABLE S1
Comparison of adverse event signals between LCM and PER in psychiatric disorders.

SUPPLEMENTARY TABLE S2
Comparison of adverse event signals between LCM and PER in nervous system disorders.

SUPPLEMENTARY TABLE S3
Comparison of adverse event signals between LCM and PER in general disorders and administration site conditions.

References

Abou-Khalil, B. W. (2019). Update on antiepileptic drugs 2019. *Contin. (Minneap Minn)* 25, 508–536. doi:10.1212/CON.0000000000000715

Beghi, E., Giussani, G., and Sander, J. W. (2015). The natural history and prognosis of epilepsy. *Epileptic Disord.* 17, 243–253. doi:10.1684/epd.2015.0751

Bresnahan, R., Hill, R. A., and Wang, J. (2023). Perampanel add-on for drug-resistant focal epilepsy. *Cochrane Database Syst. Rev.* 4, CD010961. doi:10.1002/14651858.CD010961.pub2

Charalambous, M., Brodbelt, D., and Volk, H. A. (2014). Treatment in canine epilepsy--a systematic review. *BMC Vet. Res.* 10, 257. doi:10.1186/s12917-014-0257-9

Gaitatzis, A., and Sander, J. W. (2013). The long-term safety of antiepileptic drugs. *CNS Drugs* 27, 435–455. doi:10.1007/s40263-013-0063-0

Gasparini, S., Ferlazzo, E., Neri, S., Cianci, V., Iudice, A., Bisulli, F., et al. (2022). Effectiveness of perampanel as the only add-on: retrospective, multicenter, observational real life study on epilepsy patients. *Epilepsia Open* 7, 687–696. doi:10.1002/epi4.12649

Harris, J. A., and Murphy, J. A. (2011). Lacosamide and epilepsy. *CNS Neurosci. Ther.* 17, 678–682. doi:10.1111/j.1755-5949.2010.00198.x

Hophing, L., Kyriakopoulos, P., and Bui, E. (2022). Sex and gender differences in epilepsy. *Int. Rev. Neurobiol.* 164, 235–276. doi:10.1016/bs.irn.2022.06.012

Hu, Q., Zhang, F., Teng, W., Hao, F., Zhang, J., Yin, M., et al. (2018). Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis. *J. Neurol.* 265, 1–11. doi:10.1007/s00415-017-8621-x

Hu, W., Chen, L., Li, H., and Liu, J. (2022). Eye disorders associated with newer antiepileptic drugs: a real-world disproportionality analysis of FDA adverse event reporting system. *Seizure* 96, 66–73. doi:10.1016/j.seizure.2022.01.011

Kamel, J. T., DeGruyter, M. A., D'Souza, W. J., and Cook, M. J. (2013). Clinical experience with using lacosamide for the treatment of epilepsy in a tertiary centre. *Acta Neurol. Scand.* 127, 149–153. doi:10.1111/j.1600-0404.2012.01704.x

Kamitaki, B. K., Minacapelli, C. D., Zhang, P., Wachuku, C., Gupta, K., Catalano, C., et al. (2021). Drug-induced liver injury associated with antiseizure medications from the FDA Adverse Event Reporting System (FAERS). *Epilepsy Behav.* 117, 107832. doi:10.1016/j.yebeh.2021.107832

Kang, H.-J., Kang, E., Jo, M.-W., Park, E.-J., Yoon, S., and Lee, E.-K. (2014). The utility score of epilepsy with partial seizure measured by TTO, VAS, and EQ-5D in the general Korean population. *Epilepsy Res.* 108, 963–971. doi:10.1016/j.eplepsyres.2014.02.014

Kanner, A. M., and Bicchi, M. M. (2022). Antiseizure medications for adults with epilepsy: a review. *JAMA* 327, 1269–1281. doi:10.1001/jama.2022.3880

Li, J., Sun, M., and Wang, X. (2020). The adverse-effect profile of lacosamide. *Expert Opin. Drug Saf.* 19, 131–138. doi:10.1080/14740338.2020.1713089

Liu, P., Zhang, Y., Xu, X., Zhou, M., Fei, Y., and Zhang, L. (2023). Mining and analysis of adverse drug reactions associated with perampanel based on FAERS database. *Epilepsy Behav.* 145, 109283. doi:10.1016/j.yebeh.2023.109283

Manford, M. (2017). Recent advances in epilepsy. *J. Neurol.* 264, 1811–1824. doi:10.1007/s00415-017-8394-2

Mesraoua, B., Deleu, D., Hassan, A. H., Gayane, M., Lubna, A., Ali, M. A., et al. (2020). Dramatic outcomes in epilepsy: depression, suicide, injuries, and mortality. *Curr. Med. Res. Opin.* 36, 1473–1480. doi:10.1080/03007995.2020.1776234

Palleria, C., Cozza, G., Khengar, R., Libri, V., and De Sarro, G. (2017). Safety profile of the newest antiepileptic drugs: a curated literature review. *Curr. Pharm. Des.* 23, 5606–5624. doi:10.2174/1381612823666170809115429

Pascarella, A., Gasparini, S., Manzo, L., Marsico, O., Torino, C., Abelardo, D., et al. (2023). Perampanel as only add-on epilepsy treatment in elderly: a subgroup analysis of real-world data from retrospective, multicenter, observational study. *J. Neurol. Sci.* 455, 122797. doi:10.1016/j.jns.2023.122797

Pascarella, A., Iannone, L. F., Di Gennaro, G., D'Aniello, A., Ferlazzo, E., Gagliostro, N., et al. (2020). The efficacy of perampanel as adjunctive therapy in drug-resistant focal epilepsy in a "real world" context: focus on temporal lobe epilepsy. *J. Neurol. Sci.* 415, 116903. doi:10.1016/j.jns.2020.116903

Perucca, P., Scheffer, I. E., and Kiley, M. (2018). The management of epilepsy in children and adults. *Med. J. Aust.* 208, 226–233. doi:10.5694/mja17.00951

Roberti, R., Di Gennaro, G., Anzellotti, F., Arnaldi, D., Belcastro, V., Beretta, S., et al. (2024). A real-world comparison among third-generation antiseizure medications: results from the COMPARE study. *Epilepsia* 65, 456–472. doi:10.1111/epi.17843

Rohracher, A., Kalss, G., Leitinger, M., Granbichler, C., Deak, I., Dobesberger, J., et al. (2016). Two-year real-world experience with perampanel in patients with refractory focal epilepsy: Austrian data. *Ther. Adv. Neurol. Disord.* 9, 445–453. doi:10.1177/1756285616661115

Sarkis, R. A., Nicolas, J., and Lee, J. W. (2017). Tolerability of lacosamide or zonisamide in elderly patients with seizures. *Seizure* 49, 1–4. doi:10.1016/j.seizure.2017.04.010

Thijs, R. D., Surges, R., O'Brien, T. J., and Sander, J. W. (2019). Epilepsy in adults. *Lancet* 393, 689–701. doi:10.1016/S0140-6736(18)32596-0

Villanueva, V., Garces, M., Lopez-Gomariz, E., Serratosa, J. M., Gonzalez-Giraldez, B., Parra, J., et al. (2015). Early add-on lacosamide in a real-life setting: results of the REALLY study. *Clin. Drug Investig.* 35, 121–131. doi:10.1007/s40261-014-0255-5

Wheless, J., Wechsler, R. T., Penovich, P., Segal, E., Chez, M., Coppola, A., et al. (2023). Effectiveness, safety and tolerability of perampanel by age group when used to treat people with focal and generalized epilepsy in clinical practice: the PERMIT Extension study. *Epilepsy Behav.* 147, 109369. doi:10.1016/j.yebeh.2023.109369

Yamamoto, T., Gil-Nagel, A., Wheless, J. W., Kim, J. H., and Wechsler, R. T. (2022). Perampanel monotherapy for the treatment of epilepsy: clinical trial and real-world evidence. *Epilepsy Behav.* 136, 108885. doi:10.1016/j.yebeh.2022.108885

Zaccara, G., Giovannelli, F., Cincotta, M., Verrotti, A., and Grillo, E. (2013). The adverse event profile of perampanel: meta-analysis of randomized controlled trials. *Eur. J. Neurol.* 20, 1204–1211. doi:10.1111/ene.12170

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 20 September 2024
DOI 10.3389/fphar.2024.1463560

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Lin Song,
Chongqing Medical University, China
Na Su,
Sichuan University, China

*CORRESPONDENCE
Jinjing Zhao,
zjjjwj1983@163.com
Qiang Zhao,
andy1273@126.com

†These authors have contributed equally to this work

RECEIVED 12 July 2024
ACCEPTED 11 September 2024
PUBLISHED 20 September 2024

CITATION
Tang H, Xu J, Zhang X, Chen C, Song G, Ma R, Zhao J and Zhao Q (2024) A real-world pharmacovigilance analysis of eslicarbazepine acetate using the FDA adverse events reporting system (FAERS) database from 2013 (Q4) to 2024 (Q1).
Front. Pharmacol. 15:1463560.
doi: 10.3389/fphar.2024.1463560

A real-world pharmacovigilance analysis of eslicarbazepine acetate using the FDA adverse events reporting system (FAERS) database from 2013 (Q4) to 2024 (Q1)

Huafei Tang[1†], Jing Xu[2†], Xian Zhang[1], Chunliang Chen[1], Ge Song[3], Rui Ma[1], Jinjing Zhao[3*] and Qiang Zhao[1*]

[1]Department of Pharmacy, The 305 Hospital of PLA, Beijing, China, [2]Department of Pharmacy, Daping Hospital, Army Medical University, Chongqing, China, [3]Department of Neurology, The 305 Hospital of PLA, Beijing, China

Background: The approval of eslicarbazepine acetate (ESL) by the Food and Drug Administration (FDA) in 2013 marked an advancement in the treatment of adult patients with partial-onset seizures. However, there still remains a paucity of real-world studies regarding the adverse events (AEs) associated with this compound. The principal aim of the present study was to scrutinize ESL-related AEs by leveraging data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: By extracting all available data since the FDA approval of ESL (2013Q4-2024Q1), disproportionality analysis was performed using reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN) and multi-item gamma Poisson shrinker (MGPS) algorithms. AE signals that simultaneously met the requirements of all four algorithms were identified as significant positive signals. Demographic information, time of onset and gender-specific signal detection were also examined. In addition, a special screening process for designated medical events (DME) was implemented to focus on the evaluation and comparison of safety signals within DME and System Organ Classification (SOC) level, as well as SMQ (Standardised MedDRA Queries) level. Stratified analysis by logistic regression is employed to examine the variations across different gender (male and female) and age groups (<18 years old, 18–64 years old, >65 years old).

Results: A total of 5,719 AE reports and 1,907 reported cases were obtained. ESL related AEs were identified in relation to 27 SOCs, among which the significant positive SOCs were nervous system disorders, injury poisoning and procedural complications, etc. There were 86 severely disproportional preferred terms that complied with the four algorithms. Most AEs occurred within the first month after treatment. According to the 86 valuable positive signals with DME screening results, 3 signals of dermatitis exfoliative, stevens-johnson syndrome, drug reaction with eosinophilia and systemic symptoms were consistent with PT signals on the DME-list, with the 3 PTs focusing on skin and subcutaneous tissue disorders and hypersensitivity. Males are more commonly affected by seizures than females. Seizures, hyponatremia, and confusional states were

more frequently observed in the elderly population, while aggression, irritability, DRESS (drug reaction with eosinophilia and systemic symptoms), and abnormal behavior were found to be more common in the pediatric population. Both the children and elderly groups exhibited a higher proportion of agitation than the adult group.

Conclusion: Our research enhances the safety and tolerability profile of ESL, but the clinical use of ESL should be noticed and avoided in relation to AEs since it raises the risk of dermatitis exfoliative, stevens-johnson syndrome. Particular attention should be paid to DRESS in children and hyponatremia in the elderly.

KEYWORDS

eslicarbazepine acetate, ESL, FDA, pharmacovigilance analysis, AES

Introduction

Epilepsy is one of the oldest known diseases, with its earliest documented records dating back to 4000 BCE (Kaculini et al., 2021). Despite the recognition of its mechanism and the development of treatments, it remains a common chronic disease of the nervous system that presents significant challenges to the health of patients. The latest data from the Global Disease Burden (GBD) 2021 show that epilepsy has a globally prevalence of 308.9 (95%UI 236.2-390.1), deaths of 1.7 (95%UI 1.5-1.9) and disability-adjusted life years (DALYs) of 183.9 (95%CI 141.0-237.2) in age-standardized rates (per 100,000 people) (GBD 2021 Nervous System Disorders Collaborators, 2024). The focus and complexity of epilepsy lies in the diagnosis and classification of the disease, which is necessary to guide the best possible management of the condition (GBD 2021 Nervous System Disorders Collaborators, 2024; Thijs et al., 2019). In terms of treatments, options encompass the utilization of the ketogenic diet, pharmaceutical intervention, and surgical procedures, with anti-epileptic drugs (AEDs) being the most important method. Unfortunately, epilepsy is not yet curable, but many people can achieve seizure-free with the appropriate treatment. Nevertheless, approximately one-third of patients continue to experience seizures despite the administration of dual AEDs or in the presence of intolerable side effects, a condition commonly referred to as drug-resistant epilepsy (Asadi-Pooya et al., 2023). Hence, a compelling need for the continuous innovation and progression of pioneering AEDs still exists.

Eslicarbazepine acetate (ESL), a voltage-gated sodium channel antagonist, was initially approved by the European Medicines Agency (EMA) in 2009 and subsequently by the US Food and Drug Administration (FDA) in 2013 for the adjunctive treatment of patients with partial onset seizures. Being the third generation of the dibenzazepine carboxamide family, this compound possesses structural advantages with a hydroxy group rather than a keto group in the 10th position of the ring, which leads to a safer profile by producing less toxic metabolites and minimizing enzymatic induction of the cytochrome P450 (CYP) system (Galiana et al., 2017). The existing pre- and post-clinical trials indicate that ESL has comparable efficacy to carbamazepine and oxcarbazepine, with the additional benefits of improved tolerability and patient compliance (Lattanzi et al., 2018). However, there is a paucity of evidence from large population research on the adverse events (AEs) of ESL, particularly in relation to children, older individuals over the age of 65, and individuals of different genders. Consequently, the objective of this study is to analyse adverse event signals associated with ESL using the FDA Adverse Event Reporting System (FAERS) in order to provide insights for its clinical application from a real-world perspective.

Materials and methods

Data source

The FAERS database is the largest publicly accessible pharmacovigilance database in the world, receiving AE reports from a multitude of sources across the globe. Its extensive size and global coverage make it particularly well-suited for identifying potential associations between drugs and AEs. All the data for this retrospective pharmacovigilance study on ESL was retrieved from the FAERS between the fourth quarter (Q4) of 2013 and the first quarter of 2024 (Q1). The steps for data processing include the followings: 1) To eliminate duplicates prior to statistical analysis, the higher PRIMARYID was selected when the CASEID and FDA_DT were identical, and the most recent FDA_DT was chosen when the CASEID and FDA_DT were identical, following by removed the deleted cases; 2) To guarantee that all reports of ESL have been extracted from the Drug file, we employ the Medical Subject Headings (MeSH) to search for all ESL referent names, including trade names such as Zebinix, Aptiom, Zebinix eslicarbazepine acetate, compound codes and chemical formulas; 3) To enhance the credibility of the results, we only extract reports in which ESL was deemed to cause adverse events with a role_cod of PS (Primary Suspect); 4) Using the Medical Dictionary for Regulatory Activities (MedDRA) (version 26.1) to identify each individual report of ESL AEs at the Preferred Term (PT), System Organ Class (SOC) and Standardised MedDRA Queries (SMQ) levels; 5) The inaccurate and missing records of date were eliminated, and the following formula was used to calculate the time-to-onset of AEs brought on by ESL: (Time-to-onset = Adverse event onset date - start date of ESL use). The methodology employed for the identification and analysis of ESL-associated AEs from the FAERS database is illustrated in Figure 1.

Data analysis

Our study employed disproportionality analysis to detect AEs as signals. This approach assesses the relative occurrence of AEs associated with a specific medication in comparison to all other pharmaceuticals.

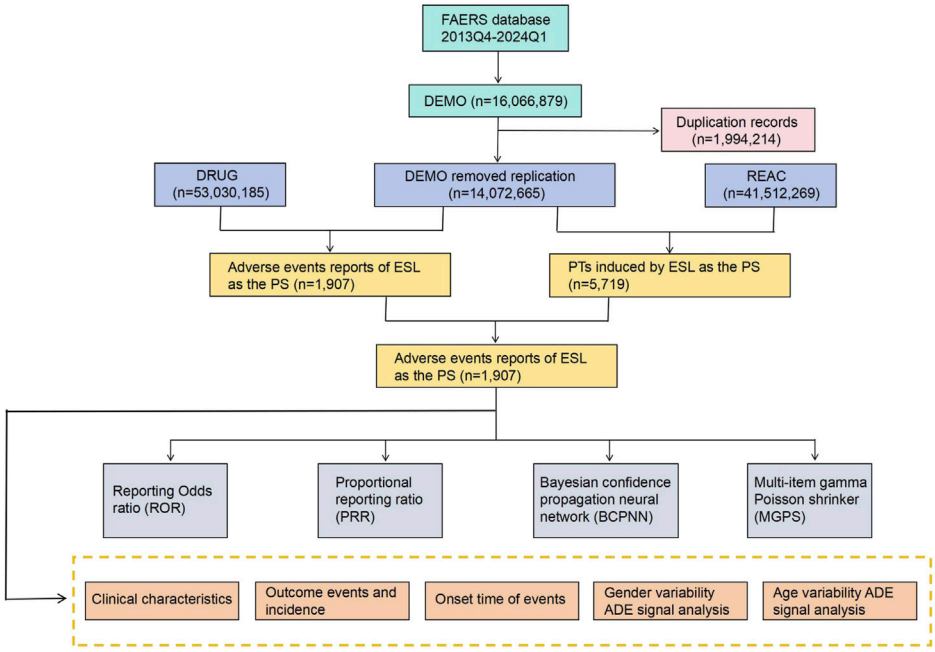


FIGURE 1
The process of searching and analyzing eslicarbazepine acetate-associated adverse events from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), ADE: adverse drug events.

TABLE 1 Detailed formulas for disproportionality analysis.

Methods	Formula	Signal standard
ROR	ROR = ad/bc ROR 95%CI = eln (ROR)±1.96 $(1/a+1/b+1/c+1/d)^{0.5}$	a≥3 lower limit of ROR 95%CI > 1
MHRA	PRR = a (c + d)/c (a+b) PRR 95%CI = eln (PRR)±1.96 $(1/a-1/(a+b)+1/c-1/(c + d))^{0.5}$	a≥3 lower limit of PRR 95%CI > 1
BCPNN	$IC = \log_2 [a (a+b + c + d)]/[(a+b) (a+c)]$ $\gamma = \gamma_{ij} [(N+\alpha) (N+\beta)]/[(a+b+\alpha_i) (a+c+\beta_j)]$ $E (IC) = \log_2 [(a+\gamma_{ij}) (N+\alpha) (N+\beta)]/[(N+\gamma) (a+b+\alpha_i) (a+c+\beta_j)]$ $V(IC)=(\log 2)^{-2}\{(N-a+\gamma-\gamma_{ij})/[(a+\gamma_{ij}) (1 + N+\gamma)] +$ $(N-a-b+\alpha-\alpha_i)/[(a+b+\alpha_i) (1 + N+\alpha)] +$ $(N-a-c+\beta-\beta_i)/[(a+b+\beta_i) (1 + N+\beta)]\}$ $SD = 2(V(IC))^{0.5}$ IC-2SD = E (IC)-2SD	a≥3 IC-2SD > 0
MGPS	EBGM = a (a+b + c + d)/[(a+c) (b + d)] EBGM05 = eln (EBGM)±1.96 $(1/a+1/b+1/c+1/d)^{0.5}$	a>0 EBGM05 > 2

Note: γ, γ_{ij} are the Dicichlet distribution parameter; α_i, α, β_j, β are Beta distribution parameter; SD, is the standard deviation; IC-2SD, is the lower limit of IC, 95% CI; hypothesis $\alpha = \beta = 2$, $\gamma_{ij} = \beta_j = \alpha_i = 1$; ROR: reporting odds ratio; MHRA:medicines healthcare products regulatory agency; PRR: proportional reporting ratio; BCPNN: bayesian confidence propagation neural network; MGPS: Multi-Item Gamma Poisson Shrinker; EBGM: empirical bayesian geometric mean; EBGM05: lower limit of EBGM, 95%CI., 95% CI: 95% Confidence Interval.

Four methods were employed for AE signal mining, including the Reporting Odds Ratio (ROR) method, the Medicines Healthcare Products Regulatory Agency (MHRA) method, the Bayesian Confidence Propagation Neural Network (BCPNN) method, and the Multi-Item Gamma Poisson Shrinker (MGPS) method (see in Table 1). A significant signal for PTs is detected when the specific AE occurrence rate of the target medication exceeds the background frequency and simultaneously meets the threshold or criteria of the four indices mentioned above (see in Table 2). To evaluate some serious and specific safety events related to ESL administration, this study further screened the Designated Medical Events (DME) list for valuable positive signals. Reporting odds ratio and stratified analysis by logistic regression is employed to examine different gender (male and female, see in Table 3) and age groups (<18 years old, 18–64 years old, >65 years old) respectively, in order to determine if there are variations in the occurrence of AEs. All analyses were performed using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered statistically significant, and the Bonferroni correction method was used for multiple comparisons.

TABLE 2 Two-by-two contingency table for disproportionality analysis.

	Number of target adverse events reports	Number of other adverse events reports	Total
ESL	a	b	a+b
Other drugs	c	d	c + d
Total	a+c	b + d	N = a+b + c + d

TABLE 3 Two-by-two contingency table for disproportionality analysis (stratified by case sex).

	Number of target adverse events reports	Number of other adverse events reports	Total
Male	a	b	a+b
Female	c	d	c + d
Total	a+c	b + d	N = a+b + c + d

Results

General characteristics

The FAERS database yielded a total of 14, 072, 665 reports between 2013 (Q4) and 2024 (Q1) after the removal of duplicates. We extracted 1,907 AEs reports related to ESL as PS, with 5,719 AE records. The general descriptions were presented in Table 4. It appears that ESL-related AEs were more common in females than males, with the exception of those whose gender is unknown. No discernible correlation was identified between body weight level and the occurrence of AEs. Among individuals with known ages, AEs were concentrated in the age group of 18–64.9 years (24.6%), followed by those aged 65–85 years (5.3%). The AE reports were primarily self-sponsored by patients (78.3%), in a manner similar to other AEDs that necessitate long-term medication. For severe outcomes, the most frequently reported were OT (Other serious medical events, 51.8%) and HO (Hospitalization, 13.8%). With regard to the report country, America (78.8%) submitted the greatest number of reports, followed by Portugal (8.9%), France (3.3%), Spain (2.4%), and Canada (2.0%). During the study period, the number of reports of ESL-related AEs exhibited a gradual increase from 2014, reaching a peak in the year 2019, followed by a subsequent decline to 2023.

Risk signal detection results

Figure 2 depicts signal strengths and reports of ESL at the SOC level, with 27 SOCs affected by ESL-induced AEs. The significant SOCs for which at least one of the four algorithms met the criteria were injury, poisoning, and procedural complications (SOC: 10,022,117), nervous system disorders (SOC: 10,029,205), metabolism and nutrition disorders (SOC: 10,027,433), surgical and medical procedures (SOC: 10,042,613), and psychiatric disorders (SOC: 10,037,175).

At the PT level, in accordance with the specifications of four distinct algorithms, they were identified as ROR (139 positive PTs), PRR (158 positive PTs), BCPNN (101 positive PTs) and EBGM (210 positive PTs), resulting in a total of 86 effective PTs (simultaneously met four algorithms criteria, 31.0% for all positive PTs) (Figure 3; Supplementary Table S1). A volcano plot was generated for the 86 effective PTs, displaying the log2-transformed ROR values on the horizontal axis and the log10-transformed corrected p-values (P.adj, adjusted by Bonferroni) on the vertical axis (Figure 4). The ROR indicated the strength of the association between ESL and AEs, with PTs on the right side (higher log2-transformed ROR) exhibiting a stronger relationship than those on the left. Five of the PTs displayed values above the upper limit of the figure, which was attributed to the presence of small p-values. The five PTs were as follows: hyponatremia (PT: 10,021,036), seizure (PT: 10,039,906), partial seizures (PT: 10,061,334), brain operation (PT: 1,0,061,732), and drug dose titration not performed (PT: 10,074,906) from left to right. It was notable that certain PTs could be grouped together based on their similar presentation or common pathological pathway. Subsequently, the SMQ level was employed to categorize the PTs (34 PTs with Narrow SMQ match), with the creation of a distribution map serving to illustrate this categorization in greater detail (Figure 5; Supplementary Table S2). The top five SMQs were convulsions (SMQ: 20,000,079, 15 PTs, n = 827), hyponatremia/SIADH (SMQ: 20,000,141, 3 PTs, n = 197), medication errors (SMQ: 20,000,224, 2 PTs, n = 70), hypersensitivity (SMQ: 20,000,214, 7 PTs, n = 57), and depression and suicide/self-injury (SMQ: 20,000,035, 1 PT, n = 57).

DME list screening

3 of the 86 positive signals, including dermatitis exfoliative, stevens-johnson syndrome, and drug reaction with eosinophilia and systemic symptoms, were matched with the DME list. All of these signals focus on skin and subcutaneous tissue disorders (SOC level) and hypersensitivity (Narrow SMQ level). The results indicated the presence of five positive signals in AEs related to skin and subcutaneous tissue disorders (Table 5). The highest signal value was observed in dermatitis exfoliative, with a ROR value of 13.7 and a lower 95% CI of 5.14.

Subgroup analysis

Gender-differentiated signal detection

In order to ascertain whether gender is a factor in the AEs of ESL, the ROR method was employed to identify the 86 PTs with a disproportionate AE incidence between males and females. Figure 6 presents the initial 50 PTs in order of incidence number, categorized by SOC. A total of 4 gender-differentiated signals for males involving 2 SOCs were generated by gender-differentiated analysis. In the context of nervous system disorders, males were more commonly affected by seizure (PT: 10,039,906, ROR = 1.64,

TABLE 4 Clinical characteristics of eslicarbazepine acetate associated reports from the FAERS database (2013 Q4 to 2024 Q1).

Characteristics	Case Number, n	Proportion, %
Number of events	1,907	
Sex		
Female	799	41.6
Male	545	28.6
Unknown	563	29.5
Weight (kg)		
<50	25	1.3
>100	48	2.5
50–100	174	9.1
Unknown	1,660	87.0
Age (years)		
<18	75	3.9
18–64.9	470	24.6
65–85	101	5.3
>85	12	0.6
Unknown	1,249	65.5
Reporter		
Consumer (CN)	1,493	78.3
Health professional (HP)	56	2.9
Physician (MD)	220	11.5
Other health professional (OT)	98	5.1
Pharmacist (PH)	26	1.4
Unknown	14	0.7
Serious Outcome		
Death (DE)	56	2.6
Hospitalization (HO)	302	13.8
Disability (DS)	21	1.0
Congenital anomaly (CA)	10	0.5
Life-threatening (LT)	37	1.7
Required intervention to prevent permanent impairment/damage (RI)	1	0.0
Other serious medical events (OT)	1,136	51.8
Unknown	632	28.8
Reported countries (Top 5)		
America (US)	1,503	78.8
Portuguese (PT)	169	8.9
France (FR)	62	3.3
Spain (ES)	46	2.4
Canada (CA)	39	2.0
Reporting year		
2013Q4	8	0.42
2014	38	1.99
2015	119	6.24
2016	129	6.76
2017	206	10.80
2018	287	15.05
2019	298	15.63
2020	221	11.59
2021	255	13.37
2022	128	6.71
2023	144	7.55
2024Q1	74	3.88

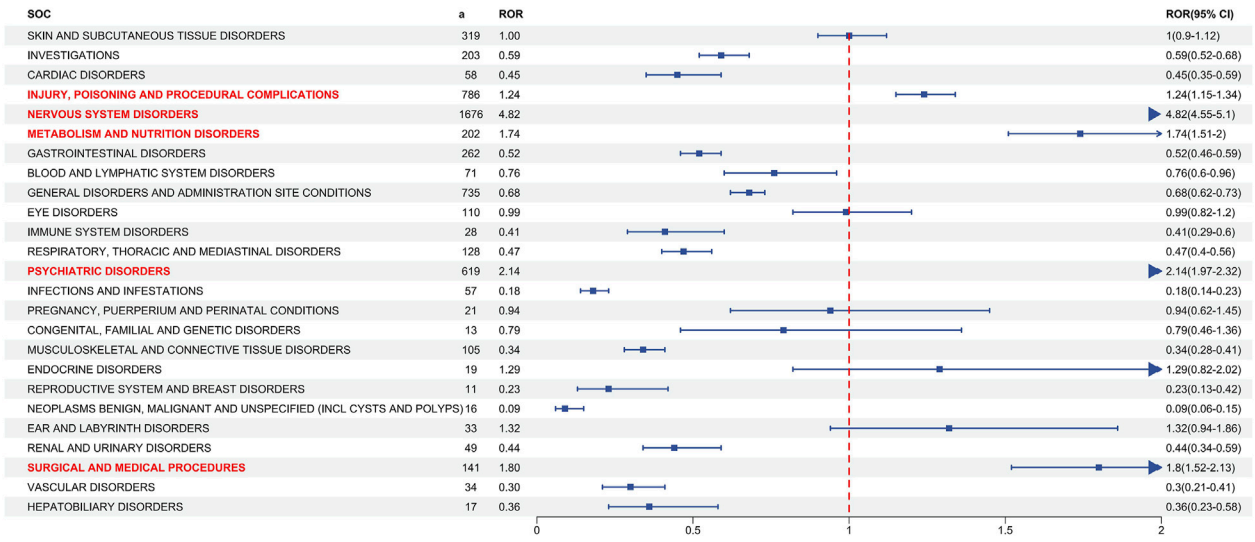


FIGURE 2
Signal detection at the SOC level. The ROR values and their 95% confidence intervals (95% CI) are visualized. The SOCs exhibiting positive signal values were highlighted in red for clarity. The blue arrows signify that the lower limit of the 95% confidence interval of the ROR exceeds 2. a: number of the cases, SOC: System Organ Class, ROR, reporting odds ratio. The p-value is adjusted with Bonferroni correction method.

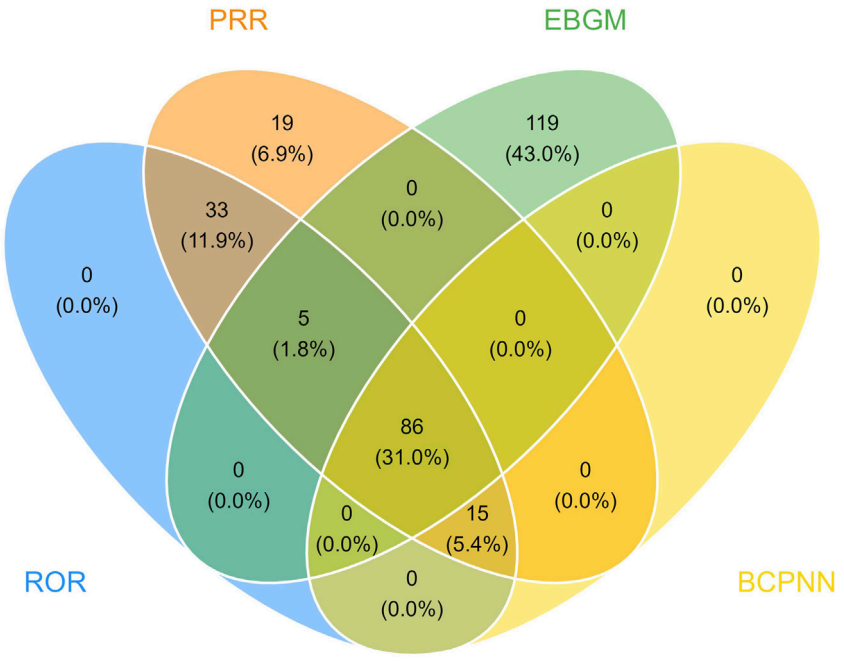


FIGURE 3
The meticulous application of four distinct methodologies resulted in the identification of 86 efficacious PTs. Out of an assemblage of 1,907 signals, the ROR method surfaced 139 relevant signals, the PRR method identified 158, the BCPNN method segregated 101, and the EBGM method segregated 210 effective signals.

95% CI: 1.35–1.99) and simple partial seizures (PT: 10,040,703, ROR = 5.59, 95% CI: 1.13-27.72). For psychiatric disorders, high-risk ADEs including agitation (PT: 10,001,497, ROR = 2.93, 95% CI: 1.13–7.58) and aggression (PT: 10,001,488, ROR = 4.97, 95% CI: 1.32–18.77) were more common in males. No significant differences were identified between the various genders with regard to the other PTs.

Age subgroup analysis

To investigate the relationship between age and AEs of ESL, we stratified age into three subgroups: children (aged <18 years), adult (aged 18–65 years), and elderly (aged >65 years). The adult group was considered to be the reference group. A total of 650 reports with complete and relevant information were extracted from the 1,907 AE

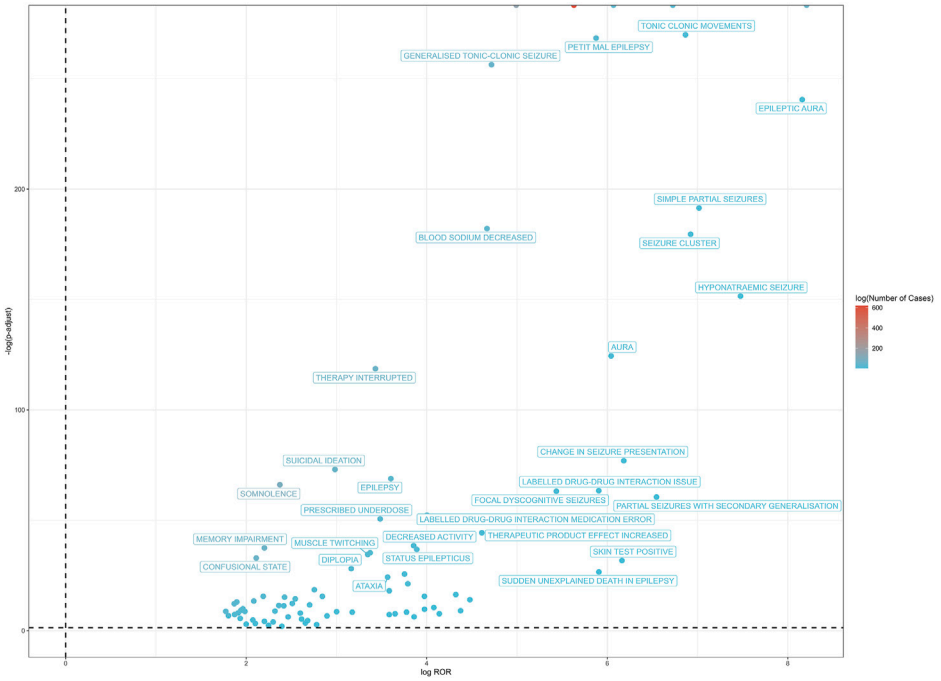


FIGURE 4
The positive risk signal volcano plot for ESL. The horizontal coordinate shows the log2 ROR value and the vertical coordinate indicates the adjusted p-value after -log10 conversion. Significant signals are highlighted and annotated in prominent colors. Five of the PTs displayed values above the upper limit of the figure, including hyponatremia, seizure, partial seizures, brain operation, and drug dose titration not performed from left to right. The p-value is adjusted with Bonferroni correction method.

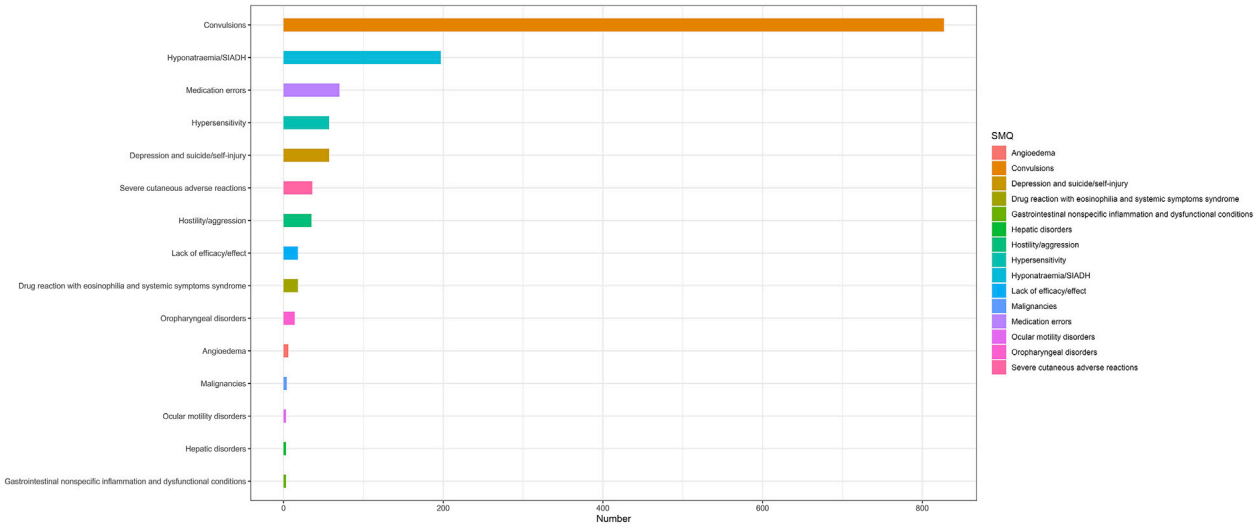


FIGURE 5
The SMQ attribution of PTs that simultaneously satisfy the 4 methods of disproportionality analysis with positive signal values. 34 of the 86 positive PTs were matched with Narrow SMQ and classified into the corresponding SMQ. SMQ: Standardised MedDRA Queries, MedDRA: Medical Dictionary for Regulatory Activities.

reports, including 256 males, 394 females, 73 children, 456 adults and 112 elderly. Logistic univariate and multivariate regression (considering age and gender factors) analyses were then conducted on the 86 positive PTs, respectively (see in Figure 7; Supplementary Table S3). It is important to note that when the number of occurrences within a specific subgroup is insufficient, it is not possible to calculate the odds ratio (OR) value. The results demonstrated that the occurrence of seizure (PT: 10,039,906), hyponatremia (PT: 10,021,036) and confusional state (PT: 10,010,305) was more prevalent in the elderly group than in the adult group. Notably, seizure was significant with

TABLE 5 DME list screening results.

PT	a	ROR	Lower limit of 95% CI	Instructions included or not
Dermatitis exfoliative	4	13.7	5.14	Yes
Toxic skin eruption	6	7.44	3.34	Yes
Drug reaction with eosinophilia and systemic symptoms	18	6.75	4.25	Yes
Rash maculo-papular	12	6.51	3.69	Yes
Stevens-johnson syndrome	8	5.52	2.76	Yes

PT: preferred term, a: number of the PT, reports, ROR: reporting odds ratio, DME: designated medical events, 95% CI: 95% confidence interval. The bold PTs, are positive and matched with the DME, list.

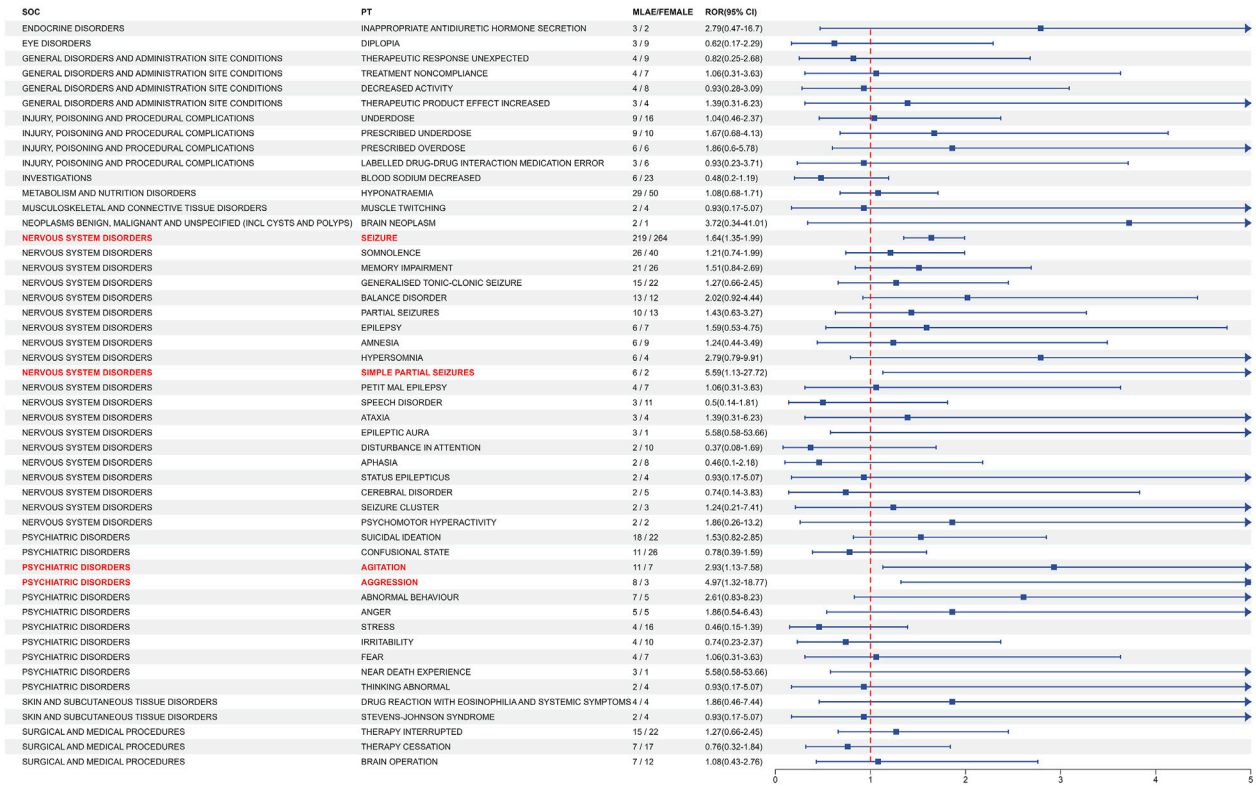


FIGURE 6
Analysis of gender-differentiated risk signals in ESL. The top 50 PTs in case number were displayed in order of SOC alphabet, with positive gender-related ADEs highlighted in red. ROR: Reporting odds ratios, 95% CI: 95% confidence interval. The blue arrows signify that the lower limit of the 95% confidence interval of the ROR exceeds 5. The p-value is adjusted with Bonferroni correction method.

crude OR (0.64, 95%CI 0.40–0.99, p = 0.049) for the elderly group. Conversely, aggression (PT: 10,001,488), irritability (PT: 10,022,998), drug reactions with eosinophilia and systemic symptoms (PT: 10,073,508), and abnormal behaviour (PT: 10,061,422) were more frequently observed in the children group than in the adult group. Notably, agitation (PT: 10,001,497) was more common in both the children group and the elderly group than in the adult group.

Onset time of events

Following the exclusion of inaccurate, missing, or unknown reports of onset, a total of 109 AEs were collected. The median TTO (Time to onset) was determined to be 27 days (interquartile range [IQR] 8–62 days). As illustrated in Figure 8, the majority of cases occurred within the initial month (n = 60, 55.05%) of ESL administration. The number of AEs decreased over time, with 27 AEs (24.77%) occurring in the 31–90 days and 7 AEs (6.42%) in the 91–180 days. Notably, in 2.75% of cases, AEs could still occur even after 1 year of treatment with ESL. To ascertain whether the risk of ESL-associated AEs exhibited a temporal trend, we conducted Weibull distribution tests. In the context of the overall analysis, the calculated shape parameter (β) was 0.69, with the upper limit of its 95% confidence interval (CI) being 0.78. Both values were below 1, indicating a decline in the prevalence of AEs over time (Early failure type, see in Table 6).

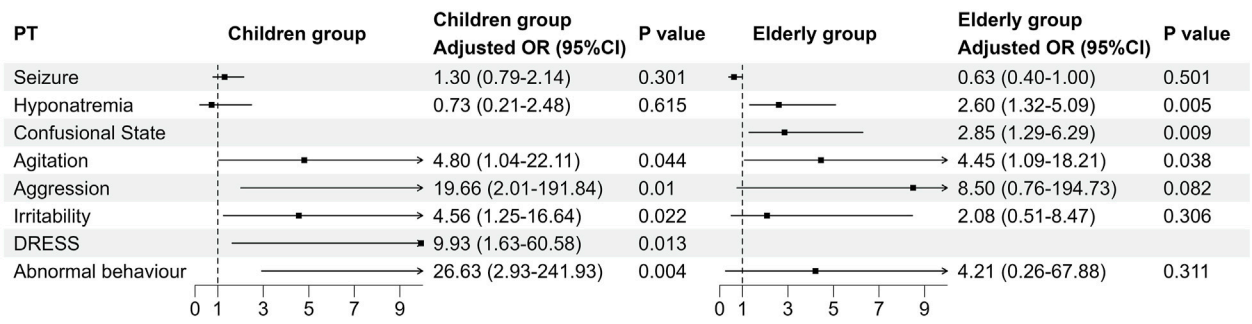


FIGURE 7
Logistic regression of the different age groups for the 86 positive PTs. The adult group was the reference group. The OR was adjusted for age and gender. Eight of the 86 PTs were statistically significant, as illustrated in the figure. The adjusted OR values for the "confusional state" of the children group and the "DRESS" of the elderly group are unavailable due to the limited number of positive cases. PT, Preferred term; OR, Odds ratio; DRESS, Drug reaction with eosinophilia and systemic symptoms.

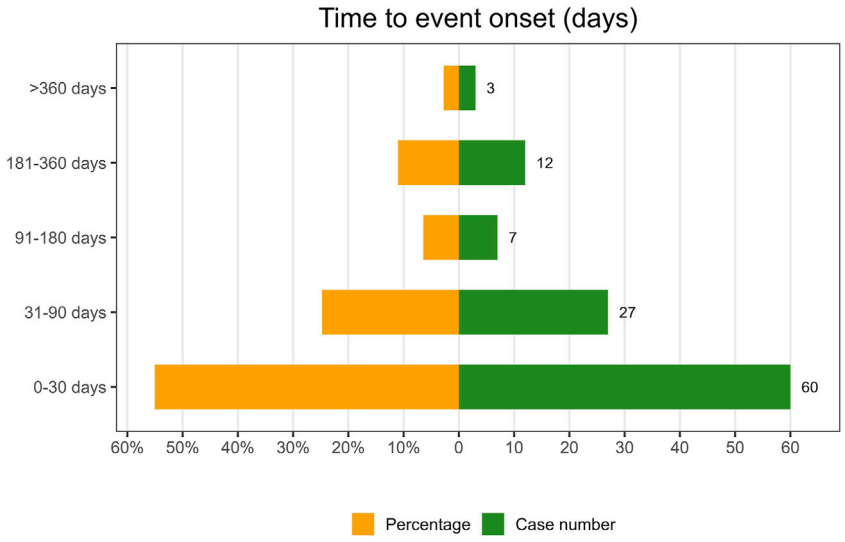


FIGURE 8
Time to onset of ESL-related AEs.

TABLE 6 Weibull distribution of the ESL-related AEs.

Cases n	Time to onset (days)		Weibull distribution				Failure type
			Scale parameter		Shape parameter		
	Media (IQR)	Min-MMin-Maxax	α 95% CI		β 95% CI		
109	27 (8–62)	1–803	53.29	37.88–68.70	0.69	0.59–0.78	Early failure

IQR: interquartile range.

Discussion

Epilepsy is a common chronic brain disorder characterised by a long-standing tendency to recurrent seizures (Scheffer et al., 2017). Given that epilepsy is not a singular disease entity, it is crucial to be as precise as possible in the diagnosis, following the classification system of the International League Against Epilepsy (ILAE) (Fisher et al., 2017). Pathologically, both focal onset seizures and generalized onset seizures share the same mechanism of an imbalance between excitatory and inhibitory activity within a neuronal network (Pitkänen and Engel, 2014). Nevertheless, the spectrum of affected areas of the brain and the choice of anti-seizure medications represent two key differences between the two conditions (Nevitt et al., 2022). In clinical practice, the most

common type of seizure is the partial-onset (focal) seizure, which is characterised by an initial activation of only part of one cerebral hemisphere (Galiana et al., 2017). Carbamazepine (CBZ), discovered serendipitously by Walter Schindler in 1953, has been the therapy of choice for this condition since the 1960s (Asadi-Pooya et al., 2023). As the inaugural member of the dibenzazepine carboxamide class, carbamazepine exerts its anti-seizure effects by blocking the voltage-gated sodium channel (VGSC), thereby reducing membrane excitability. However, it has still been limited by the occurrence of AEs and the complexity of its pharmacokinetics (Verrotti et al., 2014). In response to the growing demand for more effective anti-epileptic drugs, the second-generation (oxcarbazepine, OXC) and the third-generation (eslicarbazepine acetate, ESL) members of the dibenzazepine carboxamide family were developed. So far, ESL has shown promising results and demonstrated superiority over CBZ/OXC as an effective and safe alternative for treating partial-onset seizures (Rocamora et al., 2020). Its structurally configuration by a 5-carboxamide substitute at the 10,11 position of the dibenzazepine nucleus, leading to differences from CBZ/OXC in pharmacodynamics, pharmacokinetics, and metabolism (Shorvon et al., 2017). Different from traditional VGSC blockers interfering with the fast inactivation pathway, ESL's active form (eslicarbazepine) enhances slow activation of VGSC and can also block the Cav3.2 T-type Ca2+ channel (Shorvon et al., 2017; Doeser et al., 2015). Additionally, unlike CBZ, ESL is not metabolized into the CBZ 10,11-epoxide, an active and potentially toxic compound, thus minimizing the enzymatic induction of the cytochrome P450 (CYP) system and autoinduction. In contrast to OXC, ESL is metabolized almost exclusively to the (S)-enantiomer with less than a 5% chiral conversion to the (R)-enantiomer, whereas OXC is converted to both (S)- and (R)- enantiomers in about a 4-5: 1 proportion (Hwang et al., 2022). ESL's stereoselective metabolism avoids the early peak in OXC concentration observed in plasma and CSF following immediate-release OXC administration, which correlates with OXC-related adverse events (dizziness, headache, etc.) (Keating, 2014). To date, several clinical studies, in addition to a descriptive analysis on the Argus Safety™ database, have provided evidence on the tolerability and safety profile of ESL (Guedes et al., 2023; Zhu et al., 2020). Building on the aforementioned foundation, this pharmacovigilance study further investigates ELS-related adverse events and their differences among subgroups using the FAERS database for the first time.

The FAERS database supports the FDA's post-marketing monitoring of drugs and therapeutic biological products. It contains information on AEs and medication errors collected by the FDA, which can be analyzed by researchers to identify potential risk factors, high-risk groups, and emerging clinical safety issues. The data of the present study was retrospectively obtained from the FAERS database, beginning with the approval of ESL and extending to the most recent release in the first quarter of 2024. According to our findings, females (41.6%) accounted for a higher proportion of ESL-related ADRs compared to males (28.6%). It is notable that previous studies did not identify a significant difference in efficacy or AEs between the sexes. One potential explanation for this discrepancy may be the limited number of clinical study populations compared to the FAERS database, which may have resulted in undetected differences. In addition, a study by Amílcar Falcão suggested that women absorb more drugs than men, but it did not definitively confirm that gender influences the pharmacokinetics of ESL (Falcão et al., 2007). Nevertheless, this finding warrants further attention as a potential cause of increased AEs in women. Due to the spontaneous nature of the FAERS reporting system, the majority of our target cases lack information on age and weight. But it is also noteworthy that the remaining cases involved individuals aged 16–64.9 years old (24.6%) and weighing between 50-100 kg (9.1%), which exhibited the highest proportion of AEs. ESL is biotransformed into eslicarbazepine by hepatic hydrolysis and eliminated by renal excretion (Almeida et al., 2008). The pharmacokinetics of eslicarbazepine are linear, with the main pharmacokinetics parameters (C_{max} and $AUC_{0\text{-}24}$) demonstrating dose-proportionality across the dose range of 400–2,400 mg/day (Elger et al., 2013). And its pharmacokinetics are not significantly affected by concomitant intake of food (Almeida et al., 2010) or age (Almeida et al., 2005). The discrepancy in AEs across weight categories suggests that the dosage applications may not be optimal. While among different age groups, the variation in the distribution of AEs may be attributed to the bimodal pattern of epilepsy, which shows peaks in infants under 1 year old and individuals over 50 years old (Thijs et al., 2019). Nevertheless, for example, a higher incidence of hyponatremia was observed, particularly in elderly patients who had experienced a stroke and had seizures (Gupta et al., 2015). This suggests that specific PTs may have differential occurrences across age groups, which require further investigation. The most common AEs associated with ELS are dizziness, headache, fatigue, and diplopia, which are typically of mild or moderate severity (Ley et al., 2015). It is also possible that serious dermatological and electrolyte AEs may be caused by ESL (Guedes et al., 2023). However, their incidence is relatively rare, consistent with our findings that serious adverse outcomes such as death and life-threatening conditions accounted for a small fraction of ESL-related outcomes (4.1%) (Shorvon et al., 2017; Zhu et al., 2020). With regard to the countries from which the reports originated, the majority were from the United States and Portugal. As China has not yet established a definitive timeline for ESL, it is not possible to identify any relevant adverse reaction data, nor to analyse the racial differences from other countries. In Korea, a randomized controlled trial (RCT) conducted by Hwang involving 29 Korean and 20 White subjects suggests that ESL was well-tolerated in healthy Korean and White subjects, and that its pharmacokinetic (PK) characteristics were comparable between the two ethnic groups (Hwang et al., 2022). However, a series of studies on ESL pharmacogenetics have demonstrated a significant association between drug resistance and the increased efflux of eslicarbazepine by P-glycoprotein (Pgp, ABCB1, or MDR1) *in vitro* (Zhang et al., 2011). Similarly, *in vivo* evidence indicated that one of the three ABCB1 common polymorphisms, ABCB1 C1236 T C/C diplotype, has been identified as a significant risk factor for the occurrence of AEs (Zubiaur et al., 2021). The divergent conclusions underscore the necessity for further studies to be conducted in order to facilitate a comparison of the results obtained here. We also observed that the number of AEs reports of ESL exhibited an upward trend prior to 2019, followed by a downward trend afterwards. The global sales volume of ESL is exhibiting a growth rate of approximately 10% per annum, whereas the increase in the use of ESL has not resulted in a continuous increase in the number of AE reports. We postulated

that this may be attributable to the more judicious application of ESL, guided by medical professionals, although it is necessary to monitor whether the downward trend in adverse reactions to ESL will persist in the future.

At the system-organism level, ADRs related to ESL (n = 5,719) were distributed across 27 SOCs, with the nervous system being the most affected (n = 1,676). Further disproportionality analysis identified five significant SOCs that exceed at least one of the four algorithms' threshold. "Nervous system disorders" was both the positive and most frequent affected SOC related to ESL, which aligns with the drug label's mention of dizziness, somnolence, disturbance in gait and coordination, cognitive dysfunction, and visual change as the most frequent AEs. Although the incidence of these AEs is relatively high, the intensity is often mild or moderate (Ley et al., 2015; Sperling et al., 2015a). Another SOC commonly associated with anti-epileptic drugs (AED) is psychiatric disorders, which is also identified as a positive signal for ESL in this study. In some perspectives, psychiatric conditions are frequently observed in individuals diagnosed with epilepsy, while AEDs such as ESL may potentially elevate the risk of psychiatric AEs, including depression and suicidal ideation (Andermann et al., 2018). On the contrary, a recent study, which employed post-hoc analysis of data from three Phase III RCTs, found no discernible difference in the incidence of psychiatric AEs between patients who received a placebo and those who received ESL (Altalib et al., 2022). Based on our research, depression and suicidal ideation ranked prominently within the SOC of "Psychiatric disorders" and yielded positive signals. Although our findings do not indicate that ESL increases the risk of suicide, they do suggest that patients with epilepsy who are taking ESL may be at risk of suicide. Consequently, we also recommend that continuous attention be paid to the emergence or worsening of depressive symptoms, as well as any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour or thoughts about self-harm during the administration of ESL medication. Such occurrences should be promptly reported to the relevant health providers, as the consequences may be fatal. Signal of "Metabolism and nutrition disorders" was positive at SOC level, primarily due to the ESL-related AEs of hyponatremia, which was also an important AE for CBZ and OXC. Compared to other AED drugs, ESL appears to have a lower incidence of hyponatremia, occurring in only 0.6%–1.5% of patients. The reduction in sodium levels was most pronounced within 8 weeks of treatment, after which the levels remained relatively stable. Results from a Phase III clinical trial showed that 1.4% of patients receiving a dosage of 1,200 mg ESL experienced severe hyponatremia leading to discontinuation, while none of the patients taking 800 mg experienced this AE prompting withdrawal (Sperling et al., 2015b). Monitoring serum sodium levels is necessary for patients (particularly the elderly), who are undergoing maintenance treatment with ESL. This is especially important if the patient is taking other medications (e.g., diuretic, vinca alkaloids, platinum, SSRIs, TCAs, PPIs, CCBs) known to lower serum sodium levels. Additionally, when symptoms of hyponatremia such as nausea, vomiting, malaise, or headache develop, serum sodium level monitoring should be carried out promptly. "Injury, poisoning, and procedural complications" exhibited a positive signal at SOC level mainly attributed to issues related to dosage. As with other AEDs, ESL should be introduced gradually and doses increased in steps, contingent on the presenting symptoms. The drug is recommended at a dosage of 400 mg once daily, with weekly titration to the maximum tolerated dose (800–1,600 mg once daily) if seizures persist. Hence, the process of adjusting drug doses is relatively complex and vulnerable to unsuitableness, whether during the initial treatment or the maintenance phase of ESL. In the event of any intolerability issues or a lack of efficacy at the maximum tolerated dose being observed, a reduction in dose or an alteration in the first-line drug should be considered. This, in turn, also generates a positive signal at the SOC level in the context of "Surgical and medical procedures" regarding the interruption or cessation of therapy. Notably, "brain operation" was a positive PT under this SOC, however, it is considered to be correlated with the progression of the underlying medical condition rather than being AEs caused by ESL itself.

At the PT level, a total of 86 effective PTs were identified as meeting the criteria of all four algorithms simultaneously. Among these PTs, suicidal ideation, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), toxic skin eruption, dermatitis exfoliative, pharyngeal oedema, hyponatremia, somnolence, balance disorder, memory impairment, amnesia, diplopia, eye movement disorder, and ammonia increased were in accordance with the drug instructions. Furthermore, the study identified a number of additional AEs, including seizure/epilepsy (different presentations), over/under dose, agitation, anger, stress, aggression, fear, irritability, increased appetite, change of bowel habit, and so forth, which were not listed in the instructions. Here, it is noticeable that several unexpected PTs belonging to psychiatric disorders were detected. Apart from the SOC, PTs could also be categorized at the SMQ level for their similar clinical presentation or shared pathological pathway. At the SMQ level, the top five classification in number of cases for the 86 significant PTs were as follows: convulsions, hyponatremia/SIADH, medication errors, hypersensitivity, and depression and suicide/self-injury. The reason why convulsions was the most common may be partially attributed to the inherent drug-resistant nature of epilepsy, which could be observed in approximately one-third of cases. Along with the fact that even ESL showed its short-term effectiveness with proportion of responder rates (patients with ≥50% reduction in standardized seizure frequency) ranged from 33.8% to 43.1% in a pooled analysis of four RCTs (Elger et al., 2017), as well as one-year long-term effectiveness with a responder rate of 60.3% and seizure freedom rate of 14.7% (Lee et al., 2024), the remaining individuals may still report seizure/epilepsy to FAERS during the initial or maintenance treatment period. To assess the serious and specific safety events associated with ESL administration, we further examined the DME list to identify valuable positive signals based on these 86 PTs. Three signals including dermatitis exfoliative, stevens-johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) were consistent with the PT signals on the DME list, focusing on the SOC of "skin and subcutaneous tissue disorders." Two additional PTs of toxic skin eruption and rash maculo-papular were also found under the corresponding SOC, yet they were seen as different stages of the same dermatological condition spectrum. The pathogenesis may be attributed to the damage caused to endothelial cells by 10,11-epoxide metabolites,

which in turn led to the release of cellular antigens and the occurrence of epitope spreading, resulting in an autoimmune response. However, further clinical confirmation is needed to determine the effect of ESL on the immune system. Due to the strong association between life-threatening cutaneous AEs and the HLA-B*15:02 or HLA-A*31:01 allele, it may be advisable to consider screening for human leucocyte antigen (HLA) before initiating ESL in individuals of Asian descent (Amstutz et al., 2014). A report has documented the successful alteration of ESL without encountering any AEs in a patient with the HLA-A*31:01 haplotype, who previously experienced a severe cutaneous reaction following administration of CBZ (Kay et al., 2017). Nevertheless, it was proposed that ESL should be considered with great caution in the context of the HLA-B*15:02 or HLA-A*31:01 haplotype, where the potential benefits may not outweigh the risks. The instructions for ESL explicitly delineate the AEs associated with serious dermatologic reactions, including SJS and toxic epidermal necrolysis (TEN), and DRESS, which may be fatal and necessitate heightened caution. Although serious AEs occur infrequently during treatment with ESL, it is important to consider discontinuing ESL immediately if any dermatologic reactions or early signs of hypersensitivity appear (Galiana et al., 2017). Patients and caregivers should also be adequately informed and educated about potential indicators associated with serious AEs.

Subgroup analysis provides a novel perspective on the AEs of ESL in different gender and age groups. Previous research indicates that while hyponatremia is more prevalent in the elderly population, there is no significant variance in ESL-related AEs across different gender and age groups (Falcão et al., 2007; Almeida et al., 2005; Elger et al., 2017). However, our findings indicate that males are more commonly affected by seizures, agitation, and aggression than females. Compared to the adult group, seizures, hyponatremia, and confusional states were more frequently observed in the elderly population, while aggression, irritability, DRESS, and abnormal behavior were found to be more common in the pediatric population. Furthermore, both the paediatric and geriatric individuals exhibited a higher proportion of agitation than the adult group. Consequently, these findings indicate the necessity to monitor the occurrence of AEs in specific population subgroups, with particular attention being paid to DRESS in children. Nevertheless, it is important to recognize that these novel perspectives are merely indicative evidence, and that further clinical studies are required in order to substantiate these conclusions.

The TTO analysis revealed a median onset time of 27 days, with the majority of AEs occurring within the initial 30 days following exposure to ESL. Furthermore, 79.81% of all AEs occurred during the first 3 months. This finding was consistent with the results of a one-year open-label extension study, which indicated that ESL-related AEs were most prevalent during the initial 3 months of treatment (Halász et al., 2010). Consequently, it was important that clinicians maintain close contact with patients who were utilizing ESL, particularly within the initial 90-day period. Notable, AEs may still occur up to a year later, although in a reduced proportion. The Weibull distribution tests indicated the presence of an early failure type, which suggests a decline in the occurrence of AEs over time.

Limitations

The limitations of this study can be attributed to the following factors: Firstly, it should be noted that the FAERS database is a spontaneous reporting database, and as such, the quality and quantity of information provided by reporters is not subject to rigorous control. Other general limitations of pharmacovigilance, such as under-reporting, difficulty in identifying low risks, and the difficulty or impracticality of quantifying risks, are also inevitable in this study. Secondly, while the utilization of analytical methodologies can undoubtedly facilitate our comprehension of the strength of the relationship between drugs and AEs, it is imperative to recognize that well-designed clinical trials remain indispensable in determining causation. Thirdly, certain confounding factors, such as potential interactions between medications, pre-existing medical conditions, and the use of multiple drugs, were not accounted for in the study. Further investigation is still required through the implementation of extensive clinical studies in order to address the aforementioned issues. Despite the limitations of the FAERS database for pharmacovigilance research, the comprehensive analysis AEs associated with ESL in this study provides substantial evidence for the safe usage of ESL and further clinical investigation.

Conclusion

This comprehensive and systematic pharmacovigilance analysis demonstrates several common and rare side effects of ESL use and variations among different gender and age groups. Careful monitoring of dermatitis exfoliative, stevens-johnson syndrome is recommended, particularly DRESS in children and hyponatremia in the elderly. The current data supports the known safety and tolerability profile of ESL, with most AEs being non-serious. As such, it is our conviction that the investigation of novel indications and the implementation of more prudent clinical applications will result in substantial benefits for a broader range of patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

HT: Data curation, Formal Analysis, Methodology, Project administration, Software, Writing–original draft. JX: Formal Analysis, Data curation, Project administration, Resources, Software, Writing–original draft. XZ: Data curation, Formal Analysis, Software, Investigation, Writing–review and editing. CC: Formal Analysis, Methodology, Software, Writing–review and editing. GS: Data curation, Project administration, Resources, Software, Writing–review and editing. RM: Investigation, Methodology, Software, Writing–review and editing. ZJ: Formal Analysis, Methodology, Resources, Supervision, Validation, Writing–review and editing. QZ: Formal Analysis, Resources, Software, Visualization, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1463560/full#supplementary-material

References

Almeida, L., Falcão, A., Maia, J., Mazur, D., Gellert, M., and Soares-da-Silva, P. (2005). Single-dose and steady-state pharmacokinetics of eslicarbazepine acetate (BIA 2-093) in healthy elderly and young subjects. *J. Clin. Pharmacol.* 45 (9), 1062–1066. doi:10.1177/0091270005279364

Almeida, L., Nunes, T., Sicard, E., Rocha, J. F., Falcão, A., Brunet, J. S., et al. (2010). Pharmacokinetic interaction study between eslicarbazepine acetate and lamotrigine in healthy subjects. *Acta neurol. Scand.* 121 (4), 257–264. doi:10.1111/j.1600-0404.2009.01233.x

Almeida, L., Potgieter, J. H., Maia, J., Potgieter, M. A., Mota, F., and Soares-da-Silva, P. (2008). Pharmacokinetics of eslicarbazepine acetate in patients with moderate hepatic impairment. *Eur. J. Clin. Pharmacol.* 64 (3), 267–273. doi:10.1007/s00228-007-0414-1

Altalib, H., Grinnell, T., Cantu, D., Ikedo, F., Vieira, M., Zhang, Y., et al. (2022). Psychiatric adverse events in three phase III trials of eslicarbazepine acetate for focal seizures. *Epilepsia open* 7 (4), 616–632. doi:10.1002/epi4.12635

Amstutz, U., Shear, N. H., Rieder, M. J., Hwang, S., Fung, V., Nakamura, H., et al. (2014). Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia* 55 (4), 496–506. doi:10.1111/epi.12564

Andermann, E., Biton, V., Benbadis, S. R., Shneker, B., Shah, A. K., Carreño, M., et al. (2018). Psychiatric and cognitive adverse events: a pooled analysis of three phase III trials of adjunctive eslicarbazepine acetate for partial-onset seizures. *Epilepsy and Behav. E&B* 82, 119–127. doi:10.1016/j.yebeh.2017.12.017

Asadi-Pooya, A. A., Brigo, F., Lattanzi, S., and Blumcke, I. (2023). Adult epilepsy. *Lancet (London, Engl.)* 402 (10399), 412–424. doi:10.1016/S0140-6736(23)01048-6

Doeser, A., Dickhof, G., Reitze, M., Uebachs, M., Schaub, C., Pires, N. M., et al. (2015). Targeting pharmacoresistant epilepsy and epileptogenesis with a dual-purpose antiepileptic drug. *Brain a J. neurology* 138 (Pt 2), 371–387. doi:10.1093/brain/awu339

Elger, C., Bialer, M., Falcão, A., Vaz-da-Silva, M., Nunes, T., Almeida, L., et al. (2013). Pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine at steady state in healthy volunteers. *Epilepsia* 54 (8), 1453–1461. doi:10.1111/epi.12242

Elger, C., Koepp, M., Trinka, E., Villanueva, V., Chaves, J., Ben-Menachen, E., et al. (2017). Pooled efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: data from four double-blind placebo-controlled pivotal phase III clinical studies. *CNS Neurosci. and Ther.* 23 (12), 961–972. doi:10.1111/cns.12765

Falcão, A., Maia, J., Almeida, L., Mazur, D., Gellert, M., and Soares-da-Silva, P. (2007). Effect of gender on the pharmacokinetics of eslicarbazepine acetate (BIA 2-093), a new voltage-gated sodium channel blocker. *Biopharm. and drug Dispos.* 28 (5), 249–256. doi:10.1002/bdd.549

Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., et al. (2017). Operational classification of seizure types by the international League against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia* 58 (4), 522–530. doi:10.1111/epi.13670

Galiana, G. L., Gauthier, A. C., and Mattson, R. H. (2017). Eslicarbazepine acetate: a new improvement on a classic drug family for the treatment of partial-onset seizures. *Drugs R&D* 17 (3), 329–339. doi:10.1007/s40268-017-0197-5

GBD 2021 Nervous System Disorders Collaborators (2024). Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet. Neurology* 23 (4), 344–381. doi:10.1016/S1474-4422(24)00038-3

Guedes, L., Vieira, M., Gama, H., Magano, D., Fernandes, M., Calero, P., et al. (2023). Thirteen years of experience with eslicarbazepine acetate in the United Kingdom and Republic of Ireland: a safety perspective. *Epileptic Disord. Int. epilepsy J. videotape* 25 (6), 803–814. doi:10.1002/epd2.20146

Gupta, D. K., Bhoi, S. K., Kalita, J., and Misra, U. K. (2015). Hyponatremia following esclicarbazepine therapy. *Seizure* 29, 11–14. doi:10.1016/j.seizure.2015.03.005

Halász, P., Cramer, J. A., Hodoba, D., Członkowska, A., Guekht, A., Maia, J., et al. (2010). Long-term efficacy and safety of eslicarbazepine acetate: results of a 1-year open-label extension study in partial-onset seizures in adults with epilepsy. *Epilepsia* 51 (10), 1963–1969. doi:10.1111/j.1528-1167.2010.02660.x

Hwang, S., Lee, S., Kim, E., Hwang, I., Cho, J. Y., Chung, J. Y., et al. (2022). The pharmacokinetic, safety, and tolerability profiles of eslicarbazepine acetate are comparable between Korean and White subjects. *Clin. Transl. Sci.* 15 (9), 2116–2126. doi:10.1111/cts.13344

Kaculini, C. M., Tate-Looney, A. J., and Seifi, A. (2021). The history of epilepsy: from ancient mystery to modern misconception. *Cureus* 13 (3), e13953. doi:10.7759/cureus.13953

Kay, L., Willems, L. M., Zöllner, J. P., Reif, P. S., Klein, K. M., Rosenow, F., et al. (2017). Eslicarbazepine acetate as a therapeutic option in a patient with carbamazepine-induced rash and HLA-A*31:01. *Seizure* 47, 81–82. doi:10.1016/j.seizure.2017.02.019

Keating, G. M. (2014). Eslicarbazepine acetate: a review of its use as adjunctive therapy in refractory partial-onset seizures. *CNS drugs* 28 (7), 583–600. doi:10.1007/s40263-014-0182-2

Lattanzi, S., Brigo, F., Cagnetti, C., Verrotti, A., Zaccara, G., and Silvestrini, M. (2018). Eslicarbazepine acetate in the treatment of adults with partial-onset epilepsy: an evidence-based review of efficacy, safety and place in therapy. *Core Evid.* 13, 21–31. doi:10.2147/CE.S142858

Lee, S. K., Lee, S. A., Hong, S. B., Cho, Y. W., Castilla-Fernández, G., Fonseca, M. M., et al. (2024). Long-term effects of adjunctive eslicarbazepine acetate in adult Asian patients with refractory focal seizures: *post hoc* analysis of a phase III trial. *Clin. Transl. Sci.* 17 (5), e13802. doi:10.1111/cts.13802

Ley, M., Principe, A., Jiménez-Conde, J., and Rocamora, R. (2015). Assessing long-term effects of eslicarbazepine acetate on lipid metabolism profile, sodium values and liver function tests. *Epilepsy Res.* 115, 147–152. doi:10.1016/j.eplepsyres.2015.06.013

Nevitt, S. J., Sudell, M., Cividini, S., Marson, A. G., and Tudur Smith, C. (2022). Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane database Syst. Rev.* 4 (4), CD011412. doi:10.1002/14651858.CD011412.pub4

Pitkänen, A., and Engel, J. (2014). Past and present definitions of epileptogenesis and its biomarkers. *Neurotherapeutics* 11 (2), 231–241. doi:10.1007/s13311-014-0257-2

Rocamora, R., Peltola, J., Assenza, G., McMurray, R., and Villanueva, V. (2020). Safety, tolerability and effectiveness of transition to eslicarbazepine acetate from carbamazepine or oxcarbazepine in clinical practice. *Seizure* 75, 121–128. doi:10.1016/j.seizure.2019.12.022

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., et al. (2017). ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia* 58 (4), 512–521. doi:10.1111/epi.13709

Shorvon, S. D., Trinka, E., Steinhoff, B. J., Holtkamp, M., Villanueva, V., Peltola, J., et al. (2017). Eslicarbazepine acetate: its effectiveness as adjunctive therapy in clinical trials and open studies. *J. neurology* 264 (3), 421–431. doi:10.1007/s00415-016-8338-2

Sperling, M. R., Abou-Khalil, B., Harvey, J., Rogin, J. B., Biraben, A., Galimberti, C. A., et al. (2015b). Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: results of a phase III, double-blind, randomized, placebo-controlled trial. *Epilepsia* 56 (2), 244–253. doi:10.1111/epi.12894

Sperling, M. R., Harvey, J., Grinnell, T., Cheng, H., Blum, D., and 045 Study Team (2015a). Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a randomized historical-control phase III study based in North America. *Epilepsia* 56 (4), 546–555. doi:10.1111/epi.12934

Thijs, R. D., Surges, R., O'Brien, T. J., and Sander, J. W. (2019). Epilepsy in adults. *Lancet (London, Engl.)* 393 (10172), 689–701. doi:10.1016/S0140-6736(18)32596-0

Verrotti, A., Loiacono, G., Rossi, A., and Zaccara, G. (2014). Eslicarbazepine acetate: an update on efficacy and safety in epilepsy. *Epilepsy Res.* 108 (1), 1–10. doi:10.1016/j.eplepsyres.2013.10.005

Zhang, C., Zuo, Z., Kwan, P., and Baum, L. (2011). *In vitro* transport profile of carbamazepine, oxcarbazepine, eslicarbazepine acetate, and their active metabolites by human P-glycoprotein. *Epilepsia* 52 (10), 1894–1904. doi:10.1111/j.1528-1167.2011.03140.x

Zhu, L. N., Chen, D., Tan, G., Wang, H. J., Chu, S., and Liu, L. (2020). The tolerability and safety profile of eslicarbazepine acetate in neurological disorders. *J. neurological Sci.* 413, 116772. doi:10.1016/j.jns.2020.116772

Zubiaur, P., Del Peso-Casado, M., Ochoa, D., Enrique-Benedito, T., Mejía-Abril, G., Navares, M., et al. (2021). ABCB1 C3435T, G2677T/A and C1236T variants have no effect in eslicarbazepine pharmacokinetics. *Biomed. and Pharmacother. = Biomedecine and Pharmacother.* 142, 112083. doi:10.1016/j.biopha.2021.112083

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 27 September 2024
DOI 10.3389/fphar.2024.1361443

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Magesh Muthu,
Wayne State University, United States
Carolina Dagli Hernandez,
State University of Campinas, Brazil

*CORRESPONDENCE
Shaohui Zhang,
zshtjmu@hotmail.com
Minyu Zhong,
zmy405645073@163.com

†These authors have contributed equally to this work

RECEIVED 26 December 2023
ACCEPTED 02 September 2024
PUBLISHED 27 September 2024

CITATION
Dong J, Li L, Deng T, Song H, Zhang S and Zhong M (2024) Interstitial lung disease associated with ALK inhibitors and risk factors: an updated comparative pharmacovigilance analysis.
Front. Pharmacol. 15:1361443.
doi: 10.3389/fphar.2024.1361443

Interstitial lung disease associated with ALK inhibitors and risk factors: an updated comparative pharmacovigilance analysis

Junli Dong[1,2], Lulu Li[1,2], Tiying Deng[1,2], Haibin Song[3,4], Shaohui Zhang[1,2]*† and Minyu Zhong[3,4]*†

[1]Department of Pharmacy, Traditional Chinese and Western Medicine Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2]Department of Pharmacy, Wuhan No.1 hospital, Wuhan, China, [3]Department of Oncology, Traditional Chinese and Western Medicine Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [4]Department of Oncology, Wuhan No.1 hospital, Wuhan, China

Background: Inhibitors of the anaplastic lymphoma kinase (ALK) gene mutation are first-line treatments in patients with ALK-positive lung cancer. The FDA label warns of the risk of interstitial lung disease (ILD) in patients receiving ALK TKIs. However, ILD associated with ALK TKIs is not fully understood. The aim of this study was to characterize the features of ALK TKI-related ILD and to explore risk factors for ALK TKI-related ILD.

Methods: FDA's Adverse Event Reporting System (FAERS) reports from 2011 Q1 to 2023 Q2 were extracted and combined. Standardized MedDRA queries (SMQs) were used to search for AEs at the preferred term (PT) level. Four algorithms were employed to quantify the signals of ILD associated with ALK TKIs. The risk of ILD was further analyzed using logistic regression.

Results: A total of 20,064 reports of ALK TKIs and 640 (3.2%) reports of ILD AEs were extracted. Significant disproportionality was detected in all five ALK TKIs. Interstitial lung disease and pneumonitis were the most common lung toxicities induced by ALK TKIs. Results of further analyses revealed a different spectrum of lung toxicity among the various TKIs. The median time to onset of ILD related to ALK TKIs was 53 days (Q1:12, Q3:209), and more than 70% of AEs occurred within the first 2 months. Logistic regression analysis and risk prediction model both showed that different ALK TKIs and their combination with PPIs, amlodipine, and magnesium oxide were independent risk factors for ILD ($p<0.05$).

Conclusion: ALK TKIs have different safety profiles regarding lung toxicity, which normally occurs within the first 2 months. Administration in combination with PPIs, amlodipine, and magnesium oxide significantly increases the risk of ILD. These results provide risk prediction for ILD related to ALK TKIs and support pharmacovigilance to promote safe prescribing in oncology.

KEYWORDS

FDA adverse event reporting system, ALK TKIs, interstitial lung disease, pharmacovigilance, adverse events

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths globally (Sung et al., 2021). A rearranged anaplastic lymphoma kinase (ALK) gene/fusion is a unique biomarker in NSCLC patients, presenting in approximately 3%–7% of cases (Horn and Pao, 2009). Over the past decade, the emergence of ALK tyrosine kinase inhibitors (TKIs) has significantly transformed the treatment landscape and outcomes for ALK+ NSCLC patients (Solomon et al., 2014; Shaw et al., 2014; Peters et al., 2017; Camidge et al., 2018; Shaw et al., 2020).

In 2011, the Food and Drug Administration (FDA) approved crizotinib as the first ALK TKI for patients with ALK+ NSCLC (Crino et al., 2011; Kim et al., 2012). This multi-targeted TKI demonstrated efficacy against MET (mesenchymal–epithelial transition, a prototypical receptor tyrosine kinase, whose alterations are drivers of human cancer), ALK, and ROS1 (ROS proto-oncogene 1, a receptor tyrosine kinase, which is involved in genetic rearrangement in a variety of human cancers), ALK, and ROS1, and was proven to improve progression-free survival (PFS) compared with traditional chemotherapy (median 10.9 months vs. 7.0 months; HR 0.45; 95% CI 0.35–0.60; $p < 0.001$) in patients with ALK-positive lung cancer (Shaw et al., 2103). However, crizotinib has been widely replaced by next-generation TKIs in first-line therapy due to its poor intracranial activity and shorter PFS (Gadgeel et al., 2120; Crinò et al., 2016). Currently, second-generation ALK TKIs have been developed, including ceritinib, alectinib, and brigatinib, which address the crizotinib resistance and offer better blood–brain barrier (BBB) penetration in patients with CNS involvement (Mok et al., 2011; Ou et al., 2016; Dong-Wan et al., 2017; D Ross Camidge et al., 2018). Alectinib exhibits longer PFS than crizotinib (median 34.8 months vs. 10.9 months) (Camidge et al., 2019); however, it has also been associated with the problem of drug resistance (Gainor et al., 2016). Lorlatinib, an ATP-competitive macrocyclic small-molecule inhibitor, was developed to resolve the problem of resistant mutations that occur during treatment with the first second-generation ALK TKIs (Abbattista et al., 2019; Zou et al., 2015). To date, the FDA has approved five ALK TKIs (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib) as the first-line and follow-up treatment drugs for patients with ALK+ NSCLC (Pirker and Filipits, 2019).

Treatment with ALK TKIs is normally well-tolerated. However, the patterns and frequency of side effects differ among ALK TKIs (Omar et al., 2021), which may be a key consideration for physicians when choosing a medication. Interstitial lung disease (ILD) is a heterogeneous group of parenchymal lung diseases with high morbidity and mortality (Antoniou et al., 2014). Several risk factors for ILD also coexist, including anticancer drugs (Spagnolo et al., 2022). A system study found that ALK TKIs showed significant respiratory system toxicity, with pneumonia being the most common serious adverse event with the highest incidence (Hou et al., 2019). Recently, a report characterized interstitial pneumonitis (IP) associated with ALK TKIs in the real world and indicated a fatal risk of IP induced by ALK TKIs (Ma et al., 2023; Zhao et al., 2023). The FDA released a hazard alert on ALK TKIs for ILD; however, a comprehensive evaluation of ILD induced by five ALK TKIs and the risks of ILD was still inadequate.

Therefore, it is important to explore the clinical characteristics and risk factors of ALK TKI-induced ILD to ensure appropriate drug selection. The aim of this study was to comprehensively characterize ILD with ALK TKIs in real-world patterns by investigating the FDA's Adverse Event Reporting System (FAERS) and to evaluate the risk of ILD. A risk model for predicting ILD with ALK TKIs was constructed using logistic regression, and risk factors were determined for medication decisions.

Materials and methods

Data sources

This observational, retrospective pharmacovigilance analysis was conducted using data from adverse event reports recorded in the FAERS database, which are available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The data downloaded were limited to the period from 1 January 2011 to June 2023 (the most recent available data), which comprised seven tables named "DEMO," "DRUG," "REAC," "OUTC," "RPSR," "THER," and "INDI". The "DEMO" tables were used in the missing value imputation and case de-duplication steps. AEs were coded according to the Medical Dictionary for Regulatory Activities Terminology (MedDRA) at the preferred term (PT) level. For signal detection, the drug was considered the primary suspect.

Data processing

Data processing included missing value imputation, case de-duplication, and standardization (Supplementary Figure S1), with reference to the study by Nigam H. Shah et al. (Banda et al., 2016). First, a single missing value imputation was performed for four fields, including event date, age, sex, and reporter country. For other versions of the same case, the maximum demographic values from the fully populated case versions were employed to fill in single missing values. Then, a two-step de-duplication was performed. If all available cases shared identical values for case ID, initial/follow-up code, case event date, age, sex, reporter country, drug names, and outcomes, the most recent case version was retained. Based on four demographic data fields (event date, age, sex, and reporter country), data from the DEMOyyQq tables were de-duplicated and linked to DRUG, INDI, and REAC, respectively, by primaryid,. The adverse events in which ALK inhibitors were the primary suspect were included, while the cases with ages less than 18 years were excluded. Finally, data from DRUG, INDI, and REAC were standardized by using the Observational Health Data Sciences and Informatics (OHDSI) Vocabulary 5.0 and the Medical Dictionary for Regulatory Activities (MedDRA). We screened available standardized MedDRA queries (SMQs) for "Interstitial lung disease (20000042)." Associated PTs were acute interstitial pneumonitis (10066728), idiopathic interstitial pneumonia (10078268), interstitial lung abnormality (10087834), interstitial lung disease (10022611), pneumonitis (10035742), pulmonary fibrosis (10037383), etc. Supplementary Table S1 shows the full list of PTs within the ILD SMQs.

TABLE 1 Demographics related to ILD reported in patients receiving ALK TKIs.

	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib	*p*-Value
Total cases, n (%)	294 (45.9)	51 (8.0)	157 (24.5)	94 (14.7)	44 (6.9)	
Age (years), mean ± SD	61.9 ± 13.3	56.9 ± 14.8	63.6 ± 12.0	63.3 ± 13.1	58.9 ± 13.9	0.495
18–64	127	23	53	34	23	
65–84	108	14	60	32	12	
>85	4	0	1	2	1	
Unknown	55	14	43	26	8	
Weight (kg), mean ± SD	61.6 ± 17.2	70.2 ± 18.0	67.1 ± 19.5	64.0 ± 16.0	66.1 ± 17.1	0.211
Sex, n (%)						0.066
Male	131 (44.6)	21 (41.2)	80 (51.0)	30 (31.9)	25 (56.8)	
Female	140 (47.6)	23 (45.1)	62 (39.5)	48 (51.1)	16 (36.4)	
Unknown	23 (7.8)	7 (13.7)	15 (9.5)	16 (17.0)	3 (6.8)	
Report source, n (%)						<0.001
Physician	191 (65.0)	13 (25.5)	105 (66.9)	58 (61.7)	28 (63.6)	
Pharmacist	25 (8.5)	3 (5.9)	13 (8.3)	6 (6.4)	4 (9.1)	
Consumer	35 (11.9)	18 (35.3)	20 (12.7)	14 (14.9)	6 (13.6)	
Other	42 (14.3)	16 (31.4)	19 (12.1)	16 (17.0)	5 (11.4)	
Unknown	1 (0.3)	1 (2.0)	0 (0)	0 (0)	1 (2.3)	
Outcome						<0.001
Hospitalization	166 (35.0)	24 (40.7)	71 (53.0)	56 (55.4)	20 (33.3)	
Disability	10 (2.1)	1 (1.7)	1 (0.7)	1 (1.0)	0 (0)	
Life-threatening	51 (10.8)	6 (10.2)	13 (9.7)	7 (6.9)	6 (10.0)	
Death	98 (20.7)	11 (18.6)	18 (13.4)	15 (14.9)	14 (23.3)	
Other	149 (31.4)	17 (28.8)	31 (23.1)	22 (21.8)	20 (33.3)	

TABLE 2 Signal detection of ILD for each ALK inhibitor at the SMQ level.

Drug	ROR (95% CI)	PRR (x^2)	IC(IC025)	EBGM(95% CI)
ALK TKIs	4.58 (4.23, 4.96)	4.47 (1723.87)	2.15 (1.99, 2.33)	4.45 (4.16, 4.75)
Crizotinib	4.71 (4.2, 5.3)	4.59 (829.53)	2.2 (1.95, 2.47)	4.58 (4.16, 5.05)
Ceritinib	3.81 (2.88, 5.03)	3.73 (102.68)	1.9 (1.44, 2.51)	3.73 (2.96, 4.71)
Alectinib	4.84 (4.13, 5.68)	4.71 (461.36)	2.23 (1.9, 2.62)	4.7 (4.12, 5.37)
Brigatinib	6.38 (5.19, 7.85)	6.15 (407.55)	2.62 (2.13, 3.22)	6.14 (5.16, 7.3)
Loratinib	2.55 (1.89, 3.44)	2.52 (40.72)	1.33 (0.99, 1.8)	2.52 (1.97, 3.24)

Statistical analyses

The measurement data were characterized by median and interquartile ranges, while enumeration data were presented as numbers and percentages. The correlation between an AE and the drug was investigated by disproportionality analysis, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the information component (IC), and the empirical Bayes geometric mean (EBGM). Odds ratios (ORs) were calculated using a logistic regression model to assess the association between potential risk factors and ILD in patients receiving ALK TKIs. Additionally, a nomogram was constructed to estimate the probability of developing ILD in NSCLC patients receiving different ALK TKIs. Each variable corresponds to a line segment with scales marked, which represents the range of values that the variable can take, and the length of the line segment reflects the contribution of that factor to the occurrence of ILD.

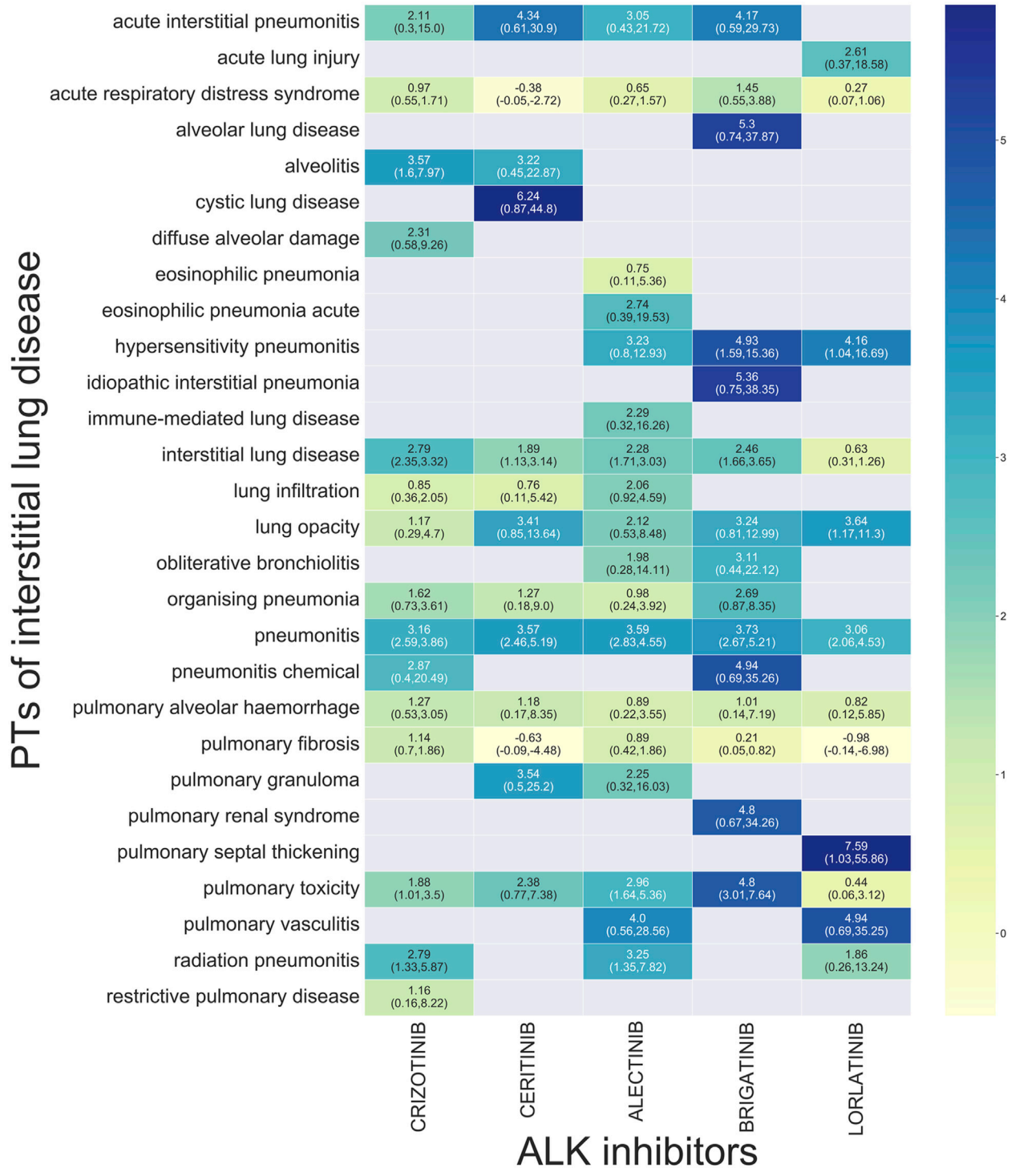


FIGURE 1
Signal profiles of ILD for each ALK inhibitor.

Results

Descriptive analysis

From January 2011 to June 2023, 15,656,531 reports were recorded in FAERS. After excluding duplicate cases (2,126,495) and aberrant cases with age less than 18 years (439,205), 13,090,831 reports were included in the present analysis. Of these, 20,064 AE reports were related to ALK TKIs (0.15%), including 9,130 for crizotinib, 1,929 for ceritinib, 4,673 for alectinib, 2,138 for brigatinib and 2,492 for lorlatinib (Supplementary Table S2).

AE reports of ILD among ALK TKI users accounted for 3.2% (640/20,064) of the total AEs related to ALK TKIs; of these, 45.9%

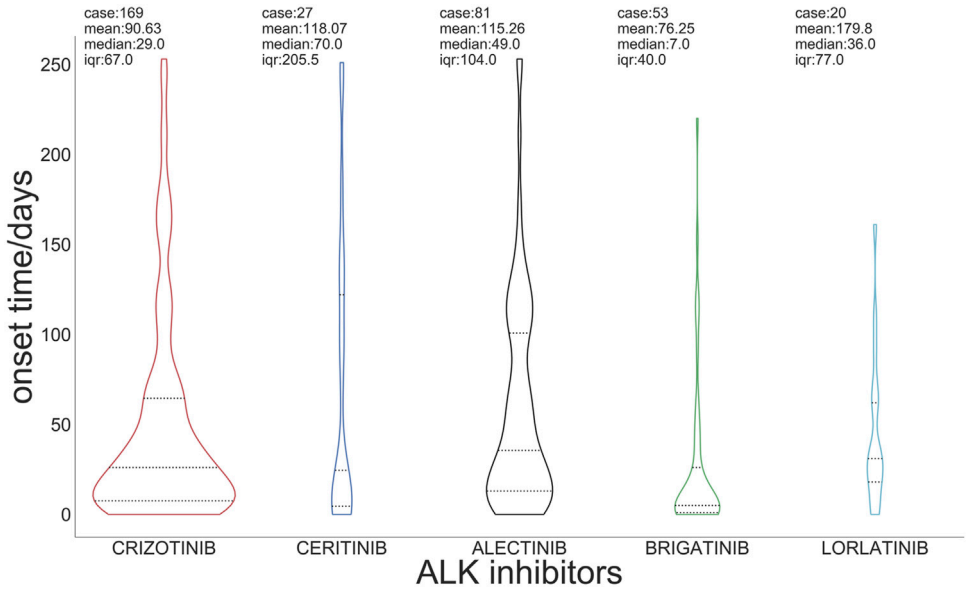


FIGURE 2
Time to onset of interstitial lung disease induced by ALK inhibitors.

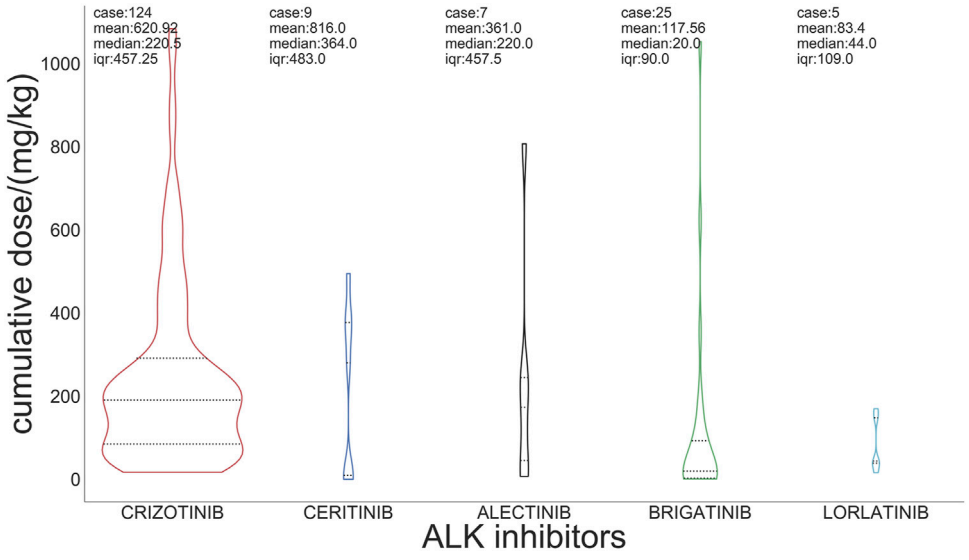


FIGURE 3
Cumulative dose of ALK inhibitors associated with ILD.

were related to crizotinib, 8.0% to ceritinib, 24.5% to alectinib, 14.7% to brigatinib, and 6.9% to lorlatinib. The average age of ALK TKI users differed: for alectinib and brigatinib, it was 63 years, and the lowest mean age for ceritinib was 56 years. Comparable percentages of male and female patients were observed for all five drugs. Of note, the majority of reports were submitted by physicians with the highest percentage of reports for crizotinib (65.0%), alectinib (66.9%), brigatinib (61.7%), and lorlatinib (63.6%), or by consumers with the highest percentage of reports for ceritinib (35.3%). Hospitalization and death were recorded in 40.7% and 18.8% of cases, respectively (Table 1).

Disproportionality analysis

As shown in Table 2, the signal of ILD was detected in all ALK TKIs. Treatment with ALK TKIs was significantly associated with ILD, with ROR (4.58, 95% CI 4.23–4.96), PRR (4.47), IC (2.15, IC025 1.99–2.33), and EBGM (4.45, 95% CI 4.16–4.75). Brigatinib reported the highest ROR for ILD (6.38, 95%CI 5.19–7.85) with alectinib (4.84, 95% CI 4.13–5.68) and crizotinib (4.71, 95%CI 4.2–5.3) following.

Disproportionality analysis for subgroups of ILD showed that 28 preferred terms (PTs) were significantly associated with ALK

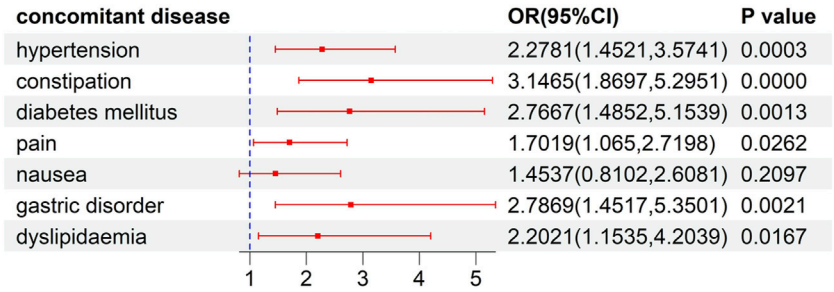


FIGURE 4
The risk of ILD induced by concurrent diseases.

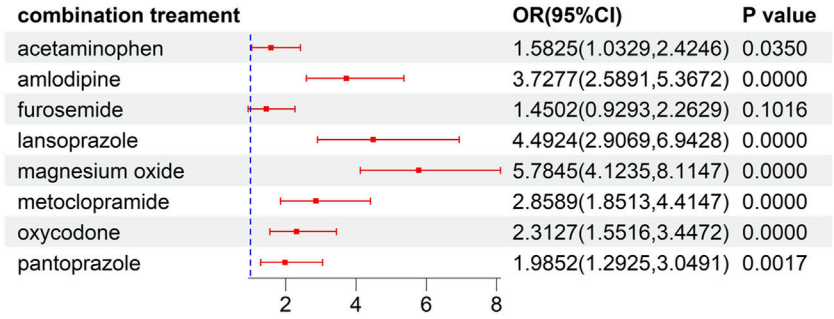


FIGURE 5
The risk of ILD induced by combination treatment.

TKIs overall. Twelve PTs were significantly associated with crizotinib and ceritinib, and seven PTs were associated with alectinib and brigatinib. In contrast, only five PTs were associated with lorlatinib. Our analysis found a significant signal for pneumonitis for all analyzed ALK TKIs. Concerning acute interstitial pneumonitis, a significant signal was found for all ALK TKIs, with the exception of lorlatinib. Only crizotinib was associated with acute eosinophilic pneumonia and immune-mediated lung disease. Signals of alveolar lung disease, idiopathic interstitial pneumonia, and pulmonary-renal syndrome were only found for ceritinib. Only brigatinib was associated with diffuse alveolar damage. Only lorlatinib was associated with a significant ROR for acute lung injury and pulmonary septal thickening (Figure 1).

Time of onset and cumulative dose of ALK TKI-associated ILD

Of the patients who developed ILD, 56.8% developed ILD within 4 weeks of initiating ALK TKI therapy, and 70.4% developed it within 8 weeks. For crizotinib, 56.8% and 72.3% of cases developed ILD within 4 and 8 weeks, respectively. For ceritinib, 59.1% of cases developed ILD within 8 weeks. For alectinib, 44.4% and 61.1% of cases developed ILD within 4 and 8 weeks, respectively. For brigatinib, 77.6% and 85.7% of cases developed ILD within 4 and 8 weeks, respectively. For lorlatinib, 47.1% and 64.7% of cases developed ILD within 4 and 8 weeks, respectively (Supplementary Table S3).

Figure 2 presents the box plots and medians of the onset time of ILD with regard to ALK TKIs. The median onset time of ILD related to total ALK TKIs was 53 days (Q1:12, Q3:209). The median time of onset was 29 days for crizotinib, 70 days for ceritinib, 49 days for alectinib, 7 days for brigatinib, and 36 days for lorlatinib (Supplementary Table S3).

For the incidence of ILD, the median cumulative dose of crizotinib was 220 mg/kg, and the doses of ceritinib, alectinib, brigatinib, and lorlatinib were 364 mg/kg, 220 mg/kg, 20 mg/kg, and 44 mg/kg, respectively (Figure 3).

Risk factors for developed ILD and nomogram

This analysis of risk factors for developed ILD was conducted on patients receiving ALK TKI therapy. The results of univariate logistic regression, as illustrated in Supplementary Table S4, indicated that female gender, concomitant disease, and concomitant drug significantly increased the risk of the developed ILD ($P<0.05$). To further explore the effects of concomitant factors on the developed ILD, we observed that patients with gastric disorder, pain, diabetes mellitus,

TABLE 3 Multivariable logistic regression analysis of drug-induced ILD.

Characteristics	Odds ratio	95% CI	*p*-Value
Age	3.087	2.579, 3.695	0.191
Sex	2.160	1.826, 2.555	0.002
Concomitant diseases			
Hypertension	2.541	1.444, 4.474	0.809
Diabetes mellitus	4.541	2.201, 9.372	0.262
Dyslipidemia	3.080	1.420, 6.682	0.766
Gastric disorder	6.018	2.969, 12.198	0.105
Pain	3.235	1.878, 5.573	0.563
Nausea	2.157	1.113, 4.180	0.436
Constipation	2.934	1.570, 5.483	0.818
Combined drug category			
Amlodipine	10.129	6.657, 15.414	<0.001
Furosemide	2.623	1.649, 4.171	0.878
Magnesium oxide	33.730	22.511, 50.541	<0.001
Lansoprazole	9.759	6.001, 15.872	0.001
Pantoprazole	4.943	3.139, 7.783	0.043
Acetaminophen	2.489	1.555, 3.986	0.701
Oxycodone	3.548	2.265, 5.558	0.302
Metoclopramide	4.374	2.660, 7.192	0.125
Crizotinib	4.939	3.525, 6.921	0.007
Ceritinib	4.022	2.605, 6.212	0.136
Alectinib	5.409	3.789, 7.720	0.004
Brigatinib	8.086	5.490, 11.909	<0.001

hypertension, dyslipidemia, and constipation might be at a higher risk than those without concomitant diseases (Figure 4). Meanwhile, the risks of ILD associated with ALK inhibitors in combination with acetaminophen, amlodipine, lansoprazole, magnesium oxide, metoclopramide, oxycodone, and pantoprazole were higher than the risks of ALK inhibitor monotherapy (Figure 5).

According to multivariate logistic regression analysis with adjustment for confounding variables, as shown in Table 3, amlodipine, magnesium oxide, lansoprazole, and pantoprazole had a significant effect on the development of ILD in patients receiving ALK TKIs ($P<0.05$).

Based on the results of univariate and multivariate logistic regression, sex, concomitant diseases, and concomitant drugs were included in the nomogram model. Figure 6 represents the nomogram for predicting the risk of developing ILD in patients receiving ALK TKIs. The results suggested that women were at higher risk than men. Between the two PPIs, lansoprazole posed a greater risk of ILD than pantoprazole. Furthermore, brigatinib caused the highest risk among five ALK TKIs, whereas ceritinib and loratinib did not significantly contribute to the risk of ILD.

Discussion

Pulmonary toxicities induced by targeted anticancer therapy are overall infrequent but potentially life-threatening (Teuwen et al., 2015). Especially combined with risk factors, the management of pulmonary toxicities can become a substantial therapeutic challenge and significantly influence the overall prognosis of cancer patients.

ALK TKI has become the standard treatment for NSCLC. However, the safety profile of each ALK TKI is different with regard to pulmonary toxicity. The retrospective studies indicated that the median age of diagnosis for ALK+ NSCLC was approximately 60 years (Auliac et al., 2017; Lim et al., 2017), and these older patients have comorbidities and polypharmacy (Decoster and Schallier, 2019), which may increase TKI-mediated toxicities during long-term treatment. Although the present study characterizes a different toxicity profile of ALK TKIs regarding ILD (Zhao et al., 2023), a comprehensive risk evaluation of ILD induced by ALK TKIs was still inadequate. Therefore, our pharmacovigilance analysis further illuminated the complex safety profile of ALK TKIs and independent risk factors by characterizing global data from the FAERS database.

ILD is a fatal but less frequently occurring category of adverse reactions. The FAERS database showed that ILD occurred in 3.2% (1.8%–4.4%) of the reports treated with ALK TKIs from 2011 to 2023. The proportion of ILD was the highest in brigatinib reports (4.4%) and lowest in lorlatinib reports (1.8%), which is consistent with the ALTA-1L clinical trials (Camidge et al., 2018) (D Ross Camidge et al., 2020) and FDA labeling (Fdalabel, 2023).

All five ALK TKIs could induce pulmonary toxicity; however, the adverse event profiles at the PT level were different between different ALK TKIs. Brigatinib was associated with the strongest and most robust disproportionality signal of ILD, which was consistent with the evidence from a systematic study (Pellegrino et al., 2018). All ALK TKIs present pneumonitis and lung opacities, but alectinib was associated with more PTs than acute eosinophilic pneumonia, and lung infiltration was not shown with other inhibitors. The mechanism of ILD induced by ALK TKI is not fully understood. Research has demonstrated that cross-reactivity with other kinases, such as EGFR, MET, and ROS1, may significantly contribute to the inhibition of normal signaling and impairment of the lung epithelium (Hwang et al., 2018; Harada et al., 2011). Gurule et al. speculated that TKI may be related to the disruption of normal epithelial tissue homeostasis and the induction of an innate inflammatory immune response (Gurule and Heasley, 2018). The mechanism underlying superimposed lung damage may be complex and must be further explored.

More than 70% of cases of ALK TKI-related ILD occurred within the first 2 months of initiating ALK TKI treatments. However, the median time to onset of ILD varied among ALK TKIs, with ceritinib exhibiting a notably longer delay, whereas brigatinib displayed the shortest time to onset. In clinical trials, early-onset pulmonary events were observed in the brigatinib group, especially within the first 3–8 days of treatment (Camidge et al., 2018). This indicates that early monitoring for pulmonary toxicity associated with brigatinib is necessary, especially for the prompt diagnosis of signs and typical symptoms such as dyspnea, hypoxia, and dry cough.

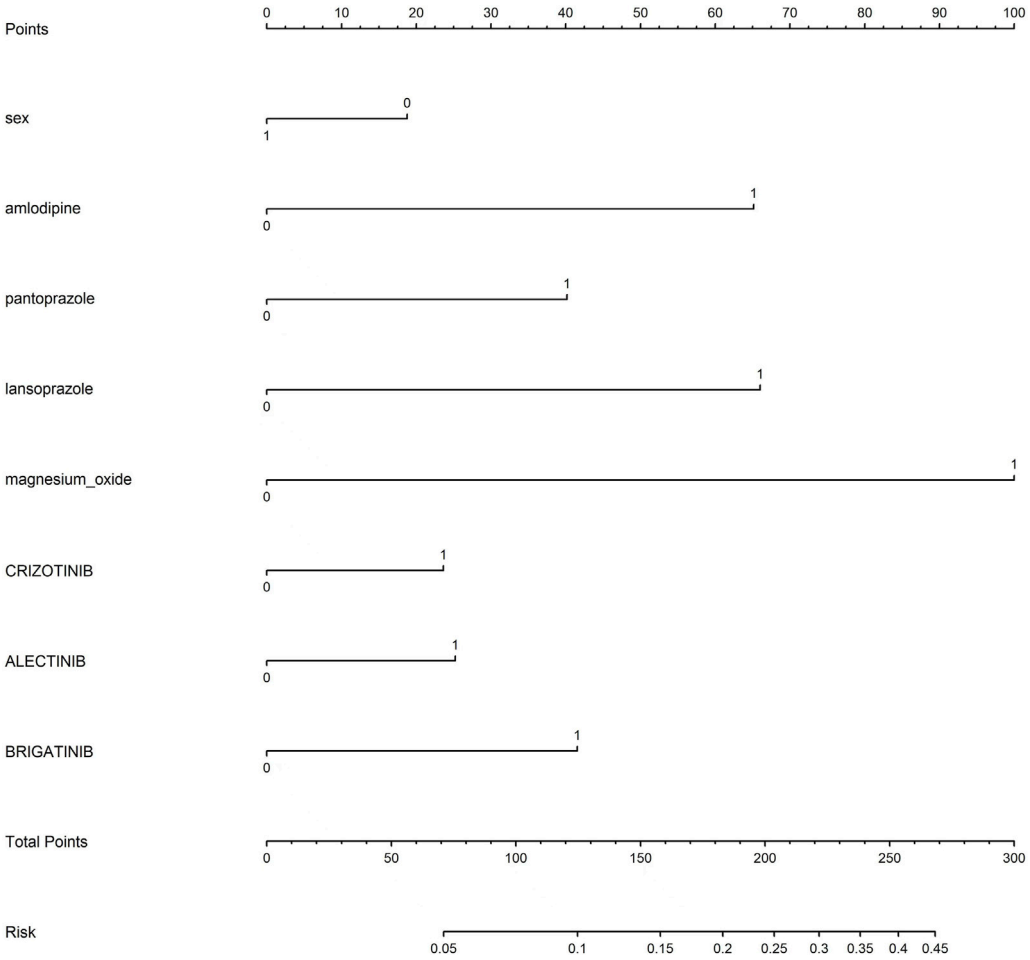


FIGURE 6
Nomogram for predicting interstitial lung disease in patients receiving ALK TKIs.

In a further investigation of factors affecting ALK TKI-related ILD, we observed a higher risk of ALK TKI-related ILD in the female group. A retrospective study showed that sex has no impact on lung toxicity in NSCLC patients exposed to ALK TKIs (Hwang et al., 2019), but another study suggested that ILD onset in patients receiving crizotinib was affected by sex in the univariate model (Gemma et al., 2019). The controversy regarding the effect of sex on ILD in ALK TKIs may be due to a variety of reasons, including variations in sampling, disparities between study cohorts, and different adjustments for confounding variables.

To date, no study has examined how coadministration with other medications influences the development of ILD with ALK TKIs. We observed that amlodipine, PPIs, and magnesium oxide were significantly associated with an increased risk of ALK TKI-related ILD. There was evidence indicating an increased risk of ILD in patients receiving lansoprazole (Kambara Kh et al., 2020; Atkins et al., 2014). According to the report by Kawamura et al., patients receiving a concomitant PPI demonstrated a higher incidence and risk of acute exacerbation of interstitial pneumonia (Kawamura et al., 2019). These studies indicate a strong correlation between PPI use and the occurrence of ILD. There was little evidence of a relationship between amlodipine, magnesium oxide, and ILD. However, amlodipine has been reported to improve the anticancer effects of gefitinib and regorafenib (Fu et al., 2022; Alandağ et al., 2022). The mechanism of the synergistic anticancer effect was that amlodipine can enhance the intracellular uptake of anticancer drugs (Li et al., 2006) as a Ca^{2+} channel blocker. Therefore, we speculated that the cytotoxicity of the targeted drug was probably potentiated by amlodipine, which resulted in an increased risk of ADR with concomitant use of amlodipine in patients receiving targeted therapy. These findings underscore the need for ongoing epidemiologic monitoring and urgent clarification through large-scale, population-based studies in addition to specialized RCTs.

A model to predict the risk of ILD after administration of ALK TKIs in NSCLC patients was developed based on univariate and multivariable regression. The risk of ILD caused by ALK inhibitors is approximately 3%, but we could observe that the risk of developing ILD increased to approximately 10% in a female lung cancer patient who was receiving treatment with brigatinib and concurrently taking amlodipine, as determined by the accumulation of individual risk factors. The results indicate that patients, particularly women receiving ALK inhibitors, need to avoid or cautiously combine the use of drugs with a higher risk of

developing ILD. The predictors used in our study are available in the clinic, including sex and concomitant drugs, such as amlodipine prescribed to patients with hypertension and PPIs used by patients with gastric ulcers. The model allows physicians to assess the risk of ILD in cancer patients with concomitant drugs and make treatment decisions.

Our study has certain limitations. First, as a spontaneous reporting system, the FAERS database often contains incomplete or missing information and lacks data on population exposure. This precluded us from providing incidence rates of ADR (Bate and Evans, 2009). Furthermore, insufficient clinical features (such as body mass and patient history) and instrumental assessments (e.g., CT imaging and laboratory parameters) to support disease diagnosis, severity assessment, and prediction of potential ILD risk limit in-depth analysis and understanding of adverse events. Finally, the contribution of ALK TKIs to ILD-related deaths cannot be determined but is worth confirmation in a large-scale prospective study. Nonetheless, the results of our study highlight an increased risk of ILD associated with ALK TKIs for the treatment of NSCLC and provide a better basis for understanding potential ILD associated with ALK TKIs, which helps clinicians pay attention to risk management.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

JD: conceptualization, writing–original draft, and writing–review and editing. LL: writing–original draft. TD: writing–original draft. HS: writing–review and editing. SZ: project administration and writing–review and editing. MZ: writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Wuhan Pharmaceutical Association. (Project No: WHPA202305016).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1361443/full#supplementary-material

References

Abbattista, H. T., Satouchi, M., Ross Camidge, D., Kao, S., Chiari, R., Gadgeel, S. M., et al. (2019). ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. *J. Clin. Oncol.* 37, 1370–1379. doi:10.1200/JCO.18.02236

Alandağ, C., Karaman, E., and Yüce, E. (2022). Amlodipine improves the outcomes of regorafenib in metastatic colorectal cancer. *Anti-Cancer Drugs* 33, 389–393. doi:10.1097/CAD.0000000000001273

Antoniou, K. M., Margaritopoulos, G. A., Tomassetti, S., Bonella, F., Costabel, U., and Poletti, V. (2014). Interstitial lung disease. *Eur. Respir. Rev.* 23, 40–54. doi:10.1183/09059180.00009113

Atkins, C., Maheswaran, T., Rushbrook, S., and Kamath, A. (2014). Lansoprazole-induced acute lung and liver injury: a case report. *Int. J. Clin. Pharmacol. Ther.* 52, 1102–1104. doi:10.5414/CP202110

Auliac, J.-B., Monnet, I., Dubos-Arvis, C., Chiappa, A. M., Baize, N., Bota, S., et al. (2017). Non-small-cell lung cancer (NSCLC) harboring ALK translocations: clinical characteristics and management in a real-life setting: a French retrospective analysis (GFPC 02–14 study). *Target. Oncol.* 12, 833–838. doi:10.1007/s11523-017-0520-7

Banda, J. M., Evans, L., Vanguri, R. S., Tatonetti, N. P., Ryan, P. B., and Shah, N. H. (2016). A curated and standardized adverse drug event resource to accelerate drug safety research. *Sci. Data* 3, 160026. doi:10.1038/sdata.2016.26

Bate, A., and Evans, S. J. W. (2009). Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol. Drug Saf.* 18, 427–436. doi:10.1002/pds.1742

Camidge, D. R., Dziadziuszko, R., Peters, S., Mok, T., Noe, J., Nowicka, M., et al. (2019). Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX study. *J. Thorac. Oncol.* 14, 1233–1243. doi:10.1016/j.jtho.2019.03.007

Camidge, D. R., Kim, H. R., Ahn, M. J., Yang, J. C. H., Han, J. Y., Lee, J. S., et al. (2018). Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* 379, 2027–2039. doi:10.1056/NEJMoa1810171

Crinò, L., Ahn, M.-J., De, M. F., Groen, H. J., Wakelee, H., Hida, T., et al. (2016). Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non–small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. *J. Clin. Oncol.* 34, 2866–2873. doi:10.1200/jco.2015.65.5936

Crino, L., Kim, D., and GjjjoCO, R. (2011). Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005. *J. Clin. Oncol.* 29, 7514. doi:10.1200/jco.2011.29.15_suppl.7514

Decoster, L., and Schallier, D. (2019). Treatment of older patients with advanced non-small cell lung cancer: a challenge. *J. Geriatric Oncol.* 10, 528–533. doi:10.1016/j.jgo.2018.09.008

Dong-Wan, K. M. T., Ahn, M.-Ju, Reckamp, K. L., Hansen, K. H., Kim, S.-We, Huber, R. M., et al. (2017). Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J. Clin. Oncol.* 35, 2490–2498. doi:10.1200/JCO.2016.71.5904

D Ross Camidge, D.-W. K., Tiseo, M., Tiseo, M., Langer, C. J., Ahn, M. J., Shaw, A. T., et al. (2018). Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain metastases in two clinical trials. *J. Clin. Oncol.* 36, 2693–2701. doi:10.1200/JCO.2017.77.5841

D Ross Camidge, H. R. K., Ahn, M.-Ju, Ahn, M. J., Yang, J. C. H., Han, J. Y., Hochmair, M. J., et al. (2020). Brigatinib versus crizotinib in advanced ALK inhibitor-

naive ALK-positive non-small cell lung cancer: second interim analysis of the phase III ALTA-1L trial. *J. Clin. Oncol.* 38, 3592–3603. doi:10.1200/JCO.20.00505

Fdalabel (2023). Lorlatinib. Available at: https://nctr-crs.fda.gov/fdalabel/ui/spl-summaries/criteria/380270.

Fu, B., Dou, X., Zou, M., Lu, H., Wang, K., Liu, Q., et al. (2022). Anticancer effects of amlodipine alone or in combination with gefitinib in non-small cell lung cancer. *Front. Pharmacol.* 13, 902305. doi:10.3389/fphar.2022.902305

Gadgeel, S. P. S., Mok, T., Shaw, A. T., Kim, D. W., Ou, S. I., Pérol, M., et al. (2120). Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study2018. *Ann. Oncol.* doi:10.1093/annonc/mdy405

Gainor, J. F., Dardaei, L., Yoda, S., Friboulet, L., Leshchiner, I., Katayama, R., et al. (2016). Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov.* 6, 1118–1133. doi:10.1158/2159-8290.CD-16-0596

Gemma, A., Kusumoto, M., Kurihara, Y., Masuda, N., Banno, S., Endo, Y., et al. (2019). Interstitial lung disease onset and its risk factors in Japanese patients with ALK-positive NSCLC after treatment with crizotinib. *J. Thorac. Oncol.* 14, 672–682. doi:10.1016/j.jtho.2018.11.022

Gurule, N. J., and Heasley, L. E. (2018). Linking tyrosine kinase inhibitor-mediated inflammation with normal epithelial cell homeostasis and tumor therapeutic responses. *Cancer Drug Resist.* 1, 118–125. doi:10.20517/cdr.2018.12

Harada, C., Kawaguchi, T., Ogata-Suetsugu, S., Yamada, M., Hamada, N., Maeyama, T., et al. (2011). EGFR tyrosine kinase inhibition worsens acute lung injury in mice with repairing airway epithelium. *Am. J. Respir. Crit. Care Med.* 183, 743–751. doi:10.1164/rccm.201002-0188OC

Horn, L., and Pao, W. (2009). EML4-ALK: honing in on a new target in non-small-cell lung cancer. *J. Clin. Oncol.* 27, 4232–4235. doi:10.1200/JCO.2009.23.6661

Hou, H., Sun, D., Liu, K., Jiang, M., Liu, D., Zhu, J., et al. (2019). The safety and serious adverse events of approved ALK inhibitors in malignancies: a meta-analysis. *Cancer Manag. Res.* 11, 4109–4118. doi:10.2147/CMAR.S190098

Hwang, A., Iskandar, A., and Dasanu, C. A. (2018). Successful re-introduction of alectinib after inducing interstitial lung disease in a patient with lung cancer. *J. Oncol. Pharm. Pract.* 25, 1531–1533. doi:10.1177/1078155218820580

Hwang, H. J., Kim, M. Y., Choi, C.-M., and Lee, J. C. (2019). Anaplastic lymphoma kinase inhibitor related pneumonitis in patients with non-small cell lung cancer: clinical and radiologic characteristics and risk factors. *Medicine* 98, e18131. doi:10.1097/MD.0000000000018131

Kambara Kh, H., Nakatsuji, T., Ueno, S., Oyama, S., Inada, A., Niinomi, I., et al. (2020). Safety profile of vonoprazan compared with proton pump inhibitors: insight from a pharmacovigilance study2020. *Pharmazie.*, 75, 527–530.

Kawamura, K., Ichikado, K., Ichiyasu, H., Anan, K., Yasuda, Y., Suga, M., et al. (2019). Acute exacerbation of chronic fibrosing interstitial pneumonia in patients receiving antifibrotic agents: incidence and risk factors from real-world experience. *BMC Pulm. Med.* 19, 113. doi:10.1186/s12890-019-0880-0

Kim, D. W., Ahn, M. J., Shi, Y., Pas, T. M. D., and Shaw, A. T. (2012). Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer NSCLC. *J. Clin. Oncol.* 30 (15_suppl), 7533–7533.

Li, X., Ruan, G.-R., Lu, W.-L., Hong, H. Y., Liang, G. W., Zhang, Y. T., et al. (2006). A novel stealth liposomal topotecan with amlodipine: apoptotic effect is associated with deletion of intracellular Ca2+ by amlodipine thus leading to an enhanced antitumor activity in leukemia. *J. Control. Release* 112, 186–198. doi:10.1016/j.jconrel.2006.01.007

Lim, S. H., Yoh, K. A., Lee, J. S., Ahn, M. J., Kim, Y. J., Kim, S. H., et al. (2017). Characteristics and outcomes of ALK+ non-small cell lung cancer patients in Korea. *Asia-Pacific J. Clin. Oncol.* 13, e239–e245. doi:10.1111/ajco.12645

Ma, Z., Pei, J., Zhang, Y., Li, H., Sun, D., Zhang, Y., et al. (2023). Interstitial pneumonitis associated with EGFR/ALK tyrosine kinase inhibitors used in non-small cell lung cancer: an observational, retrospective, pharmacovigilance study. *Expert Opin. Drug Saf.* 22, 237–242. doi:10.1080/14740338.2022.2110235

Mok, T. S., Spigel, D. R., and Felip, E. (2011). ASCEND-2: a single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ).

Omar, N. E., Fahmy Soliman, A. I., Eshra, M., Saeed, T., Hamad, A., and Abou-Ali, A. (2021). Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS). *ESMO Open* 6, 100315. doi:10.1016/j.esmoop.2021.100315

Ou, S. H., Ahn, J. S., De Petris, L., Govindan, R., Yang, J. C. H., Hughes, B., et al. (2016). Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J. Clin. Oncol.* 34, 661–668. doi:10.1200/jco.2015.63.9443

Pellegrino, B., Facchinetti, F., Bordi, P., Silva, M., Gnetti, L., and Tiseo, M. (2018). Lung toxicity in non–small-cell lung cancer patients exposed to ALK inhibitors: report of a peculiar case and systematic review of the literature. *Clin. Lung Cancer* 19, e151–e161. doi:10.1016/j.cllc.2017.10.008

Peters, S., Camidge, D. R., Shaw, A. T., Gadgeel, S., Ahn, J. S., Kim, D. W., et al. (2017). Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* 377, 829–838. doi:10.1056/NEJMoa1704795

Pirker, R., and Filipits, M. (2019). From crizotinib to lorlatinib: continuous improvement in precision treatment of ALK-positive non-small cell lung cancer. *ESMO Open* 4, e000548. doi:10.1136/esmoopen-2019-000548

Shaw, A. T., Bauer, T. M., de Marinis, F., Felip, E., Goto, Y., Liu, G., et al. (2020). First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N. Engl. J. Med.* 383, 2018–2029. doi:10.1056/NEJMoa2027187

Shaw, A. T., Kim, D. W., Mehra, R., Tan, D. S. W., Felip, E., Chow, L. Q. M., et al. (2014). Ceritinib in ALK-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* 370, 1189–1197. doi:10.1056/NEJMoa1311107

Shaw, A. T. K. D., Nakagawa, K., Seto, T., Crinó, L., Ahn, M. J., De Pas, T., et al. (2103). Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.

Solomon, B. J., Mok, T., Kim, D. W., Wu, Y. L., Nakagawa, K., Mekhail, T., et al. (2014). First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 371, 2167–2177. doi:10.1056/NEJMoa1408440

Spagnolo, P., Bonniaud, P., Rossi, G., Sverzellati, N., and Cottin, V. (2022). Drug-induced interstitial lung disease. *Eur. Respir. J.* 60, 2102776. doi:10.1183/13993003.02776-2021

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71, 209–249. doi:10.3322/caac.21660

Teuwen, L.-A., Van den Mooter, T., and Dirix, L. (2015). Management of pulmonary toxicity associated with targeted anticancer therapies. *Expert Opin. Drug Metabolism & Toxicol.* 11, 1695–1707. doi:10.1517/17425255.2015.1080687

Zhao, M., Liu, S., Xie, R., Zhang, J., and Li, J. (2023). Interstitial lung disease risk of anaplastic lymphoma kinase tyrosine kinase inhibitor treatment of non-small cell lung cancer: a real-world pharmacovigilance study. *Expert Opin. Drug Saf.* 22, 1309–1316. doi:10.1080/14740338.2023.2245324

Zou, H. Y., Friboulet, L., Kodac, D. P., Engstrom, L. D., Li, Q., West, M., et al. (2015). PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. *Cancer Cell* 28, 70–81. doi:10.1016/j.ccell.2015.05.010

frontiers | Frontiers in Immunology

TYPE Case Report
PUBLISHED 10 October 2024
DOI 10.3389/fimmu.2024.1405856

OPEN ACCESS

EDITED BY
Graham Robert Leggatt,
The University of Queensland, Australia

REVIEWED BY
Sijia Zhang,
Heidelberg University, Germany
Dmitry Aleksandrovich Zinovkin,
Gomel State Medical University, Belarus

*CORRESPONDENCE
Chunliang Wang
15958266153@163.com

RECEIVED 24 March 2024
ACCEPTED 25 September 2024
PUBLISHED 10 October 2024

CITATION
Wang C, Cai Y and Feng P (2024) Case report: A case of sintilimab-induced recurrent diabetic ketoacidosis and thyroid dysfunction in a patient with advanced cervical carcinoma.
Front. Immunol. 15:1405856.
doi: 10.3389/fimmu.2024.1405856

Case report: A case of sintilimab-induced recurrent diabetic ketoacidosis and thyroid dysfunction in a patient with advanced cervical carcinoma

Chunliang Wang[1]*, Ye Cai[1] and Pei Feng[2]

[1]Department of Endocrinology, The Affiliated People's Hospital of Ningbo University, Ningbo, China, [2]Department of Information, The Affiliated People's Hospital of Ningbo University, Ningbo, China

Immune checkpoint inhibitors (ICIs) have radically altered cancer treatment, but immune toxicities called immune-related adverse events (irAEs), particularly endocrine toxicities, such as acute-onset diabetes and thyroid dysfunction, pose challenges. Although most irAEs have mild-to-moderate severity, failure to diagnose and treat them promptly can result in life-threatening complications. This report presents the case of a 50-year-old woman who developed ICI-induced diabetes mellitus (ICI-DM) during sintilimab treatment for advanced cervical carcinoma. The patient experienced repeated episodes of diabetic ketoacidosis (DKA) and subclinical hypothyroidism. Unlike the case of patients with typical type 1 diabetes mellitus (T1DM), our patient tested negative for β cell autoantibodies and progressed rapidly. Prompt recognition and insulin treatment are crucial for helping patients overcome such crises. Eventually, sintilimab was discontinued, and chemotherapy was initiated. This case report contributes to our understanding of ICI-DM. The significance of monitoring thyroid function and blood glucose levels before initiating ICI treatment to identify irAEs early and effectively manage them are important considerations.

KEYWORDS

immune checkpoint inhibitor, immune-related endocrine event, TIDM, DKA, thyroid dysfunction

1 Introduction

The boom in immune checkpoint inhibitors (ICIs) has changed the cancer treatment landscape. In 2019, approximately 43.6% of patients with cancer in the United States received ICI therapy, of which an estimated 12% showed a positive response (1). Although ICIs have enormous potential, their success has been limited by a range of adverse drug reactions described as immune-related adverse events (irAEs) (2). Immune-related endocrine events (irEEs), including hypoadrenia (0.7%), type I diabetes mellitus (0.2–

2%), hypophysitis (5.6–11%), and thyroid disorders (30%) are common types of irAEs (3). The pathogenesis of irAEs is not completely understood, including (a) T cell-mediated mechanisms: the loss of T cell tolerance; expansion of autoreactive T cells can target shared antigens of normal and tumoral tissues; the breach in peripheral tolerance due to an imbalance of Treg cells; (b) B cells and autoAbs mediated mechanisms; (c) The activation of autoreactive B and T cells produce auto-Abs; (d) the activation of the classic complement cascade mediated tissue damage; (e) hyperinflammatory status resulting from massive cytokine release; and (f) other factors such as genetics and epigenetics, the environment and the microbiota, and the underlying immune status (4). Autoantibodies are often monitored in patients with ICI-DM or thyroid dysfunction. Furthermore, with expanding indications for ICIs and improved patient survival rates, the incidence of irAEs is expected to increase accordingly. However, toxicities associated with ICI treatment are a matter of significant clinical concern. In rare cases, these toxicities can cause treatment delays, discontinuation, and life-threatening complications. Therefore, a thorough understanding of irAEs, early diagnosis, and prompt treatment are crucial. We report the case of an older woman who received sintilimab after being diagnosed with malignant cervical cancer (IV B). The patient presented with subclinical hypothyroidism approximately 9 weeks after treatment with sintilimab. At 17 weeks, the patient developed ICI-induced diabetes mellitus (ICI-DM) with symptoms of recurrent fatigue, anorexia, nausea, and vomiting without the classic symptoms of diabetes, which was misdiagnosed as a complication of malignancy and ignored, leading to recurrent diabetic ketoacidosis (DKA). Sintilimab was discontinued owing to severe DKA symptoms.

2 Case description

In June 2017, a 50-year-old woman was diagnosed with cervical cancer and underwent radical surgery. Histological examination revealed the presence of a high-grade neuroendocrine carcinoma. No distant metastases were observed during tumor staging. The patient achieved a complete response after 6 cycles of cisplatin and etoposide chemotherapy combined with radiotherapy. However, the patient experienced cough and expectoration without fever, gradually worsening in June 2019. The clinical stage was T4N1M1 (IVB) based on positron emission tomography-computed tomography (PET-CT) examination, and several metastases involving the lungs, adrenal glands, and lymph nodes were observed. Following chemotherapy (5 cycles of cisplatin and etoposide, and 4 cycles of nab-paclitaxel and carboplatin), anlotinib was administered, but it was ineffective in delaying the progression of the disease. A subsequent PET-CT scan in July 2021 revealed further enlargement of the tumor with multiple metastases. Sintilimab (200 mg every 3 weeks) combined with anlotinib was initiated on July 26, 2021, and the patient showed progressive clinical improvement. During these months, the patient experienced occasional nausea that was initially misdiagnosed as a complication of malignancy because the intensity of the symptoms was not considered serious.

However, 11 days after treatment with the sixth cycle of sintilimab, the patient arrived at the emergency department with anorexia, fatigue, nausea, and vomiting lasting for 2 days, without the typical diabetic symptoms of polydipsia, polyuria, or polyphagia. Laboratory tests revealed severe hyperglycemia (immediate serum glucose level, 29.7 mmol/L) and a glycated hemoglobin (HbA1c) value of 6.4%. Urine samples showed high levels of glucose (4+) and ketones (3+). Arterial blood gases indicated primary metabolic acidosis, with a pH of 7.29, a bicarbonate level of 12.5 mmol/L, and a lactate level of 1.5 mmol/L. Upon admission, the patient had a temperature of 37.2°C, blood pressure of 116/75 mmHg, heart rate of 101 beats a minute, respiratory rate of 20 a minute, and a 98% oxygen saturation (resting, room air); the BMI was 24.03 kg/m^2. Physical examination revealed drowsiness, dry skin, and clinical dehydration; however, the results of other systemic examinations were negative. The other laboratory findings are shown in Table 1.

We suspected newly developed diabetes mellitus coupled with ketoacidosis; hence, the patient was referred to the endocrinology department. Intravenous fluids to restore of circulatory volume and tissue perfusion, continuous insulin infusion treatment and correction of electrolyte imbalance were initiated immediately. After 1 day, by above active treatment, glucose gradually dropped below 13.9 mmol/L, urinary ketone turned negative, DKA resolved. Therefore, her insulin therapy was switched to subcutaneous insulin. Low levels of insulin (0.6 mIU/L) and C-peptide (0.1 ng/mL) indicated insulinogenic diabetes. The patient tested negative for typical type 1 diabetes mellitus (T1DM) autoantibodies including glutamic acid decarboxylase antibodies (anti-GAD), insulin autoantibodies (anti-insulin), and anti-islet cell antibodies (anti-ICA). Notably, the patient denied any history of diabetes or autoimmune disease. Other than sintilimab, no other potential causes of hyperglycemia (such as infection, pancreatitis, autoimmune diseases, Cushing's syndrome, or drug exposure) were identified. The Naranjo Adverse Drug Reaction Probability Assessment Scale scored to 7 which suggests probable relation between the sintilimab and its reaction in patient. Therefore, we considered the possibility of ICI-DM, and discontinuing sintilimab immunotherapies. The patient was discharged with a prescription for multiple daily injections (insulin glargine at 8 units per day and insulin lispro at 6–8 units pre-meal).

However, 3 days after discontinuing insulin treatment, the patient returned to our hospital with life-threatening DKA. Blood test results revealed severe DKA (hyperglycemia, 32.4 mmol/L, acidosis pH 7.18; serum venous bicarbonate, 5.6 mmol/L) and an HbA1c level of 9.4%. The C-peptide values remained low. Upon resolution of DKA, the patient was discharged and subcutaneous insulin was continued to manage glycemia. Over the following year, the patient was closely followed at the outpatient clinic for insulin titration; nevertheless, the patient continued to show significant glucose fluctuations, similar to those in T1DM (Figure 1A).

ICI treatment can lead to multiple co-occurring irAEs. An elevated serum thyroid-stimulating hormone (TSH) level of 26.65 mIU/mL was observed 2 months before the onset of DKA, but it did not receive attention. Thyroid function tests revealed high TSH,

10.3389/fimmu.2024.1405856

TABLE 1 Clinical characteristics of the patient during the two hospitalization events.

Variables	First hospitalization 19/11/2021	Second hospitalization 26/12/2021	Reference
random glucose (mmol/L)	29.7	32.4	
gas pH	7.29	7.18	7.35–7.45
$PaCO_2$ (mmHg)	26	15	35.0–45.0
PaO_2 (mmHg)	84		80.0–100.0
$HCO3^-$ (mmol/L)	12.5	5.6	21–27
BE (mmol/L)	-14.1	-22.8	-3–3
Lactate (mmol/L)	2.8	2.4	0.5–2.2
Potassium (mmol/L)	5.1	5.2	3.4–4.5
Sodium (mmol/L)	131	126	136–145
Urine glucose	4+	2+	–
Urine ketones	3+	3+	–
HbA1c (%)	6.4	9.4	
C-peptide (ng/ml)	0.1	0.1	1.1–4.4
Anti-GAD	–	–	
Anti-ICA	–	–	
Anti-Insulin	–	–	

normal free thyroxine (FT4), and negative thyroid peroxidase and thyroglobulin antibodies, indicating that the irAEs involved the hypothalamic-pituitary-thyroid axis. Therefore, a comprehensive assessment of the patient's endocrine system was performed. Cortisol and adrenocorticotropic hormone (ACTH) levels were within the reference range, and no symptoms of adrenal insufficiency were reported. The relationship between TSH levels and sintilimab administration is shown in Figure 1B.

The patient developed progressive dyspnea on August 17, 2022. Chest CT scans revealed enlarged lymph nodes compressing the principal bronchus (Figure 2), and bronchoscopy showed bilateral principal bronchus compression of approximately 50%, with a left lower lobar bronchus stenosis-like chink; therefore, bronchus stenting was performed. After consulting with the palliative team, the patient and her family discontinued treatment, and she transitioned to home hospice care. Unfortunately, the patient died in October 2022. The timeline for treatment is shown in Figure 3.

3 Discussion

IrAEs are systemic autoimmune diseases affecting any system through nonspecific T-cell activation. Non-endocrine irAEs are mostly associated with acute inflammation that can be resolved with glucocorticoid therapy, ultimately restoring organ function. IrEEs typically lead to chronic conditions and are frequently irreversible, requiring lifelong hormone replacement that, given ICI-induced immune activation, results in the destruction of most or all the hormone-producing cells; high-dose glucocorticoids are unlikely to reverse the damage and salvage the endocrine function of the gland. Glucocorticoids are not recommended for the treatment of ICI-DM, high doses of glucocorticoids can also increase glycemia (5). Due to clinical and pathophysiological similarities, the differential diagnosis between irEEs and primary autoimmune diseases may be challenging. IrEEs triggered by the different ICI treatments were different. Anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) agents are associated with the risk of adrenal insufficiency and hypophysis, whereas anti-programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) therapy is closely associated with insulin-dependent DM and thyroid dysfunction. Combination therapies are more toxic than ICIs. The onset time of irEEs varies among different ICI treatments. Anti-CTLA-4 therapy is usually administered within 12 weeks; however, anti-PD-1 therapy can be administered at any time between 0 and 48 weeks. ICI-DM can occur after 48 weeks and up to 2 years after initiating anti-PD-1 therapy. Therefore, the onset of ICI-DM is difficult to anticipate (6). In general, irEEs are strongly associated with high response rates and progression-free survival (7). According to the American Society of Clinical Oncology (ASCO) guidelines (8), ICIs should be discontinued, and patients should be managed for their effects until they improve if they have grade 2 adverse effects. IrEEs are distinct from other irAEs because of the typically irreversible hormonal deficits they cause, except for certain thyroid changes. The mainstay of treatment of irEEs is hormone replacement therapy. Except for endocrinopathies that improve with hormone replacement therapy, grade 4 irAEs generally require permanent discontinuation of ICIs.

ICI-DM is a comparatively rare irAE with a prevalence of 0.2–1.4% (9). ICI-DM is considered to be the result of autoimmune destruction of pancreatic β-cells. Recovery from autoimmune diabetes mellitus after the termination of ICIs treatment is not possible since the majority of β cells would be permanently damaged. Compared to classic TIDM, ICI-DM exhibits a rapid and fulminant onset of diabetes, characterized by the abrupt development of extreme hyperglycemia that the HbA1C is often elevated to 7.6%–9.7% at diagnosis so screening for HbA1c is not reliable in the patients (10). C-peptide levels remain low or absent in ICI-DM; however, 93% of patients with T1DM still showed detectable C-peptide levels 2 years after initial diagnosis (11). ICI-DM cases show obvious insulin deficiency and require lifelong insulin therapy; 60–85% of ICI-DM cases present with DKA (12,

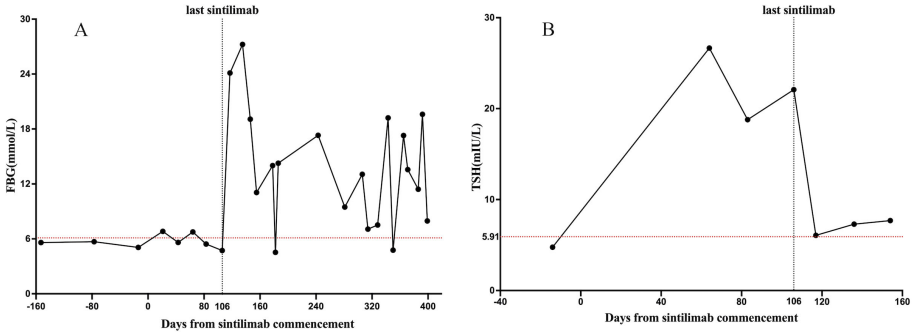


FIGURE 1
Changes in endocrine functions during sintilimab treatment. The X-axis shows the time interval since the start of the sintilimab treatment in days. The Y-axis shows the laboratory values of FBG (mmol/L) and TSH (mIU/L). **(A)** shows the change in FBG levels; **(B)** shows the change in TSH levels. The red dotted line is the upper limit for FBG and TSH. FBG, fasting blood glucose. TSH, thyroid-stimulating hormone.

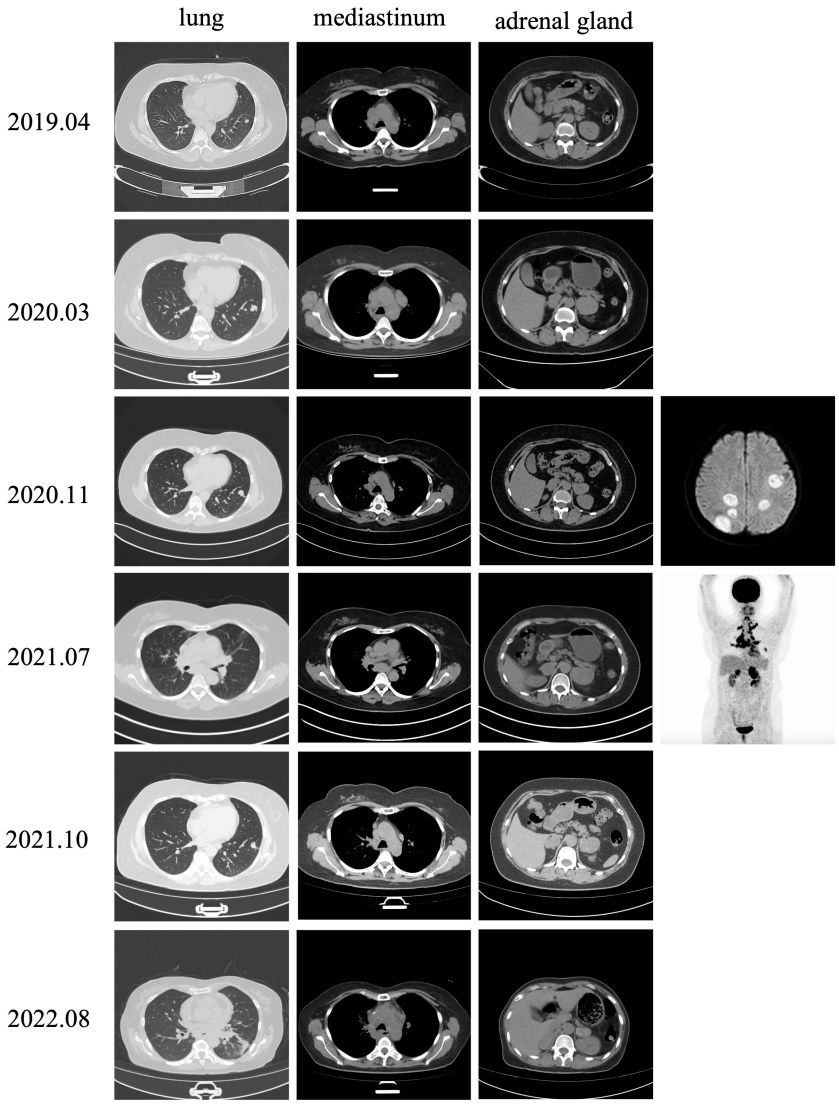


FIGURE 2
Image of disease progression.

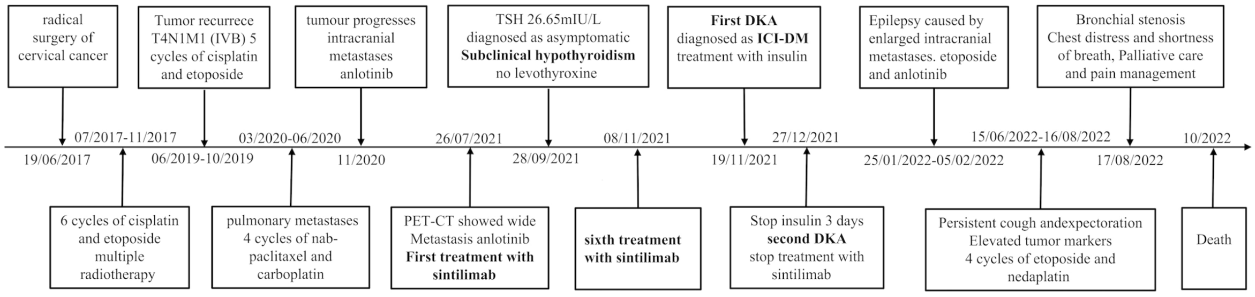


FIGURE 3
Timeline of disease progression.

13). One-third of patients with ICI-DM show elevated serum amylase and lipase, suggesting that exocrine pancreatic inflammation may also play a role in the pathogenesis (14). The level of autoantibodies in patients with T1DM is markedly lower than that in patients with classic T1DM (40–50% vs 90%), and patients with positive autoantibodies for ICI-DM have an earlier onset of diabetes and a higher risk of DKA (15). As in T1DM, genetic factors such as HLA typing correlate with the risks of developing ICI-DM, especially HLA-DR4 (16). Collectively, these studies indicate that the pathophysiology of ICI-DM is unique and distinct from that of classic T1DM.

Several treatments are effective in preventing ICI-DM in NOD mice, including JAK1/2 inhibitors, anti-CD3, anti-TNF-a, and anti-IFN-γ. However, none of these have been successful in treating humans with confirmed ICI-DM. Although two patients with ICI-DM were insulin-free after infliximab therapy, it was difficult to determine the cause of the hyperglycemia, as neither had overt insulin deficiency, such as insufficient C-peptide or obvious DKA (15). In a retrospective study of 735 patients with ICI-DM diagnosed between 2015 and 2019, the incidence increased since 2015. In patients with ICI-DM, 24.90% presented with fulminant-type 1 diabetes, whereas 45.99% had diabetic ketosis or DKA. Approximately 25% of the patients with ICI-DM show life-threatening or fatal outcomes (17). In our study, the patient not only developed ICI-DM (grade 4) after receiving sintilimab but also experienced thyroid dysfunction (grade 2). Sudden onset of DKA is the first manifestation, and the patient showed nearly undetectable levels of insulin, low C-peptide, negative islet-cell autoantibodies, and a slightly elevated HbA1c level of 6.4% at diagnosis. Acute and rapid islet dysfunction commonly occurs in patients with fulminant-type 1 diabetes mellitus. Three days after discontinuing insulin treatment, the patient returned to our hospital with life-threatening DKA.

For irEEs, except for hypophysitis with compression of the optic chiasm or optic nerve or severe thyroid eye disease, there is no need to interrupt or stop ICI treatment. Unfortunately, sintilimab treatment was discontinued because of the severe symptoms of DKA. In fact, enhanced clinical awareness of abnormal glucose levels in patients before the diagnosis of CIADM may lead to early identification of ICI-DM and prevention of potential DKA. ICI-DM is a relatively rare but potentially life-threatening adverse reaction to ICI treatment. Clinicians must take this seriously because of its high incidence, serious consequences of missed diagnosis, the need for lifelong continuous insulin treatment, related risk of diabetes mellitus complications, and reduced survival (15). The ASCO recommends monitoring random blood glucose at baseline and every cycle of ICI therapy, particularly in patients treated with anti-PD-1. In cases of new-onset hyperglycemia, the basal metabolic profile, blood pH, serum and urine ketone, HbA1c, and C-peptide levels should be determined. These assays can be used to identify patients with DKA and differentiate between different types of hyperglycemia such as stress hyperglycemia, steroid-induced hyperglycemia, and type 2 diabetes mellitus (T2DM) (8). Once DKA is confirmed, hospitalization is indicated, and a standard typical should be immediately administered, including fluid resuscitation, continuous intravenous insulin infusions, and correction of electrolyte abnormalities. In severe cases, monitoring in the intensive care unit is mandatory. It is essential to treat any correctable underlying cause of DKA, the most common incentives is infection. Evaluation of insulin, C-peptide, and insulin antibodies is recommended at ICI-DM diagnosis. Co-management with an endocrinologist may help optimize insulin doses that contribute to better glycemic control and HbA1c. Patient education is also fundamental, particularly regarding glucose monitoring and symptom management after discharge. Patients should be instructed to promptly report any symptoms of diabetes, such as acute polyuria, polydipsia, and weight loss, and seek immediate evaluation, especially in the presence of fever and/or infection, even if their symptoms are not severe.

The thyroid gland is the most commonly affected endocrine organ (30%) (5). The median time for thyroid dysfunction to appear after ICI treatment is 6 weeks. The risk factors of ICI-induced thyroid dysfunction include females, high BMI, increased 18F-deoxyglucose uptake in the thyroid, high TSH, and thyroid autoantibodies (10). Patients are often diagnosed based on abnormal thyroid function rather than symptoms, although they may present with symptoms of hypothyroidism, such as anorexia, fatigue, weight gain, and constipation. Notably, these symptoms are not always present (18). Thyroid dysfunction during PD-1 inhibitor treatment correlates with improved responses and can be used as a predictive factor for improved treatment outcomes (19). During the 9-week sintilimab treatment, our patient developed thyroid dysfunction and was diagnosed with asymptomatic subclinical hypothyroidism. In addition to sintilimab therapy, the

patient received anlotinib, a tyrosine kinase inhibitor (TKI). In a single-center retrospective study of 126 patients who received PD-1 inhibitor therapy, 23% experienced thyroid dysfunction. TKIs were identified as significant triggers of hypothyroidism in 63.2% of the patients (20). After 2 weeks of sintilimab discontinuation and continued use of arotinib, her thyroid function returned to normal without levothyroxine. Therefore, we considered sintilimab to be the prime predisposing factor for thyroid dysfunction.

The TSH level is the most sensitive and preferred biochemical test for diagnosing thyroid dysfunction in patients. Thyroid function should be assessed at least every 4–8 weeks in patients receiving ICIs to monitor for potential thyroid dysfunction. Thyroid hormone supplementation was administered to symptomatic patients with elevated TSH levels or asymptomatic patients with TSH levels >10 mIU/mL. Levothyroxine can be initiated at a daily dose of 25–50 mg, and the dosage must be adjusted based on serum TSH levels (8). Brain imaging and pituitary hormone tests should be conducted to identify central hypothyroidism if T4 and TSH levels are low (21).

Many questions about irAEs remain unanswered. These include identifying risk factors and biomarkers with predictive value, predicting the onset and severity of adverse events, and further demonstrating the relationship between irEEs and clinical outcomes. This could enable clinicians to stratify patients according to the risk and take the necessary steps to manage patients with iris to avoid permanent discontinuation of ICI therapies, especially in highly effective anti-tumor responses. In addition to retrospective studies, prospective studies are needed. IrEEs present distinct clinical challenges. Providing medical counseling to patients and their families about the possibility of irEEs before initiating ICI therapy increases awareness of potential adverse events, improves coping abilities, raises medical compliance, and improves clinical outcomes. Non-endocrinologists should identify endocrine dysfunction in patients with nonspecific symptoms or complex abnormal laboratory results. Comprehensive patient education will help in the early diagnosis of endocrine disorders. Effective cooperation between the endocrinology and oncology departments can enhance the prospects of patients with irEEs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

CW: Writing – original draft, Writing – review & editing. YC: Writing – original draft, Conceptualization. PF: Data curation, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Traditional Chinese Medicine Science and Technology Project Zhejiang Province (2024ZL927) and The Affiliated People's Hospital of Ningbo University Academy Level Project (2021-12).

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing. The authors extend appreciation to Wenhao Liu, husband of Chunliang Wang, for assistance in drawing figure and his valuable and thoughtful on the manuscript submission process.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open*. (2019) 2:e192535. doi: 10.1001/jamanetworkopen.2019.2535

2. Dougan M, Luoma AM, Dougan SK, Wucherpfennig KW. Understanding and treating the inflammatory adverse events of cancer immunotherapy. *Cell*. (2021) 184:1575–88. doi: 10.1016/j.cell.2021.02.011

3. Özdemir BC. Immune checkpoint inhibitor-related hypogonadism and infertility: a neglected issue in immuno-oncology. *J Immunother Cancer*. (2021) 9:e002220. doi: 10.1136/jitc-2020-002220

4. Casagrande S, Sopetto GB, Bertalot G, Bortolotti R, Racanelli V, Caffo O, et al. Immune-related adverse events due to cancer immunotherapy: immune mechanisms and clinical manifestations. *Cancers (Basel)*. (2024) 16:1440. doi: 10.3390/cancers16071440

5. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. *Nat Rev Endocrinol*. (2021) 17:389–99. doi: 10.1038/s41574-021-00484-3

6. Bai X, Lin X, Zheng K, Chen X, Wu X, Huang Y, et al. Mapping endocrine toxicity spectrum of immune checkpoint inhibitors: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. *Endocrine*. (2020) 69:670–81. doi: 10.1007/s12020-020-02355-9

7. Al Ashi SI, Thapa B, Flores M, Ahmed R, Rahim SEG, Amir M, et al. Endocrine toxicity and outcomes in patients with metastatic Malignancies treated with immune checkpoint inhibitors. *J Endocr Soc*. (2021) 5:bvab100. doi: 10.1210/jendso/bvab100

8. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. (2021) 39:4073–126. doi: 10.1200/JCO.21.01440

9. Wu L, Carlino MS, Brown DA, Long GV, Clifton-Bligh R, Mellor R, et al. Checkpoint inhibitor associated autoimmune diabetes mellitus is characterised by C-peptide loss and pancreatic atrophy. *J Clin Endocrinol Metab*. (2024) 109(5):1301–07. doi: 10.1210/clinem/dgad685

10. Husebye ES, Castinetti F, Criseno S, Curigliano G, Decallonne B, Fleseriu M, et al. Endocrine-related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. *Eur J Endocrinol*. (2022) 187:G1–G21. doi: 10.1530/EJE-22-0689

11. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, et al. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes*. (2012) 61:2066–73. doi: 10.2337/db11-1538

12. Yoneda S, Imagawa A, Hosokawa Y, Baden MY, Kimura T, Uno S, et al. T-lymphocyte infiltration to islets in the pancreas of a patient who developed type 1 diabetes after administration of immune checkpoint inhibitors. *Diabetes Care*. (2019) 42:e116–8. doi: 10.2337/dc18-2518

13. Zezza M, Kosinski C, Mekoguem C, Marino L, Chtioui H, Pitteloud N, et al. Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports. *BMC Endocr Disord*. (2019) 19:144. doi: 10.1186/s12902-019-0467-z

14. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes*. (2018) 67:1471–80. doi: 10.2337/dbi18-0002

15. Wu L, Tsang V, Menzies AM, Sasson SC, Carlino MS, Brown DA, et al. Risk factors and characteristics of checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM): A systematic review and delineation from type 1 diabetes. *Diabetes Care*. (2023) 46:1292–9. doi: 10.2337/dc22-2202

16. Poto R, Troiani T, Criscuolo G, Marone G, Ciardiello F, Tocchetti CG, et al. Holistic approach to immune checkpoint inhibitor-related adverse events. *Front Immunol*. (2022) 13:804597. doi: 10.3389/fimmu.2022.804597

17. Liu J, Zhou H, Zhang Y, Fang W, Yang Y, Huang Y, et al. Reporting of immune checkpoint inhibitor therapy-associated diabetes, 2015-2019. *Diabetes Care*. (2020) 43: e79–80. doi: 10.2337/dc20-0459

18. Walters AGB, Braatvedt G. Endocrine adverse effects of immune checkpoint inhibitors. *Intern Med J*. (2021) 51:1016–20. doi: 10.1111/imj.14992

19. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol*. (2017) 28:583–9. doi: 10.1093/annonc/mdw640

20. Sbardella E, Tenuta M, Sirgiovanni G, Gianfrilli D, Pozza C, Venneri MA, et al. Thyroid disorders in programmed death 1 inhibitor-treated patients: Is previous therapy with tyrosine kinase inhibitors a predisposing factor? *Clin Endocrinol (Oxf)*. (2020) 92:258–65. doi: 10.1111/cen.14135

21. Thompson JA, Schneider BJ, Brahmer J, Achufusi A, Armand P, Berkenstock MK, et al. Management of immunotherapy-related toxicities, version 1.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. (2022) 20:387–405. doi: 10.6004/jnccn.2022.0020

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 October 2024
DOI 10.3389/fphar.2024.1435923

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Moetaza M. Soliman,
Mansoura University, Egypt
Haibo Song,
National Center for ADR Monitoring, China

*CORRESPONDENCE
Yong-Ji Lai,
laiyongji1024@163.com
Yuan-Xi Mei,
meiyuanxi@hust.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 21 May 2024
ACCEPTED 30 September 2024
PUBLISHED 14 October 2024

CITATION
Xie W-L, Ge M-L, Chen D, Chen G-Q, Mei Y-X and Lai Y-J (2024) Psychiatric disorders associated with fluoroquinolones: a pharmacovigilance analysis of the FDA adverse event reporting system database.
Front. Pharmacol. 15:1435923.
doi: 10.3389/fphar.2024.1435923

Psychiatric disorders associated with fluoroquinolones: a pharmacovigilance analysis of the FDA adverse event reporting system database

Wen-Long Xie[1†], Meng-Lan Ge[1†], Dan Chen[2†], Guo-Qing Chen[3], Yuan-Xi Mei[4*] and Yong-Ji Lai[1*]

[1]Department of Pharmacy, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2]Department of Obstetrical, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [3]Department of Cardiovascular, Changjiang County Integrative Medicine Hospital, Changjiang, China, [4]Department of Pharmacology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Fluoroquinolones are broad-spectrum antibiotics with significant antimicrobial activity. Despite their therapeutic benefits, they are associated with a range of adverse drug reactions (ADRs), particularly those affecting the central nervous system (CNS). This study aimed to analyze the psychiatric ADRs linked to fluoroquinolones using data from the FDA Adverse Event Reporting System (FAERS) database.

Methods: A retrospective pharmacovigilance study was conducted using FAERS data from Q1 2004 to Q4 2023. The data processing phase involved the FDA-recommended deduplication method, and ADRs were classified according to Medical Dictionary for Regulatory Activities (MedDRA). Disproportionality analysis was performed using the reporting odds ratio (ROR), and statistical significance was assessed using the Chi-square test or Fisher's exact test.

Results: The study identified 84,777 reports associated with fluoroquinolones, with 359,480 Preferred Terms-annotated entries, 27,816 of these reports were psychiatric ADRs. Mood disorders were the most frequently reported, including anxiety, depression, and delirium, with some reports escalating to suicidal ideation and behaviors. The Standardized MedDRA Query classification system was used to categorize these ADRs into Depression, Suicide/self-injury, Psychosis and psychotic disorders, and Non-infectious encephalopathy/delirium. Ciprofloxacin was most frequently linked to depression and suicidal ideation, while moxifloxacin showed a robust correlation with delirium. The risk of psychiatric ADRs varied by age group, with affective disorders more prevalent in adults under 65 and psychosis and delirium in those over 65.

Conclusion: Fluoroquinolones are associated with a range of psychiatric ADRs, with notable differences between the drugs in the class. The study highlights the need for caution in prescribing fluoroquinolones, particularly for patients with

pre-existing mental health conditions or those in higher risk age groups. The findings also underscore the importance of considering age-specific preventive strategies when administering these antibiotics.

KEYWORDS

fluoroquinolones, psychiatric ADRs, pharmacovigilance, FAERS, disproportionality analysis

1 Introduction

Fluoroquinolones are recognized as a class of broad-spectrum antibiotics that are extensively utilized in clinical practice. They are distinguished by their high oral bioavailability and extensive distribution volume, which contribute to their potent antimicrobial efficacy against both gram-positive and gram-negative bacteria. Consequently, fluoroquinolones are frequently prescribed for a spectrum of infections, including urinary tract infections, pneumonia, sinusitis, tuberculosis, and sexually transmitted diseases (Mahoney and Swords, 2021).

The antimicrobial action of fluoroquinolones is mediated through the inhibition of bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA replication. While these agents exert a bactericidal effect, they have also been linked to a range of adverse reactions (Leone et al., 2003; Ruan et al., 2024). Notably, central nervous system (CNS)-related adverse drug reactions (ADRs) are the second most frequently reported after gastrointestinal issues and are observed more frequently with fluoroquinolones than with other classes of antimicrobials (Wierzbinski et al., 2023). A statistical review of the literature indicates that the incidence of neuropsychiatric adverse reactions in patients treated with fluoroquinolones can range from 1% to 4.4%, encompassing a spectrum of manifestations from mild symptoms such as confusion, restlessness, and insomnia, to severe conditions including encephalopathy, epileptic seizures, suicidal depression, catatonia, psychosis, and mania (Zareifopoulos and Panayiotakopoulos, 2017). Given the potential for severe side effects, particularly those involving the CNS, the U.S. Food and Drug Administration (FDA) updated the boxed warnings for all oral and injectable fluoroquinolones in 2016 to reflect these risks (Aschenbrenner, 2016).

The CNS effects observed with fluoroquinolones are largely attributed to their high permeability across the blood-brain barrier and their structural resemblance to gamma-aminobutyric acid (GABA). This similarity enables them to interact with GABA(A) receptors in the CNS, thereby competitively inhibiting GABAergic neurotransmission, as discussed in the referenced study (Akaike et al., 1991; Ilgin et al., 2015). Furthermore, the interaction of fluoroquinolones with CNS nicotinic acetylcholine receptors (nAChRs) and N-methyl-D-aspartate receptors (NMDARs) may also significantly contribute to their neuropsychiatric ADRs, as highlighted in the literature (Sanders et al., 2022; Smelt et al., 2018; Zareifopoulos and Panayiotakopoulos, 2017). Additionally, a preclinical study has suggested that the fluoroquinolone ciprofloxacin can induce mitochondrial damage, which could be a critical mechanism underlying CNS injury associated with fluoroquinolone use (Kaur et al., 2016).

The Medicines and Healthcare products Regulatory Agency (MRHA) has recently issued a directive highlighting the elevated incidence of adverse reactions associated with fluoroquinolone use. This directive advises that the prescription of fluoroquinolones be restricted to scenarios where alternative, recommended antibiotics are deemed inappropriate. This follows an earlier safety communication from the MHRA in September 2023, which cautioned about the potential for fluoroquinolones to induce psychiatric reactions, encompassing depression and psychosis, with the possibility of progressing to suicidal ideation or behavior (Author Anonymous, 2024). Given the heightened risk of disability often associated with psychiatric adverse reactions, there has been a growing concern regarding the safety profile of fluoroquinolones. However, a comparative analysis of psychiatric adverse events across the spectrum of fluoroquinolones, including ciprofloxacin, moxifloxacin, and levofloxacin, based on extensive real-world data, remains a relatively unexplored area, with limited systematic studies available to date.

The FDA Adverse Event Reporting System (FAERS) database serves as a pivotal, publicly accessible resource for global pharmacovigilance, compiling adverse event reports from an international perspective, including those within the United States. It is recognized as an authoritative source for the assessment of drug-related ADRs. The current study leverages the FAERS database, extracting data from the first quarter of 2004 through the fourth quarter of 2023, to conduct an in-depth analysis of the ADRs linked to three prevalently prescribed fluoroquinolones: ciprofloxacin, moxifloxacin, and levofloxacin. This research further aims to dissect the psychiatric ADRs attributed to fluoroquinolone use.

2 Materials and methods

2.1 Data sources

A retrospective pharmacovigilance study was conducted utilizing data extracted from the FAERS database, which is updated quarterly. The FAERS database is a publicly accessible resource that compiles adverse event reports from healthcare professionals, consumers, and other sources globally (Harpaz et al., 2016). For the purpose of this study, reports concerning fluoroquinolones and associated ADRs were systematically collected from the first quarter of 2004 to the fourth quarter of 2023. All data in this study are openly accessed as an ASCII data package from the FAERS website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Subsequently, the extracted data were

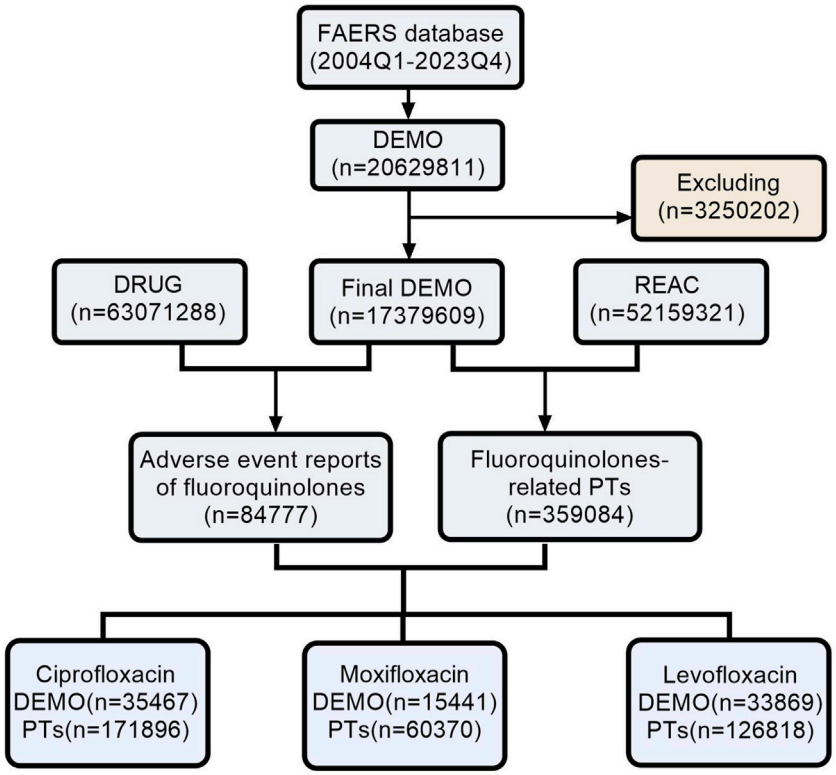


FIGURE 1
The process of searching fluoroquinolone-associated adverse events from the FAERS. (Abbreviations: FAERS, FDA Adverse Event Reporting System; DEMO, Demographics; REAC, Reactions; PT, Preferred Term).

processed and in-depth analyzed by Rstudio (Version 2023.06.2 + 561).

2.2 Data processing

The data processing phase involved the implementation of the FDA-recommended deduplication method to ensure the reliability of the dataset. Reports with identical CASEID (Number for identifying a FAERS case) in the DEMO (demographics) table were retained based on the highest FDA_DT value. In reports where both CASEID and FDA_DT (date FDA received case) were identical, the report with the maximum PRIMARYID (unique number for identifying a FAERS report) value was preserved. ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) (Version 26.0). The extraction of data was performed for fluoroquinolones, including ciprofloxacin, moxifloxacin, and levofloxacin, focusing on the System Organ Class (SOC) category of psychiatry-related ADRs. Specific High Level Group Terms (HLGT) relative to mood disorders, as well as Preferred Terms (PT) related to anxiety, depression, suicidal ideation, and other psychiatric conditions were identified and analyzed. The Standardized MedDRA Query (SMQ) was applied to categorize psychiatric ADRs into depression, suicide/self-injury, psychosis, and other psychotic disorders, as well as non-infectious encephalopathy/delirium.

2.3 Statistical analysis

The disproportionality analysis was conducted using the reporting odds ratio (ROR) and confidence propagation neural network (BCPNN) methods. The calculation formula is as Supplementary Table S1. ROR ≥1 and 95% CI (lower limit) > 1 with three or more reports considering a positive signal. A higher ROR indicates a stronger correlation between the drug and AE and consequently a stronger risk signal. In the BCPNN analysis method, the lower limit of the 95% confidence interval of the IC (Information Component) value (IC025) is greater than 0, which means that the association between the drug and the adverse event is statistically significant. For the analysis of between-group differences in categorical variables and statistical tests in disproportional analysis, we used the Chi-square test or Fisher's exact test. $P < 0.05$ was considered statistically significant (Zhou et al., 2023).

3 Result

3.1 Descriptive analysis

As shown in Figure 1, following the removal of duplicate entries, our analysis included a comprehensive dataset of 17, 379, 609 reports from the FAERS, ranging from Q1 2004 to Q4 2023. Specifically, 84,777 reports were linked to fluoroquinolone

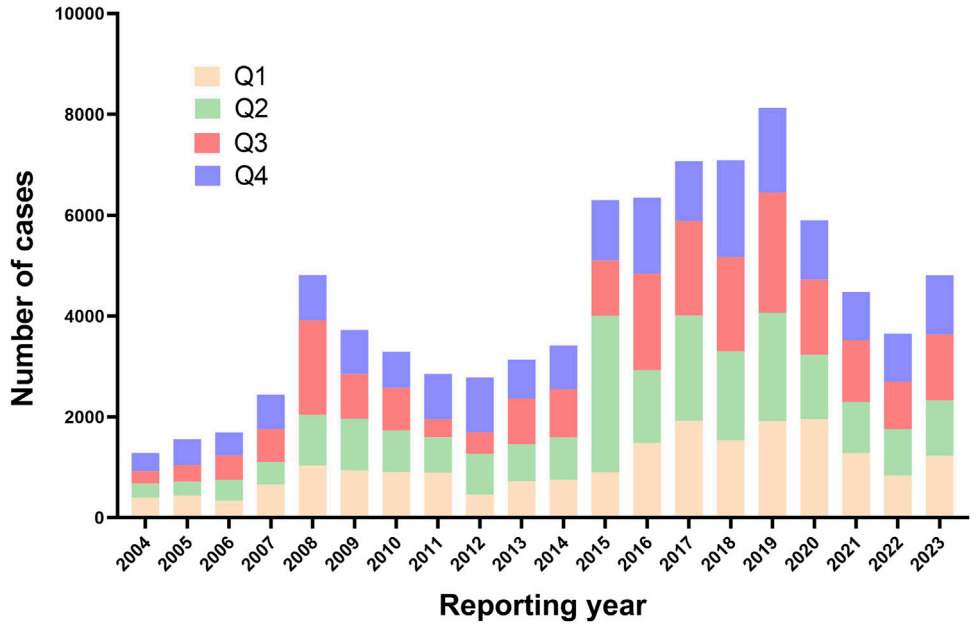


FIGURE 2
The reporting year of fluoroquinolone-associated adverse events from Q1 2004 to Q4 2023.

medications, with detailed breakdowns as follows: Ciprofloxacin (35,467), Moxifloxacin (15,441), and Levofloxacin (33,869). The temporal analysis, as shown in Figure 2, indicates an increased frequency of fluoroquinolone-related ADRs in recent years. Clinical characteristics are outlined in Table 1, with a gender prevalence of females (51.30%) over males (35.20%), a majority of patients within the 50–100 kg weight range (30.30%), and most patients aged 18–64.9 years. The primary sources of reports were Consumers (35.20%) and Physicians (20.60%), with the U.S. contributing 55.60% of reports, followed by the United Kingdom (7.80%), Italy (4.40%), Canada (4.30%), and France (3.60%).

3.2 Disproportionality analysis

3.2.1 Signal at the SOC level

The 359,480 PT-annotated ADRs within the 84,777 adverse event reports were categorized by the System Organ Class (SOC). Figure 3 illustrates the frequency and intensity of these PTs, with significant signals marked by "#." The top five SOCs by frequency were: Musculoskeletal And Connective Tissue Disorders (56,743 reports; 15.80%), General Disorders And Administration Site Conditions (47,473 reports; 13.22%), Nervous System Disorders (46,281 reports; 12.89%), Psychiatric Disorders (27,816 reports; 7.75%), and Gastrointestinal Disorders (25,560 reports; 7.12%). The corresponding RORs and 95% CIs for these SOCs are as follows: Musculoskeletal And Connective Tissue Disorders (ROR: 3.44, 95%CI: 3.41–3.47), General Disorders And Administration Site Conditions (ROR: 0.72, 95%CI: 0.71–0.73), Nervous System Disorders (ROR: 1.59, 95%CI: 1.57–1.61), Psychiatric Disorders (ROR: 1.39, 95%CI: 1.37–1.41), and Gastrointestinal Disorders (ROR: 0.82, 95%CI: 0.81–0.83).

Figure 4A presents a comparative analysis of recorded outcomes for all ADRs, categorizing them into "Psychiatric ADRs" and "Other ADRs." Statistical adverse event outcomes include Required intervention to prevent permanent impairment/damage (RI), Life-threatening (LT), Hospitalization—initial or prolonged (HO), Disability (DS), Death (DE), Congenital anomaly (CA), Other serious (OT). As shown in Figure 4B, the Psychiatry ADRs demonstrated a higher proportion of DS outcomes (17.35%) compared to the Other ADRs group (8.30%). A categorical analysis of fluoroquinolone indications, detailed in Figure 4C, reveals the top ten indications by reported ADR case volume. Notably, Epididymitis (40.91%), Prostatitis (34.97%), and Sinusitis (28.59%) showed the highest proportions of psychiatric ADRs.

3.2.2 Signal at the HLGT and PT level

The PTs under the SOC of Psychiatric Disorders were systematically classified using High-Level Group Terms (HLGTs). Figure 5 lists the top five HLGTs by reporting frequency: Anxiety Disorders And Symptoms (7,005 reports; 25.18%), Sleep Disorders And Disturbances (5,682 reports; 20.43%), Deliria (Including Confusion) (3,146 reports; 11.31%), Depressed Mood Disorders And Disturbances (2,999 reports; 10.78%), and Disturbances In Thinking And Perception (2,245 reports; 8.07%). Table 2 provides the top five PTs for each HLGT, with their ROR (95%Cl) and IC(IC025). The compilation of the most frequently reported PTs reveals that Anxiety (3,680 reports; ROR: 2.17; 95%CI: 2.10–2.25), Insomnia (3,489 reports; ROR: 2.22; 95%CI: 2.15–2.30), Depression (2,353 reports; ROR: 1.70; 95%CI: 1.63–1.77), Confusional State (1,949 reports; ROR: 2.05; 95%CI: 1.96–2.14), and Hallucination (1,089 reports; ROR: 2.58; 95%CI: 2.43–2.74) are at the forefront. Additionally, conditions such as Panic Attack (1,064 reports; ROR: 5.11; 95%CI: 4.80–5.43), Suicidal Ideation (853 reports; ROR: 1.58;

10.3389/fphar.2024.1435923

TABLE 1 Clinical characteristics of reports with fluoroquinolone from the FAERS database.

Characteristic	Total		Ciprofloxacin		Moxifloxacin		Levofloxacin	
	Case, n	Proportion	Case, n	Proportion	Case, n	Proportion	Case, n	Proportion
Total case	84,777		35,467		15,441		33,869	
Gender								
Female	43,514	51.30%	18,947	0.534	8,075	0.523	16,492	0.487
Male	29,877	35.20%	13,829	0.39	5,091	0.33	10,957	0.324
Missing	11,386	13.40%	2,691	0.076	2,275	0.147	6,420	0.19
Weight								
<50 kg	2,159	2.50%	949	0.027	385	0.025	825	0.024
>100 kg	3,250	3.80%	1,321	0.037	385	0.025	1,544	0.046
50–100 kg	25,679	30.30%	11,547	0.326	3,404	0.22	10,728	0.317
Missing	53,689	63.30%	21,650	0.61	11,267	0.73	20,772	0.613
Age								
<18	1,334	1.60%	812	0.023	151	0.01	371	0.011
>85	2,927	3.50%	1,272	0.036	480	0.031	1,175	0.035
18–64.9	34,246	40.40%	16,073	0.453	5,639	0.365	12,534	0.37
65–85	19,030	22.40%	8,665	0.244	2,820	0.183	7,545	0.223
Missing	27,240	32.10%	8,645	0.244	6,351	0.411	12,244	0.362
Reporter's type								
Consumer	29,847	35.20%	12,525	0.353	3,371	0.218	13,951	0.412
Physician	17,425	20.60%	5,995	0.169	4,709	0.305	6,721	0.198
Other health-professional	22,562	26.60%	10,408	0.293	4,762	0.309	7,392	0.219
Pharmacist	6,557	7.70%	2,761	0.078	1,210	0.078	2,586	0.076
Lawyer	917	1.10%	442	0.012	226	0.015	249	0.007
Missing	7,469	8.80%	3,336	0.094	1,163	0.075	2,970	0.088
Serious outcome								
Hospitalization—initial or prolonged	22,136	21.10%	9,685	0.216	3,458	0.188	8,993	0.216
Disability	10,357	9.90%	5,456	0.122	706	0.038	4,195	0.101
Life-threatening	5,071	4.80%	2,128	0.047	1,228	0.067	1,715	0.041
Death	3,590	3.40%	1,608	0.036	705	0.038	1,277	0.031
Required intervention to prevent permanent impairment/damage	2,256	2.20%	661	0.015	265	0.014	1,330	0.032
Congenital anomaly	146	0.10%	87	0.002	31	0.002	28	0.001
Other serious	43,765	41.70%	17,958	0.4	7,223	0.393	18,584	0.447
Reported countries (top five)								
America	47,100	55.60%	15,713	0.443	9,565	0.619	21,822	0.644
Britain	7,537	8.90%	6,214	0.176	220	0.014	1,103	0.033
Canada	4,053	4.80%	2,679	0.076	807	0.052	567	0.017
Italy	3,980	4.70%	1,235	0.035	110	0.007	2,635	0.077
France	3,353	4.00%	1,495	0.042	245	0.016	1,613	0.048

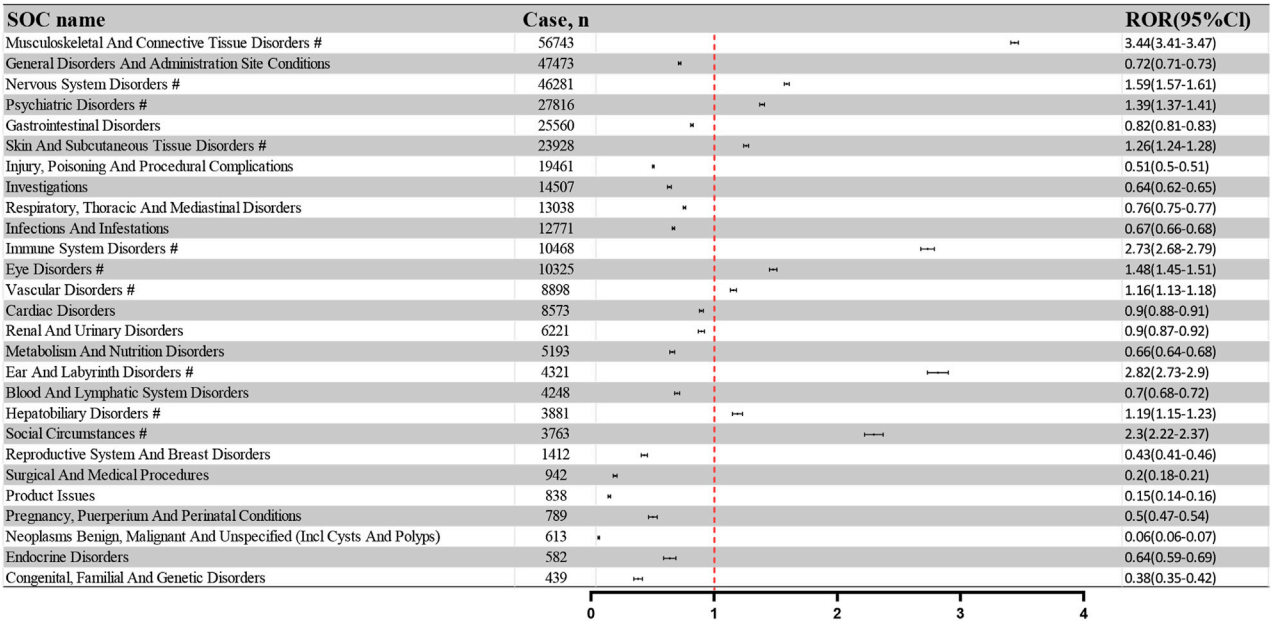


FIGURE 3
Signal strength of ADRs of fluoroquinolone at the SOC level in FAERS database.

95%CI: 1.48–1.69), Sleep Disorder (808 reports; ROR: 2.08; 95%CI: 1.94–2.23), Agitation (658 reports; ROR: 1.47; 95%CI: 1.36–1.59), and Delirium (622 reports; ROR: 3.23; 95%CI: 2.98–3.50) are also captured within the top ten most frequently reported PTs.

Supplementary Figure S1 utilizes heat maps to depict the reporting frequency and ROR values for Ciprofloxacin, Moxifloxacin, and Levofloxacin, highlighting variations in ADRs profiles. To address potential confounding factors in spontaneous reporting databases, we performed subgroup analyses. As shown in Supplementary Figures S2, S3, we subgrouped according to gender and age group and showed the top 20 PTs in terms of frequency of reporting for Females and Males, and the top 10 PTs in terms of frequency of reporting for each age group.

3.3 SMQ analysis

SMQs are utilized to focus on specific medical conditions using curated MedDRA terms, including PTs for signs, symptoms, diagnoses, and more. SMQs can be broad or narrow in scope, with the latter chosen for this study to enhance specificity. All PTs for psychiatric ADRs with positive signal were screened and categorized into narrow SMQs. Figure 6 classifies these reactions into five SMQs: Depression (excluding suicide and self-injury), Suicide/Self-Injury, Hostility/Aggression, Psychosis and Psychotic Disorders, and Noninfectious Encephalopathy/Delirium, with the heat map illustrating their frequency and ROR values. The IC (IC025) values of the three fluoroquinolones for each PT are displayed in Supplementary Table S2. Hostility/Aggression, due to its low report frequency, was not further analyzed.

Table 3 outlines the general characteristics of the four remaining SMQs and analyzes these variables for significance using the Chi-square test or Fisher's exact test, excluding missing data. Notable differences in gender and age distribution were found for the Depression SMQ ($p < 0.05$), with a higher proportion of females and concentration in the 18–64.9 age group. The suicide/self-injury age distribution also significantly differed, with 71.2% of cases in the 18–64.9 age group. Psychosis and psychotic disorders showed a significant distribution related to weight and age, with higher frequencies in the underweight and over 85 years groups. Noninfectious encephalopathy/delirium PTs were more often reported in males and underweight individuals, with a higher proportion in those over 65 years.

Figure 7 presents a comparative analysis of the reporting frequencies and RORs for four specified SMQs across three fluoroquinolone drugs: Ciprofloxacin, Moxifloxacin, and Levofloxacin. The analysis provides a detailed examination of the ADRs profiles associated with each medication. For the SMQ "Depression (excluding suicide and self-injury)," the reported reports and RORs are as follows: Ciprofloxacin (1,404 reports; ROR: 1.93; 95%CI: 1.83–2.04), Moxifloxacin (256 reports; ROR: 1.00; 95%CI: 0.88–1.13), and Levofloxacin (947 reports; ROR: 1.76; 95%CI: 1.65–1.79). In the "Suicide/Self-Injury" category, the reported reports and RORs are: Ciprofloxacin (607 reports; ROR: 2.08; 95%CI: 1.92–2.26), Moxifloxacin (104 reports; ROR: 1.01; 95% CI: 0.83–1.23), and Levofloxacin (253 reports; ROR: 1.17; 95%CI: 1.04–1.33). The IC (IC025) values of the three fluoroquinolones for each SMQ are displayed in Supplementary Table S3.

The SMQ "Psychosis and Psychotic Disorders" reveals the following reported reports and RORs: Ciprofloxacin (764 reports; ROR: 1.93; 95%CI: 1.79–2.07), Moxifloxacin (392 reports; ROR: 2.82; 95%CI: 2.55–3.11), and Levofloxacin (741 reports; ROR: 2.54; 95%CI: 2.36–2.73). Lastly, for "Noninfectious Encephalopathy/ Delirium," the reported reports and RORs are: Ciprofloxacin (146 reports; ROR: 1.56; 95%CI: 1.33–1.84), Moxifloxacin (227 reports; ROR: 6.97; 95%CI: 6.11–7.94), and Levofloxacin

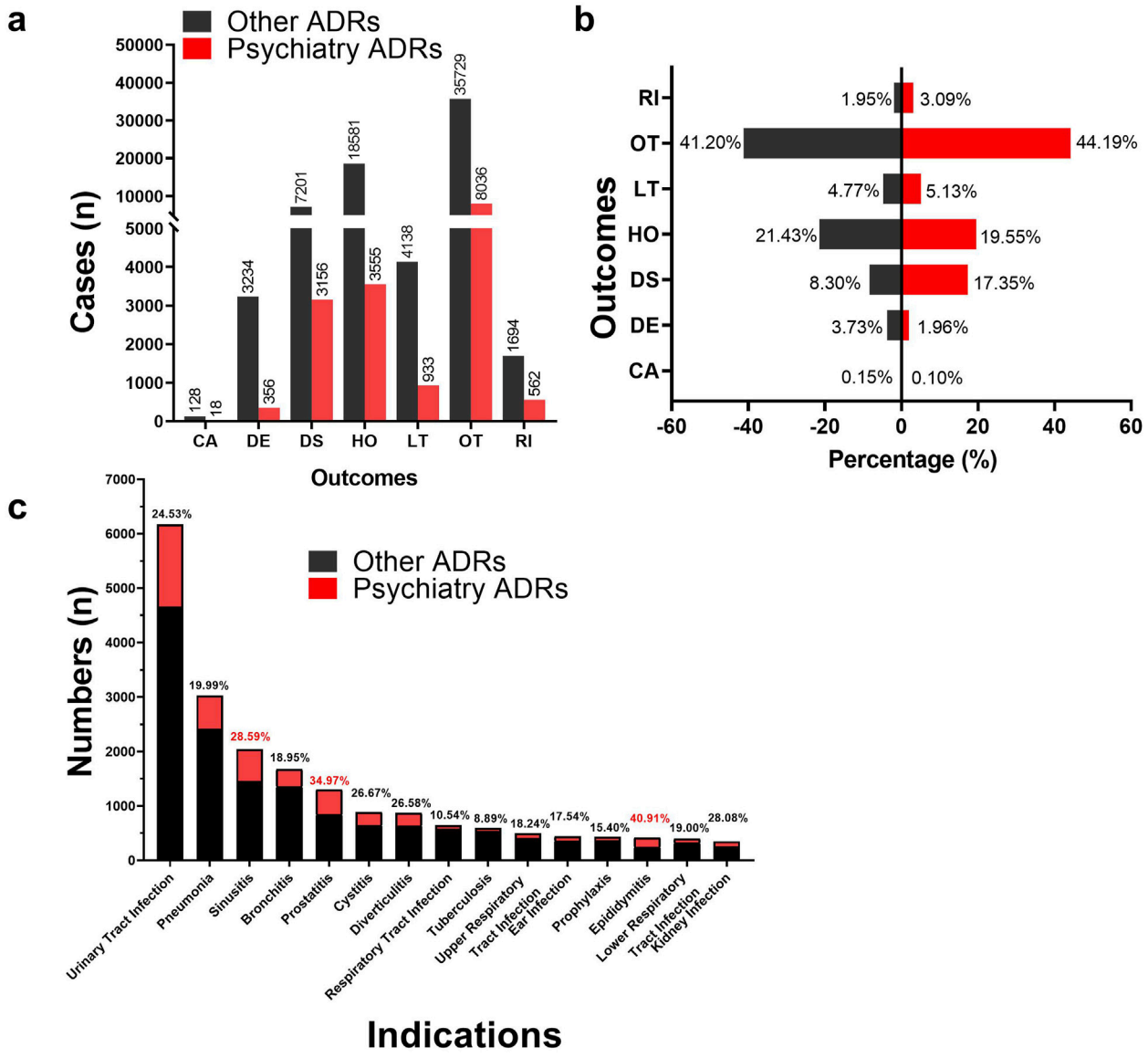


FIGURE 4
Differences in outcomes and indications between psychiatric ADRs and other ADRs. **(A, B)** Histogram of the difference in frequency and percentage of outcome information reports for psychiatric ADRs and other ADRs. **(C)** Histogram of differences in indications for psychiatric ADRs and other ADRs. (Abbreviations: RI, Required intervention to prevent permanent impairment/damage; OT, Other serious; LT, Life-threatening; HO, Hospitalization—initial or prolonged; DS, Disability; DE, Death; CA, Congenital anomaly).

(249 reports; ROR: 3.63; 95%CI: 3.20–4.11). These findings offer a nuanced perspective on the differential reporting patterns and signal intensities of psychiatric ADRs related to fluoroquinolone drugs, as identified by the respective SMQs.

4 Discussion

In the present study, we undertook a comprehensive mining and analysis of adverse event reports for fluoroquinolones, as documented in the FAERS database. Our focus was on events categorized under the SOC pertaining to mental disorders. Notably, within the HLGT designations of ADRs associated with fluoroquinolones, mood disorders were predominantly reported. This includes a spectrum of conditions such as anxiety disorders and major depressive episodes, alongside other significant psychiatric disorders like delirium. In severe instances, these events extended to manifestations of suicidal ideation or the occurrence of suicidal behaviors. SMQ classification further delineated the psychiatric ADRs into specific categories, encompassing depression, suicide/self-injury, psychosis and other psychotic disorders, and non-infectious encephalopathy/delirium. Further analysis revealed that the risk of psychiatric ADRs varied by age group, with affective disorders more prevalent in adults under 65 and psychosis and delirium in those over 65. These findings collectively imply that the prescribing and utilization of fluoroquinolones should be approached with an awareness of the potential risks to mental health.

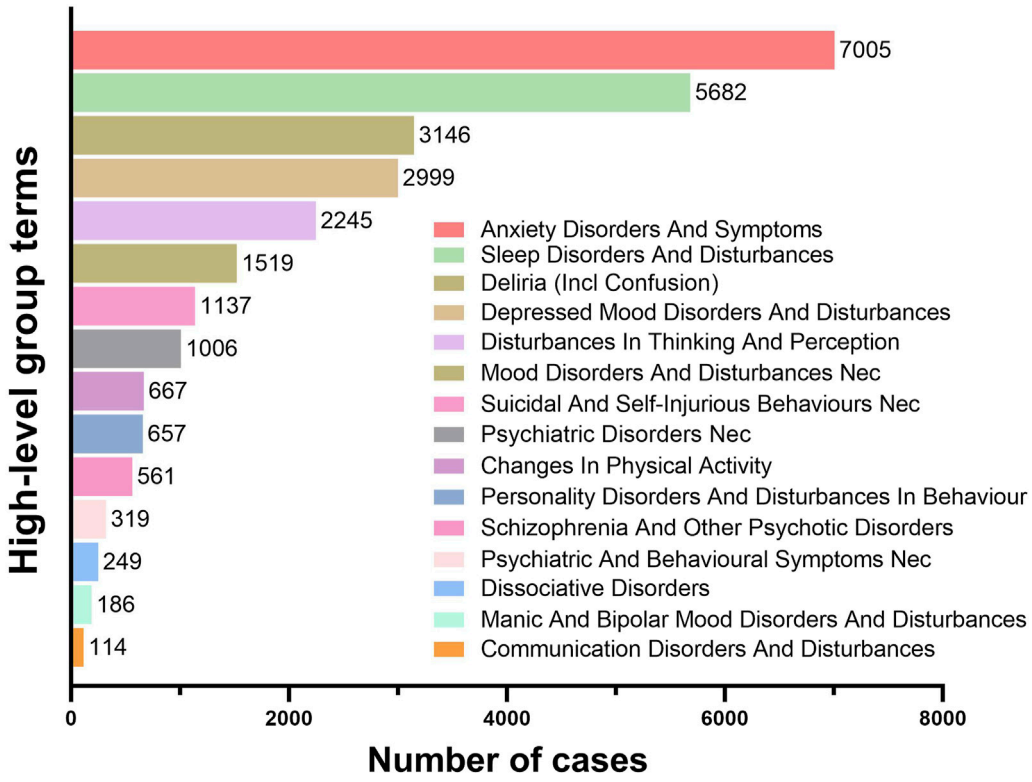


FIGURE 5
Signal strength of ADRs of fluoroquinolone at the HLGT level in FAERS database.

We systematically analyzes the psychiatric adverse events associated with fluoroquinolone drugs in the FAERS database, which shows both similarities and differences with many existing literature results. In a systematic review, a meta-analysis of psychiatric adverse reactions reported from 68 pieces of literature on fluoroquinolone drugs was conducted, which, consistent with this research, also reported adverse reactions such as delirium, psychosis, hallucinations, insomnia, and depression caused by fluoroquinolones (Wierzbinski et al., 2023). However, due to the small sample size of this paper, the statistics on the types of psychiatric adverse reactions are not as comprehensive as this study, and the impact of factors such as age and gender on the risk of adverse events cannot be assessed. A population-based cohort study in Ontario, Canada, showed that elderly patients using high doses of fluoroquinolones were more likely to experience psychiatric adverse reactions, including disturbances of consciousness such as delirium, disorientation, temporary changes in consciousness, agitation, and tension (Muanda et al., 2022). HARTINGER et al. also pointed out in a retrospective study that psychiatric adverse reactions caused by ciprofloxacin are common in elderly patients over 70 years old, with an incidence rate as high as 13.6% in the group over 80 years old (Hartinger et al., 2023). In this study, we found that in the elderly group over 65 years old, psychosis and delirium are more common adverse reactions, while the group under 65 years old is more prone to emotional disorders. This study took advantage of the large volume of data in the FAERS database for a more detailed analysis, and the study evaluated the correlation between adverse events and drugs through disassociation analysis, clearly reflecting the degree of correlation.

Within the spectrum of psychiatric ADRs induced by fluoroquinolones, a substantial proportion was attributed to Anxiety Disorders And Symptoms, with Anxiety and Panic Attack being particularly prevalent in terms of frequency and severity. While anxiety disorders are typically associated with mild outcomes that do not impede the course of treatment, they are infrequently linked to fluoroquinolone use. Nonetheless, evidence of fluoroquinolone-induced anxiety is emerging from both preclinical and clinical studies. Experimental data demonstrate that enrofloxacin can elicit anxiety-like behaviors in zebrafish via modulation of the gut-brain axis (Tian et al., 2023), and sparfloxacin has been observed to elevate anxiety levels in murine models (Bharal et al., 2006). Furthermore, oral administration of ciprofloxacin and norfloxacin has been documented to induce anxiogenic effects in rats (Sen et al., 2007). Clinical reports have also described anxiety disorders associated with the use of ciprofloxacin and levofloxacin (Maharani et al., 2019; Munjal and Smolin, 2017; Kandasamy and Srinath, 2012). In our analysis, anxiety emerged as a common ADRs, and ciprofloxacin was more frequently associated with anxiety adverse events relative to moxifloxacin and levofloxacin. Given that fluoroquinolones are known to competitively bind to the GABA-A receptor ($GABA_AR$) (Halliwell et al., 1995; Akaike et al., 1991), a mechanism that typically serves an anxiolytic function, the pathogenesis of anxiety symptoms induced by these agents may be related to their inhibitory effects on GABAergic

TABLE 2 Signal strength of ADRs of the HLGTs-PTs belongs to psychiatric disorders.

HLGTs	PTs (Top five for each hlgt)	Cases, n	ROR (95% CI)	IC (IC025)
Anxiety Disorders And Symptoms	Anxiety	3,680	2.17 (2.1–2.25)	1.1 (−0.57)
	Panic Attack	1,064	5.11 (4.8–5.43)	2.31 (0.64)
	Agitation	658	1.47 (1.36–1.59)	0.55 (−1.12)
	Nervousness	484	1.49 (1.36–1.63)	0.57 (−1.1)
	Fear	271	1.59 (1.41–1.79)	0.66 (-1.01)
Sleep Disorders And Disturbances	Insomnia	3,489	2.22 (2.15–2.3)	1.13 (−0.53)
	Sleep Disorder	808	2.08 (1.94–2.23)	1.04 (−0.62)
	Nightmare	610	2.95 (2.73–3.2)	1.54 (−0.12)
	Middle Insomnia	196	1.86 (1.61–2.14)	0.89 (−0.78)
	Abnormal Dreams	189	1.1 (0.95–1.27)	0.14 (−1.53)
Deliria (Incl Confusion)	Confusional State	1,949	2.05 (1.96–2.14)	1.02 (−0.64)
	Delirium	622	3.23 (2.98–3.5)	1.67 (0)
	Disorientation	575	2.4 (2.21–2.6)	1.25 (−0.42)
Depressed Mood Disorders And Disturbances	Depression	2,353	1.7 (1.63–1.77)	0.75 (−0.91)
	Depressed Mood	289	0.96 (0.85–1.08)	−0.06 (−1.73)
	Anhedonia	90	0.52 (0.42–0.64)	−0.95 (−2.61)
	Feeling Of Despair	58	2.18 (1.68–2.83)	1.11 (−0.55)
	Depression Suicidal	43	2.07 (1.53–2.8)	1.04 (−0.63)
Disturbances In Thinking And Perception	Hallucination	1,089	2.58 (2.43–2.74)	1.35 (−0.32)
	Hallucination, Visual	296	2.54 (2.26–2.85)	1.33 (−0.34)
	Thinking Abnormal	252	2.2 (1.94–2.49)	1.12 (−0.54)
	Hallucination, Auditory	121	1.3 (1.09–1.56)	0.38 (−1.29)
	Delusion	121	1.35 (1.13–1.62)	0.43 (−1.23)
Mood Disorders And Disturbances Nec	Emotional Distress	319	0.4 (0.36–0.45)	−1.3 (−2.97)
	Irritability	236	0.64 (0.57–0.73)	−0.63 (−2.3)
	Emotional Disorder	146	0.78 (0.67–0.92)	−0.35 (−2.02)
	Mood Altered	145	0.91 (0.77–1.07)	−0.13 (−1.8)
	Anger	132	0.63 (0.53–0.75)	−0.66 (−2.32)
Suicidal And Self-Injurious Behaviours Nec	Suicidal Ideation	853	1.58 (1.48–1.69)	0.66 (−1.01)
	Completed Suicide	105	0.21 (0.17–0.25)	−2.28 (−3.94)
	Suicide Attempt	86	0.24 (0.19–0.29)	−2.06 (−3.72)
	Self-Injurious Ideation	35	1.45 (1.04–2.02)	0.53 (−1.14)
	Suicidal Behaviour	33	1.3 (0.92–1.83)	0.38 (−1.29)
Psychiatric Disorders Nec	Mental Disorder	597	2.35 (2.17–2.55)	1.22 (−0.45)
	Mental Status Changes	186	1.12 (0.97–1.3)	0.17 (−1.5)
	Neuropsychological Symptoms	79	10 (7.96–12.56)	3.23 (1.57)
	Drug Abuse	78	0.16 (0.13–0.2)	−2.66 (−4.33)
	Drug Dependence	10	0.01 (0.01–0.02)	−6.73 (−8.4)

(Continued on following page)

TABLE 2 (*Continued*) Signal strength of ADRs of the HLGTs-PTs belongs to psychiatric disorders.

HLGTs	PTs (Top five for each hlgt)	Cases, n	ROR (95% CI)	IC (IC025)
Changes In Physical Activity	Restlessness	551	2.54 (2.34–2.76)	1.33 (−0.34)
	Catatonia	51	1.77 (1.34–2.33)	0.81 (−0.85)
	Tic	33	0.99 (0.7–1.4)	−0.01 (−1.68)
	Bruxism	9	0.28 (0.15–0.55)	−1.81 (−3.48)
	Head Banging	5	1.47 (0.61–3.55)	0.55 (−1.12)
Personality Disorders And Disturbances In Behaviour	Paranoia	270	2.62 (2.32–2.96)	1.37 (−0.29)
	Aggression	204	0.67 (0.58–0.77)	−0.58 (−2.25)
	Personality Change	54	0.93 (0.71–1.21)	−0.11 (−1.78)
	Social Avoidant Behaviour	28	0.76 (0.52–1.1)	−0.39 (−2.06)
	Violence-Related Symptom	19	1.95 (1.24–3.06)	0.95 (−0.72)

Abbreviations: HLGT, high level group terms; PT, preferred terms; ROR, reporting odds ratio; CI, confidence interval; Nec, not elsewhere classified; Incl, inclusion; IC, information component.

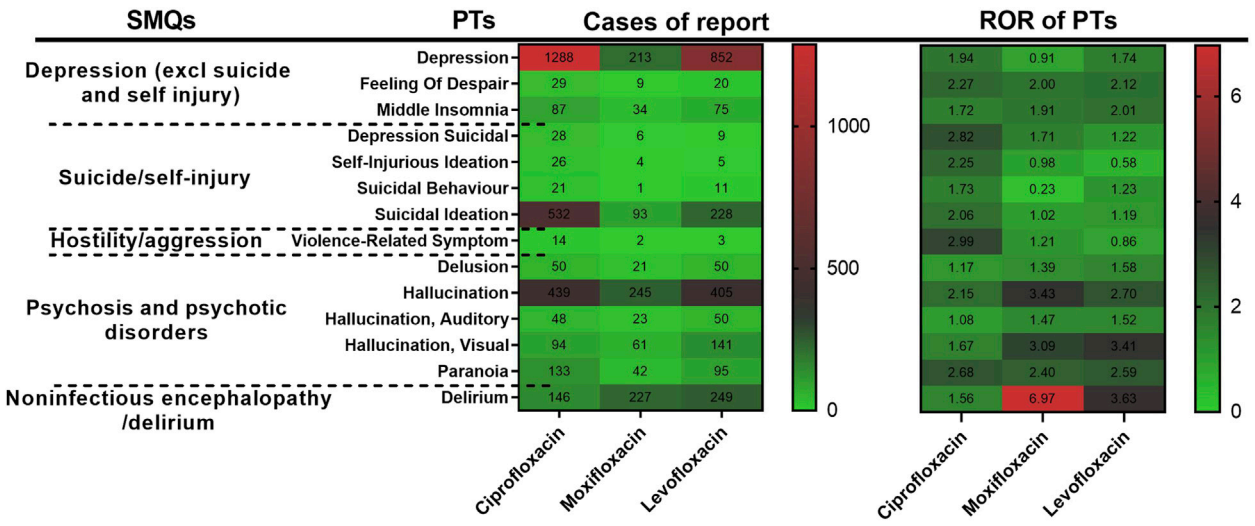


FIGURE 6
Heatmap of signal strength of PTs after SMQ clustering.

neurotransmission. Additionally, benzodiazepines, known for their sedative properties, act through the GABA system (Kim and Hibbs, 2021; Miczek et al., 1995), further underscoring the significance of this pathway in anxiety modulation. Conversely, the impact of fluoroquinolones on gut microbiota may also contribute to anxiety symptoms, as perturbations in the gut microbiota can influence anxiety levels via the gut-brain axis (Tian et al., 2023). It is conceivable that the heightened affinity of ciprofloxacin for $GABA_AR$, in conjunction with the sensitivity of certain gut microbiota to anxiety, may precipitate a higher likelihood of anxiety-related ADRs with this particular fluoroquinolone.

Clinical case reports have detailed instances of delirium induced by moxifloxacin in the geriatric population, highlighting the neuropsychiatric risks associated with this class of antibiotics (Pozo et al., 2015). Furthermore, there is documentation of levofloxacin-triggered delirium in a patient with comorbid schizophrenia and multiple sclerosis (Lertxundi et al., 2013). A retrospective analysis of 631 veterans exposed to fluoroquinolones revealed a notable rate of psychosis/delirium, approximately 3.7%, with ciprofloxacin and moxifloxacin being more strongly associated with delirium than levofloxacin (Sellick et al., 2018). While delirium as an ADR to quinolones is sometimes underappreciated, our study, employing a disproportionality analysis method, has identified a robust correlation between fluoroquinolone use and the incidence of delirium, with a particularly significant association observed for moxifloxacin. The data presented in Table 3 of our study further indicate that the frequency of reported delirium was significantly higher in those aged 65–85 years and those aged 85 years and above, suggesting that increased age is a potential risk factor for this adverse event. Additionally, our findings suggest that delirium is reported more frequently in men compared to women. These observations imply that a heightened index of suspicion and preventive measures may be warranted when

10.3389/fphar.2024.1435923

TABLE 3 Clinical characteristics of reports with fluoroquinolone at the SMQ level in FAERS database.

SMQs	Clinical characteristics	NO_target PTs	Target PTs	*p*-value
Depression (excl suicide and self injury) (DEMO, n = 2,559)	Gender			0.0486
	F	42,023 (51.1%)	1,491 (58.3%)	
	M	28,933 (35.2%)	944 (36.9%)	
	Missing	11,262 (13.7%)	124 (4.8%)	
	Weight			0.1475
	<50 kg	2,033 (2.5%)	126 (4.9%)	
	>100 kg	3,091 (3.8%)	159 (6.2%)	
	50–100 kg	24,212 (29.4%)	1,467 (57.3%)	
	Missing	52,882 (64.3%)	807 (31.5%)	
	Age			<0.0001
	<18	1,322 (1.6%)	12 (0.5%)	
	>85	2,910 (3.5%)	17 (0.7%)	
	18–64.9	32,496 (39.5%)	1750 (68.4%)	
	65–85	18,724 (22.8%)	306 (12.0%)	
	Missing	26,766 (32.6%)	474 (18.5%)	
Suicide/self-injury (DEMO, n = 931)	Gender			0.2262
	F	43,013 (51.3%)	501 (53.8%)	
	M	29,502 (35.2%)	375 (40.3%)	
	Missing	11,331 (13.5%)	55 (5.9%)	
	Weight			0.6502
	<50 kg	2,120 (2.5%)	39 (4.2%)	
	>100 kg	3,188 (3.8%)	62 (6.7%)	
	50–100 kg	25,152 (30.0%)	527 (56.6%)	
	Missing	53,386 (63.7%)	303 (32.5%)	
	Age			<0.0001
	<18	1,330 (1.6%)	4 (0.4%)	
	>85	2,923 (3.5%)	4 (0.4%)	
	18–64.9	33,583 (40.1%)	663 (71.2%)	
	65–85	18,924 (22.6%)	106 (11.4%)	
	Missing	27,086 (32.3%)	154 (16.5%)	
Psychosis and psychotic disorders (DEMO, n = 1,696)	Gender			0.0607
	F	42,553 (51.2%)	961 (56.7%)	
	M	29,278 (35.2%)	599 (35.3%)	
	Missing	11,250 (13.5%)	136 (8.0%)	
	Weight			0.0002
	<50 kg	2,064 (2.5%)	95 (5.6%)	
	>100 kg	3,167 (3.8%)	83 (4.9%)	
	50–100 kg	24,935 (30.0%)	744 (43.9%)	
	Missing	52,915 (63.7%)	774 (45.6%)	

(Continued on following page)

TABLE 3 (*Continued*) Clinical characteristics of reports with fluoroquinolone at the SMQ level in FAERS database.

SMQs	Clinical characteristics	NO_target PTs	Target PTs	*p*-value
	Age			<0.0001
	<18	1,307 (1.6%)	27 (1.6%)	
	>85	2,784 (3.4%)	143 (8.4%)	
	18–64.9	33,503 (40.3%)	743 (43.8%)	
	65–85	18,581 (22.4%)	449 (26.5%)	
	Missing	26,906 (32.4%)	334 (19.7%)	
Noninfectious encephalopathy/delirium (DEMO, n = 622)	Gender			<0.0001
	F	43,261 (51.4%)	253 (40.7%)	
	M	29,555 (35.1%)	322 (51.8%)	
	Missing	11,339 (13.5%)	47 (7.6%)	
	Weight			<0.0001
	<50 kg	2,132 (2.5%)	27 (4.3%)	
	>100 kg	3,242 (3.9%)	8 (1.3%)	
	50–100 kg	25,446 (30.2%)	233 (37.5%)	
	Missing	53,335 (63.4%)	354 (56.9%)	
	Age			<0.0001
	<18	1,321 (1.6%)	13 (2.1%)	
	>85	2,829 (3.4%)	98 (15.8%)	
	18–64.9	34,085 (40.5%)	161 (25.9%)	
	65–85	18,761 (22.3%)	269 (43.2%)	
	Missing	27,159 (32.3%)	81 (13.0%)	

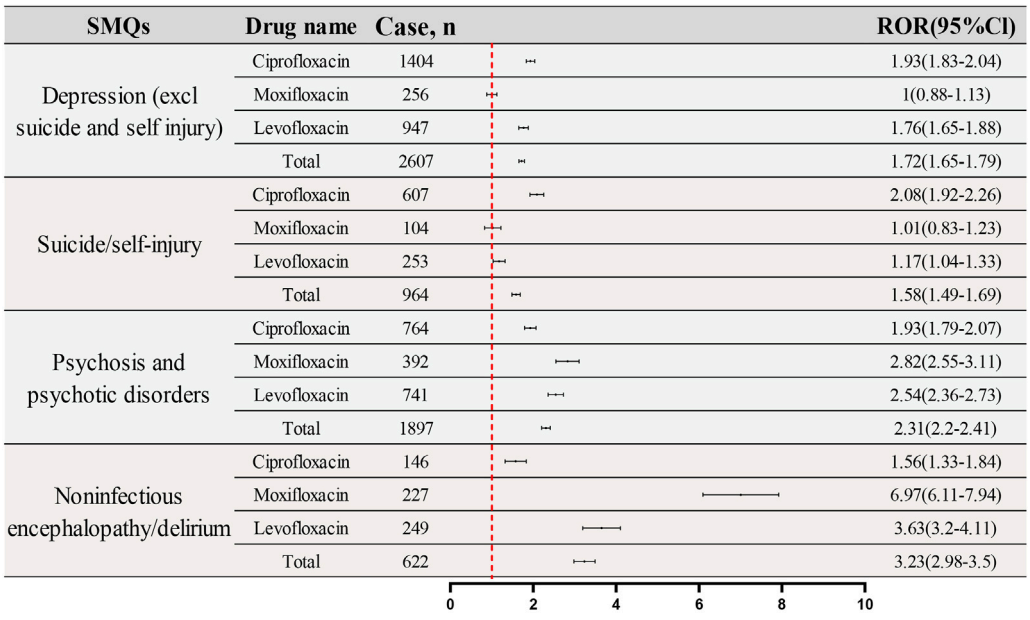


FIGURE 7
Signal strength of ADRs of fluoroquinolones at the SMQ level in FAERS database.

administering moxifloxacin to elderly male patients to mitigate the risk of delirium.

Despite the number of reports of depression- and suicide-related ADRs associated with fluoroquinolone antibiotics, the scrutiny accorded to this phenomenon has been relatively low, with a dearth of studies specifically addressing the issue. A case report documented the onset of suicidal ideation in a 75-year-old subject following treatment with levofloxacin (Lasalvia et al., 2010). Another case study revealed the emergence of depressive symptoms and suicidal ideation in a 26-year-old patient upon sequential exposure to ciprofloxacin, subsequent to a combination therapy involving levofloxacin and metronidazole (Labay-Kamara et al., 2012). A review of the FDA's adverse event reports linked to fluoroquinolones identified that incidents of suicidal behavior were frequently reported within a fortnight of the commencement of fluoroquinolone therapy (Kommalapati et al., 2018). Notably, even among patients devoid of a psychiatric history, suicidal ideation or attempts have been observed following fluoroquinolone use, with a subsequent resolution of symptoms upon cessation of the medication (Lasalvia et al., 2010; Labay-Kamara et al., 2012; Ahmed et al., 2011). In the current study, the PTs for Depression and Suicidal Ideation exhibited relatively elevated reporting frequencies within the context of ADRs associated with fluoroquinolone antibiotics. Our analysis utilizing the SMQ classification further substantiated the association of psychiatric ADRs of quinolones with Depression and Suicide/Self-Injury categories. Notably, Ciprofloxacin emerged as the fluoroquinolone most frequently implicated in reports of depression and suicidal ideation, with the highest reporting intensity observed among the trio of fluoroquinolones under review. Conversely, Moxifloxacin appeared to be associated with a potentially lower risk of Depression and Suicide/Self-Injury related ADRs. These findings underscore the importance of a nuanced approach when selecting fluoroquinolone therapy, particularly for patients with pre-existing depression or established suicide risk factors. In such cases, Moxifloxacin may be considered the treatment of choice, prioritizing patient safety and mental health considerations.

In the present study, the "Psychosis and Psychotic Disorders" category within the SMQ classification was observed to encompass a significant proportion of hallucination-related ADRs. These included, but were not limited to, "hallucination," "auditory hallucination," and "visual hallucination." Although ciprofloxacin was associated with a relatively elevated frequency of such hallucinatory ADRs, the intensity of reporting for this particular drug was found to be less pronounced in comparison to levofloxacin and moxifloxacin. Conversely, the risk of inducing paranoia was noted to be analogous across the three fluoroquinolone antibiotics under review. The etiology of hallucinatory ADRs attributed to fluoroquinolones may be multifactorial, potentially linked to both the dosage levels of fluoroquinolones and their concomitant use with other pharmacological agents (Bhattacharya et al., 2017; Chauhan et al., 2013). Additionally, the relationship between these ADRs and the patient's psychiatric history warrants further investigation, with the necessity for corroboration through extensive real-world data analysis.

Fluoroquinolones, when juxtaposed with other antibiotic classes, have been observed to elicit a higher incidence of psychiatric ADRs, particularly in the geriatric population who are more susceptible to neurotoxic symptoms (Mattappalil and Mergenhagen, 2014). However, the validity of this age-related inference is constrained by the limited sample size within the surveyed data corpus. This limitation is partially mitigated by the extensive data repository of the FAERS, which affords a broader perspective on the observed trends. Upon application of the SMQ classification framework, this study discerned significant disparities in the age distribution of subjects experiencing ADRs across four distinct categories, when compared to the general ADRs profile. The primary reported population for depression and suicide/self-injury was identified as the 18–64.9 year age group. In contrast, the proportion of individuals over 65 years of age was disproportionately higher within the Psychosis and Psychotic Disorder and Noninfectious Encephalopathy/Delirium categories. We therefore hypothesized that the incidence of psychiatric adverse effects caused by fluoroquinolones is not invariably elevated in the elderly but rather that affective disorders are more prevalent in adults below the age of 65. It is important to note that the use of fluoroquinolones in the pediatric population is often restricted, which may introduce a degree of bias into the analysis. Nevertheless, the data imply a correlation between the incidence of psychiatric adverse reactions and age, suggesting that different age cohorts may require targeted preventative strategies when administering fluoroquinolones.

FAERS is an essential drug safety monitoring tool, but it has limitations that can affect the interpretation of data on fluoroquinolone antibiotics and their potential to cause psychiatric ADRs. Voluntary reporting can lead to underreporting, especially for conditions like psychiatric disorders that may be misdiagnosed. The dataset may also be biased towards more severe reactions, potentially distorting the prevalence of certain effects. Additionally, FAERS lacks detailed patient information, such as concurrent medications, which could influence the development of psychiatric reactions and obscure the assessment of drug interactions. The database does not offer direct incidence rates, complicating the determination of actual risks associated with fluoroquinolone use. Moreover, the database's age-related data may not represent the broader population, particularly concerning the elderly who are more susceptible to neurotoxic effects. Importantly, FAERS data cannot establish causation; it only indicates potential associations. The causes of adverse reactions, like hallucinations or suicidal thoughts, are likely multifactorial and require further investigation to establish a definitive link to fluoroquinolones. In conclusion, while FAERS is a valuable resource, its limitations must be acknowledged when interpreting data on psychiatric adverse reactions related to fluoroquinolones. Further research, including prospective studies and real-world data analysis, is essential to confirm and expand upon FAERS findings.

5 Conclusion

The study presents a thorough analysis of the FAERS database to investigate the psychiatric adverse events associated with fluoroquinolone antibiotics. The research, focusing on mental disorders, revealed that mood disorders were the most frequently reported, including anxiety, depression, and delirium, with some reports escalating to suicidal ideation and behaviors. The SMQ classification system was used to categorize these ADRs into Depression, Suicide/self-injury, Psychosis and psychotic disorders, and Non-infectious encephalopathy/delirium. Anxiety disorders and

symptoms were particularly prevalent, with ciprofloxacin showing a higher anxiogenic potential, possibly due to its interaction with the GABA-A receptor and its impact on gut microbiota. Delirium, especially in the elderly, was significantly associated with fluoroquinolone use, with moxifloxacin showing a robust correlation. The potential for fluoroquinolones to induce suicidal ideation deserves more attention. Hallucination-related ADRs were significant, with a multifactorial etiology potentially involving dosage levels and concomitant medication use. The study found that the frequency of reported psychiatric ADRs varied by age group, with more ADRs related to affective disorders reported in adults under 65 years of age, compared to psychosis and delirium in the group over 65 years of age. The findings emphasize the need for caution in fluoroquinolone prescription and suggest that age-specific preventive strategies may be necessary.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: All data in this study are openly accessed as an ASCII data package from the FAERS website: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

W-LX: Data curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing–original draft, Writing–review and editing. M-LG: Data curation, Formal Analysis, Methodology, Writing–original draft, Writing–review and editing. DC: Data curation, Software, Visualization, Writing–original draft, Writing–review and editing. G-QC: Methodology, Writing–review and editing. Y-XM: Formal Analysis, Project administration, Supervision, Writing–original draft, Writing–review and editing, Visualization. Y-JL: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1435923/full#supplementary-material

References

Ahmed, A. I., van der Heijden, F. M., van den Berkmortel, H., and Kramers, K. (2011). A man who wanted to commit suicide by hanging himself: an adverse effect of ciprofloxacin. *Gen. Hosp. Psych.* 33 (1), 82.e5–e7. doi:10.1016/j.genhosppsych.2010.07.002

Akaike, N., Shirasaki, T., and Yakushiji, T. (1991). Quinolones and fenbufen interact with GABAA receptor in dissociated hippocampal cells of rat. *J. Neurophysiol.* 66 (2), 497–504. doi:10.1152/jn.1991.66.2.497

Aschenbrenner, D. S. (2016). The FDA revises boxed warning for fluoroquinolones-again. *Am. J. Nurs.* 116 (9), 22–23. doi:10.1097/01.NAJ.0000494691.55746.90

Author Anonymous (2024). MHRA issues two updates on fluoroquinolone safety. *Drug Ther. Bull.* 62 (2), 19. doi:10.1136/dtb.2023.000069

Bharal, N., Pillai, K. K., and Vohora, D. (2006). Effects of sparfloxacin on CNS functions and urinary hydroxyproline in mice. *Pharmacol. Res.* 54 (2), 111–117. doi:10.1016/j.phrs.2006.03.004

Bhattacharya, A., Sharan, R., and Praharaj, S. K. (2017). High dose ofloxacin-induced bimodal hallucinations in a 4 Years old child. *Clin. Psychopharmacol. Neurosci.* 15 (4), 416–417. doi:10.9758/cpn.2017.15.4.416

Chauhan, U., Shanbag, P., and Kashid, P. (2013). Ofloxacin-induced hallucinations. *Indian J. Pharmacol.* 45 (2), 189–190. doi:10.4103/0253-7613.108316

Halliwell, R. F., Davey, P. G., and Lambert, J. J. (1995). A patch clamp study of the effects of ciprofloxacin and biphenyl acetic acid on rat hippocampal neurone GABAA and ionotropic glutamate receptors. *Neuropharmacology* 34 (12), 1615–1624. doi:10.1016/0028-3908(95)00106-9

Harpaz, R., Dumochel, W., and Shah, N. H. (2016). Big data and adverse drug reaction detection. *Clin. Pharmacol. Ther.* 99 (3), 268–270. doi:10.1002/cpt.302

Hartinger, J. M., Dvorackova, E., Myslivecek, M., Hruskova, Z., Satny, M., Zlatohlavek, L., et al. (2023). The frequency of, and predisposing risk factors for, ciprofloxacin-induced neuro-psychiatric adverse drug reactions. *Bratisl. Lek. Listy.* 124 (10), 779–782. doi:10.4149/BLL_2023_120

Ilgin, S., Can, O. D., Atli, O., Ucel, U. I., Sener, E., and Guven, I. (2015). Ciprofloxacin-induced neurotoxicity: evaluation of possible underlying mechanisms. *Toxicol. Mech. Methods.* 25 (5), 374–381. doi:10.3109/15376516.2015.1026008

Kandasamy, A., and Srinath, D. (2012). Levofloxacin-induced acute anxiety and insomnia. *J. Neurosci. Rural. Pract.* 3 (2), 212–214. doi:10.4103/0976-3147.98256

Kaur, K., Fayad, R., Saxena, A., Frizzell, N., Chanda, A., Das, S., et al. (2016). Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: a collaborative investigation by scientists and members of a social network. *J. Community Support Oncol.* 14 (2), 54–65. doi:10.12788/jcso.0167

Kim, J. J., and Hibbs, R. E. (2021). Direct structural insights into GABA(A) receptor pharmacology. *Trends biochem. Sci.* 46 (6), 502–517. doi:10.1016/j.tibs.2021.01.011

Kommalapati, A., Wallam, S., Tella, S. H., Qureshi, Z. P., and Bennett, C. L. (2018). Fluoroquinolone-associated suicide. *Eur. J. Intern. Med.* 55, e21–e22. doi:10.1016/j.ejim.2018.07.012

Labay-Kamara, U., Manning, S., and Mcmahon, T. (2012). Fluoroquinolone-induced suicidal ideation and suicidality. *Psychosomatics* 53 (1), 97–98. doi:10.1016/j.psym.2011.05.003

Lasalvia, E. A., Domek, G. J., and Gitlin, D. F. (2010). Fluoroquinolone-induced suicidal ideation. *Gen. Hosp. Psych.* 32 (1), 108–110. doi:10.1016/j.genhosppsych.2009.03.002

Leone, R., Venegoni, M., Motola, D., Moretti, U., Piazzetta, V., Cocci, A., et al. (2003). Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Saf.* 26 (2), 109–120. doi:10.2165/00002018-200326020-00004

Lertxundi, U., Palacios, R. H., Gutierrez, F. C., Echaburu, S. D., Garcia, M. G., and Gomez, C. A. (2013). Levofloxacin-induced delirium in a patient suffering from schizoaffective disorder and multiple sclerosis. Curr. *Drug Saf.*

Maharani, B., Jafrin, A. L., Bai, K. V., and Sivagnanam, G. (2019). Levofloxacin-induced tactile hallucination and acute anxiety reaction. *Indian J. Pharmacol.* 51 (2), 123–125. doi:10.4103/ijp.IJP_291_17

Mahoney, M. V., and Swords, K. E. (2021). Fluoroquinolones: friends or foes? *Clin. Infect. Dis.* 73 (5), 857–858. doi:10.1093/cid/ciab150

Mattappalil, A., and Mergenhagen, K. A. (2014). Neurotoxicity with antimicrobials in the elderly: a review. *Clin. Ther.* 36 (11), 1489–1511. doi:10.1016/j.clinthera.2014.09.020

Miczek, K. A., Weerts, E. M., Vivian, J. A., and Barros, H. M. (1995). Aggression, anxiety and vocalizations in animals: GABAA and 5-HT anxiolytics. *Psychopharmacology* 121 (1), 38–56. doi:10.1007/BF02245590

Muanda, F. T., Sood, M. M., Weir, M. A., Sontrop, J. M., Ahmadi, F., Yoo, E., et al. (2022). Association of higher-dose fluoroquinolone therapy with serious adverse events in older adults with advanced chronic kidney disease. *JAMA Netw. Open* 5 (8), e2224892. doi:10.1001/jamanetworkopen.2022.24892

Munjal, S., and Smolin, Y. (2017). Ciprofloxacin associated exacerbation of anxiety in an elderly patient: a review of anxiogenic potential of fluoroquinolones. *J. Clin. Psychopharmacol.* 37 (3), 370–372. doi:10.1097/JCP.0000000000000696

Pozo, E. D., Arana-Asensio, E., and Garcia-Lopez, P. (2015). Acute confusional syndrome induced by moxifloxacin in an elderly man. *J. Am. Geriatr. Soc.* 63 (12), 2647–2648. doi:10.1111/jgs.13856

Ruan, S., Tu, C. H., and Bourne, C. R. (2024). Friend or foe: protein inhibitors of DNA gyrase. *Biology-Basel* 13 (2), 84. doi:10.3390/biology13020084

Sanders, V. R., Sweeney, A., Topf, M., and Millar, N. S. (2022). Stoichiometry-selective antagonism of α4β2 nicotinic acetylcholine receptors by fluoroquinolone antibiotics. *ACS Chem. Neurosci.* 13 (12), 1805–1817. doi:10.1021/acschemneuro.2c00200

Sellick, J., Mergenhagen, K., Morris, L., Feuz, L., Horey, A., Risbood, V., et al. (2018). Fluoroquinolone-related neuropsychiatric events in hospitalized veterans. *Psychosomatics* 59 (3), 259–266. doi:10.1016/j.psym.2017.11.001

Sen, S., Jaiswal, A. K., Yanpallewar, S., and Acharya, S. B. (2007). Anxiogenic potential of ciprofloxacin and norfloxacin in rats. *Singap. Med. J.* 48 (11), 1028–1032.

Smelt, C., Sanders, V. R., Newcombe, J., Burt, R. P., Sheppard, T. D., Topf, M., et al. (2018). Identification by virtual screening and functional characterisation of novel positive and negative allosteric modulators of the α7 nicotinic acetylcholine receptor. *Neuropharmacology* 139, 194–204. doi:10.1016/j.neuropharm.2018.07.009

Tian, D., Shi, W., Yu, Y., Zhou, W., Tang, Y., Zhang, W., et al. (2023). Enrofloxacin exposure induces anxiety-like behavioral responses in zebrafish by affecting the microbiota-gut-brain axis. *Sci. Total Environ.* 858 (Pt 3), 160094. doi:10.1016/j.scitotenv.2022.160094

Wierzbinski, P., Hubska, J., Henzler, M., Kucharski, B., Bies, R., and Krzystanek, M. (2023). Depressive and other adverse CNS effects of fluoroquinolones. *Pharmaceuticals* 16 (8), 1105. doi:10.3390/ph16081105

Zareifopoulos, N., and Panayiotakopoulos, G. (2017). Neuropsychiatric effects of antimicrobial agents. *Clin. Drug Invest.* 37 (5), 423–437. doi:10.1007/s40261-017-0498-z

Zhou, C., Peng, S., Lin, A., Jiang, A., Peng, Y., Gu, T., et al. (2023). Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* 59, 101967. doi:10.1016/j.eclinm.2023.101967

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 28 October 2024
DOI 10.3389/fphar.2024.1448144

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Yoshihiro Noguchi,
Gifu Pharmaceutical University, Japan
Ruo Wang,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Lubin Liu,
liulubin1975@126.com
Qian Dai,
daiqian@nsmc.edu.cn
Rutie Yin,
yinrutie@scu.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 12 June 2024
ACCEPTED 08 October 2024
PUBLISHED 28 October 2024

CITATION
Duan Y, Wang Y, Lu S, Zeng M, Liu L, Dai Q and Yin R (2024) Adverse event profile of albumin-bound paclitaxel: a real-world pharmacovigilance analysis.
Front. Pharmacol. 15:1448144.
doi: 10.3389/fphar.2024.1448144

Adverse event profile of albumin-bound paclitaxel: a real-world pharmacovigilance analysis

Yuanqiong Duan[1,2†], Ying Wang[3,4†], Shentao Lu[3,4], Mei Zeng[5,6], Lubin Liu[3,4]*, Qian Dai[5,6]* and Rutie Yin[1,2]*

[1]Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China, [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Sichuan University, Chengdu, China, [3]Department of Obstetrics and Gynecology, Women and Children's Hospital of Chongqing Medical University, Chongqing, China, [4]Department of Obstetrics and Gynecology, Chongqing Health Center for Women and Children, Chongqing, China, [5]Institute of Rheumatology and Immunology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China, [6]Innovation Centre for Science and Technology, North Sichuan Medical College, Nanchong, Sichuan, China

Background: Abraxane plays a crucial role in the treatment of various types of cancer, despite the considerable attention it has garnered for its adverse drug events (ADEs). Nevertheless, there is currently a significant lack of comprehensive real-world pharmacovigilance studies on the ADEs associated with Abraxane.

Methods: We conducted a retrospective analysis of ADEs associated with Abraxane using data mining from the FAERS database, analyzing data from 2005 to 2023. In a real-world setting, we quantified and visualized the signals of these ADEs using four pharmacovigilance algorithms.

Results: The FAERS database identified a total of 10,230 adverse event reports associated with Abraxane. The study revealed that Abraxane-related adverse drug events involved 27 system organ classes (SOC), with the strongest signals associated with the lymphatic and hematological systems and hepatobiliary disorders. Additionally, we identified 70 significant Preferred Terms (PT) signals, which included some critical adverse events not highlighted in the product labeling, such as cystoid macular edema. Further analysis of the timing of adverse reactions showed a median onset time of 41 days. Most adverse events (AEs) occurred within the first month of using Abraxane (43.5%), although some were still possible 1 year after treatment (3.5%). Gender-specific analysis indicated that high-risk AEs differed between females (nausea, vomiting, and erythema) and males (febrile neutropenia, disseminated intravascular coagulation, and upper gastrointestinal bleeding).

Conclusion: The examined results provide crucial recommendations for optimizing the administration of Abraxane, enhancing its effectiveness, and mitigating potential adverse effects. This knowledge will substantially facilitate the implementation of the substance in clinical settings.

KEYWORDS

albumin-bound paclitaxel, adverse drug events, FDA adverse event reporting system, signal mining, pharmacovigilance analysis, real-world study

1 Introduction

Taxanes, pivotal in oncology for over 50 years, have evolved from the isolation of paclitaxel to the innovative development of next-generation drugs like albumin-bound paclitaxel (nab-paclitaxel) (Mosca et al., 2021). This evolution marks a crucial advancement in cancer therapy, particularly by enhancing drug delivery and reducing side effects through novel formulations (Zierhut et al., 2019; Schiff and Horwitz, 1980). Taxanes are now widely recognized as a key chemotherapy component for several malignancies (Hellerstedt-Börjesson et al., 2018; Swain, 2011). Clinical trials have predominantly shown that taxane-based therapies excel in terms of overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) (Shepherd et al., 2000; Mamounas et al., 2005; Yoneshima et al., 2021).

Despite these advancements, conventional taxanes like paclitaxel and docetaxel present challenges, including solubility issues and severe dose-limiting toxicities like peripheral sensory neuropathy and hypersensitivity reactions (Friberg et al., 2002; Shin et al., 2021; Joerger, 2012). Nab-paclitaxel, utilizing albumin-bound nanotechnology, addresses these issues effectively (Yardley, 2013; Gradishar et al., 2005). Approved by the FDA in 2005 for treatment-resistant breast cancer, nab-paclitaxel enhances solubility, reduces hydrophobicity, and improves pharmacokinetics and pharmacodynamics, resulting in increased drug accumulation in tumors and enhanced antitumor activity (Ibrahim et al., 2002). Nab-paclitaxel's clinical trials highlighted its potential for causing significant adverse drug events (ADEs), such as neuropathy and hematological toxicities, which were manageable within trial settings but observed more severely in broader clinical use. In response, the FDA's black box warning in 2014 underscored the risk of severe bone marrow suppression linked to nab-paclitaxel, emphasizing the need for meticulous monitoring and risk management in clinical applications (Gradishar et al., 2005; Nyman et al., 2005; Lobo et al., 2007; Higuchi et al., 2019). The thorough evaluation of these safety issues emphasized the necessity for strict monitoring and management strategies to effectively reduce these risks in clinical settings. This measure not only heightened awareness among clinicians and researchers but also highlighted the critical need for post-approval studies and continuous safety monitoring throughout the drug's lifecycle.

The FDA's Adverse Event Reporting System (FAERS) is a voluntary system where healthcare providers, consumers, and pharmaceutical companies are all encouraged to submit reports (Yu et al., 2021; Zhou et al., 2023). By collecting and storing data on adverse events associated with drugs and biologics used post-market, FAERS serves as a critical platform for identifying new or rare adverse events and for modifying or enhancing the understanding of known risks (Anand et al., 2019). This ultimately improves the transparency and safety of drug usage. Moreover, FAERS plays a vital role in collecting and analyzing real-world data concerning drug adverse events (AEs). This data is invaluable in filling the gaps left by pre-market research, offering insights into long-term drug safety and tolerability (Gu et al., 2023). Therefore, FAERS is indispensable for evaluating long-term safety and tolerability, offering a more comprehensive understanding that significantly augments the insights obtained from pre-market clinical research.

This study is unique in that it provides a comprehensive analysis of real-world safety data on nab-paclitaxel from the FAERS, a domain that is still relatively unexplored in existing literature. By employing advanced data mining algorithms, this research aims to provide a nuanced understanding of the risk signals associated with nab-paclitaxel, contributing significantly to its safe and rational clinical use. Our analysis not only updates the current knowledge base but also introduces new methodologies for signal detection, offering crucial insights that can influence clinical guidelines and patient management strategies.

2 Materials and methods

2.1 Data source and processing

In this study, we utilized the R language to extract and analyze raw data from the FAERS database to establish an association between reported adverse drug events (ADEs) and specific drugs. Our detailed analysis concentrated on ADE reports from the FDA's approval period in the first quarter of 2005 to the fourth quarter of 2023, identifying albumin-bound paclitaxel as the primary suspected drug. We described the drug using its generic names, "paclitaxel for injection (Albumin Bound)," "paclitaxel protein-bound particles," "albumin-bound paclitaxel," and its brand name, "Abraxane". To ensure accuracy in our findings, we performed deduplication of all reports prior to conducting the statistical analysis. Figure 1 illustrates the flowchart of the study.

2.2 Standardization of ADE data processing

Adverse drug events (ADEs) in FAERS reports are classified using the Medical Dictionary for Regulatory Activities (MedDRA Version 26.0) Preferred Terms (PTs). Each specific AE report of Nab-paclitaxel documented at the system organ class (SOC) and PT levels was cataloged to outline the range of toxicities.

2.3 Data mining algorithm

In our pharmacovigilance study, we employed a disproportionality analysis to explore potential links between the drug Nab-paclitaxel and adverse events (AEs). Supplementary Table S1 contains a four-cell table that details the disproportionality methods. This study utilizes four statistical methods: the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multiitem Gamma Poisson Shrinker (MGPS) (Yang et al., 2023; Zhao et al., 2023). We employed the extraction rules of these algorithms to identify signals and compute scores that evaluate the relationships between drugs and AEs.

Each method applies specific criteria and equations, detailed in Supplementary Table S2, to compute scores that assess the strength of the association between the drug and reported AEs. We identify signals of AEs at the System Organ Class (SOC) level when these scores exceed predefined thresholds, indicating a strong disproportion. Moreover, our analysis identified AE signals that conformed to the criteria of all four

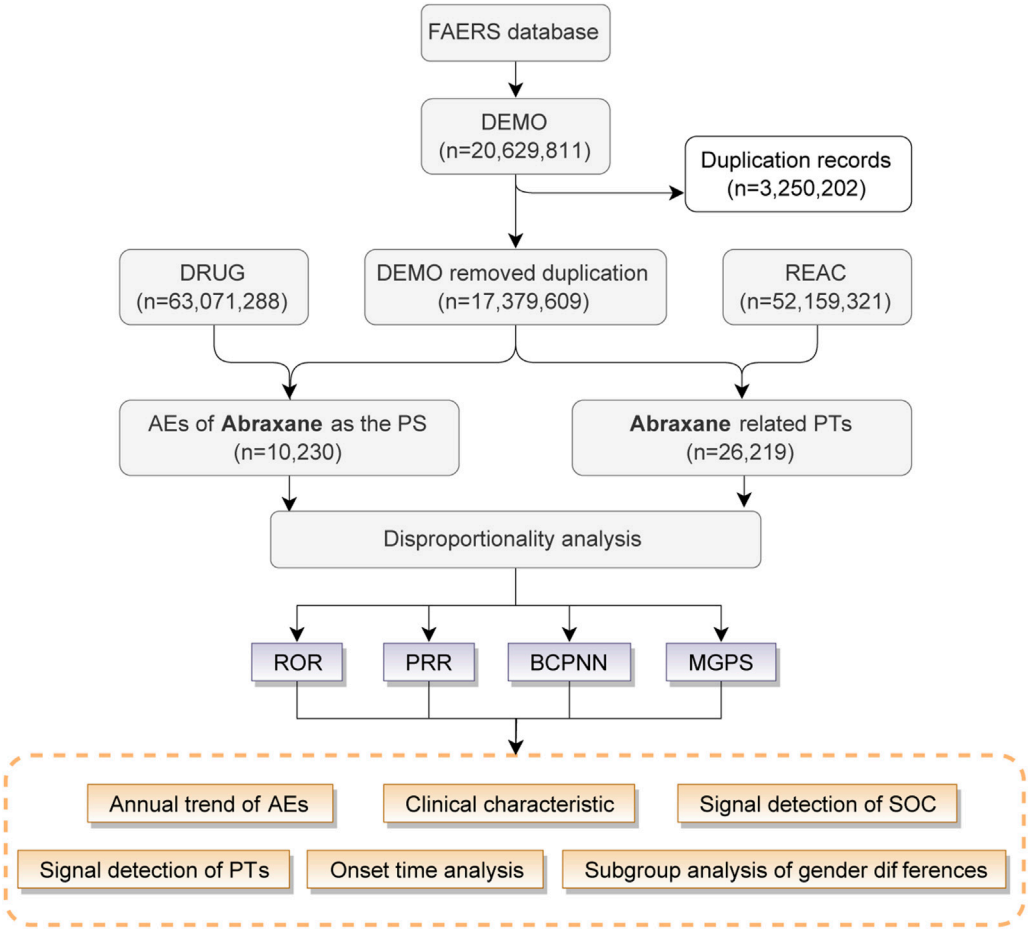


FIGURE 1
The procedure for identifying adverse drug events (ADEs) related with Abraxane form the FAERS database.

algorithms at the preferred term (PT) level. We also noted novel AE signals, characterized as significant but not previously documented in the drug's labeling. These findings suggest important implications for patient safety and drug usage.

In this study, we applied the Bonferroni correction to account for multiple comparisons and reduce the likelihood of Type I errors. We use the Bonferroni correction as a statistical adjustment method when testing multiple hypotheses simultaneously. It involves dividing the desired significance level (α) by the number of comparisons being made. For instance, if we set our significance level at 0.05 and conducted 10 tests, the Bonferroni-adjusted threshold for each individual test would be 0.005 (0.05/10). This adjustment ensures that the overall probability of falsely rejecting at least one null hypothesis remains at the intended significance level. We aimed to improve the reliability of our findings by implementing this correction, ensuring that any detected signals were statistically significant even after accounting for multiple testing.

2.4 Statistical analysis and visualization

Utilizing multivariate logistic regression, we calculated the adjusted odds ratio. The "forest plot" package facilitated the visualization of these results by producing a detailed forest diagram. We further leveraged the graphical prowess of R by using "ggplot2" and "ggpubr" for high-quality visual renditions, and employed "networkD3" packages to create informative volcano and Sankey diagrams, respectively. The volcano plot highlighted the significant variables against a backdrop of extensive testing, providing a clear link between effect sizes and their statistical significance. On the other hand, the Sankey diagram showed the clinical pathway, showing how patients responded to Abraxane treatment and how events unfolded over time. We conducted all statistical analyses and graphical illustrations in R Studio (version 4.1.2). We applied a two-tailed testing framework to adjudicate statistical significance at a *P*-value of less than 0.05.

3 Results

3.1 Descriptive analysis

Between 2005 and 2024, the FAERS database recorded 10,230 adverse drug event (ADE) reports associated with Abraxane, as illustrated in Figure 1. The biphasic annual trend of ADE reports related to albumin-bound paclitaxel, as demonstrated

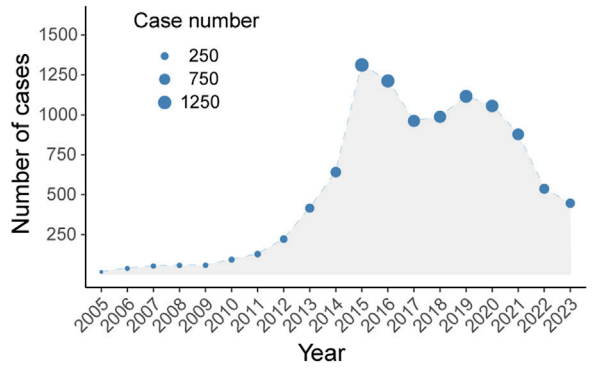


FIGURE 2
The annual trend of adverse drug event reports (ADEs) of Abraxane.

in Figure 2, shows an escalation commencing in 2005, with reports cresting in 2014. A modest decline follows this initial peak, before a second rise culminates in another peak in 2018, albeit less pronounced than the first. We observe a noticeable decline in the number of reports after 2018, which continues until the fourth quarter of 2023.

The clinical characteristics of these Nab-paclitaxel reports, indicating a slight preponderance of female (48.1%) over male (42.13%) reports, as demonstrated in Figure 3. The data revealed a concentration in adulthood: 35.88% were aged 18–65, and 36.16% were 65 years of age or older. Patient weight was reported less frequently, with 4.97% under 50 kg, 25.37% between 50 and 80 kg, and 9.94% exceeding 80 kg, while 59.73% of the reports omitted weight details. Healthcare professionals filed the bulk of the reports, accounting for 89.24% of cases, while consumers submitted 9.24%. Geographic analysis showed the United States as the predominant reporting country with 44.02% of cases, followed by Japan (12.93%), Germany (8.97%), Canada (6.97%), and Spain (3.73%). Within the reported events, death constituted the most frequent outcome at 35.88%, with hospitalization (32.47%) and other outcomes (18.98%) also being significant. 5.4% of cases reported life-threatening conditions, while 0.93% reported disability. Pancreatic cancer, at 39.6%, was the most commonly reported indication for Abraxane use, followed by breast cancer (17.86%) and lung cancer (12.49%). Reports of other malignancies, including gastric, ovarian, head and neck, cholangiocarcinoma, melanoma, oropharyngeal, and cervical cancer, were less frequent.

Furthermore, we employed a Sankey diagram to illustrate the clinical characteristics linked to AEs associated with albumin-bound paclitaxel. This visual tool effectively delineates the distribution of reports, mapping out the progression from patient demographics to clinical endpoints. As depicted in Figure 4, the diagram visually encapsulates the relationships and dynamic flow between patients' gender, age, body weight, indications for treatment, and the resulting clinical outcomes. While the Sankey diagram provides a graphical representation of the data, it is important to note that it does not imply causality or absolute frequency due to the limitations inherent in the spontaneous reporting system, such as underreporting and variability in report quality (Noguchi et al., 2021).

3.2 Signal detection of system organ class

Figure 5 depicts the ADE profile of albumin-bound paclitaxel, classified by System Organ Class (SOC). In relation to Nab-paclitaxel ADEs, we analyzed a total of 27 organ systems. To identify significant SOCs among these, we employed four statistical indices: the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi-item Gamma Poisson Shrinker (MPGS).

Blood and lymphatic system disorders have the highest ROR (6.67 [95% CI 6.41-6.94]) among SOCs, as shown in Figure 5A. This indicates a significantly stronger signal when compared to disorders in other classes. Subsequently, hepatobiliary disorders and benign, malignant, and unspecified neoplasms occur (ROR 3.36 [95% CI 3.13–3.61]; ROR 2.18 [95% CI 2.07–2.3]). Notably, cancer patients primarily use albumin-bound paclitaxel, and their underlying conditions (such as tumors) may themselves lead to certain adverse events. For instance, the drug may not be the sole cause of hepatobiliary disorders and the occurrence of neoplasms (such as hepatobiliary system disorders and benign, malignant, and unspecified neoplasms), but rather the patient's underlying disease. Therefore, the signals observed in the ROR may partially reflect the presence of the underlying condition rather than the true effect of the drug. With 4,724 cases, general disorders and administration site conditions were the most frequently reported SOCs. However, their relative risk (ROR) was only 1.04 (95% CI 1.01–1.07), suggesting a signal that was not as pronounced but still significant. Additionally, signal detection analysis for Abraxane at the SOC level revealed strong associations with two major categories. The blood and lymphatic system disorders reported 2,684 cases, with a ROR of 6.67 (95% CI: 6.41–6.94) and a PRR of 6.09 (XX: 11579.81). Meanwhile, 786 cases reported hepatobiliary disorders, with an ROR of 3.36 (95% CI: 3.13–3.61) and a PRR of 3.29 (XX: 1262.83). These results were backed up by more advanced pharmacovigilance algorithms, like BCPNN and MGPS. The IC and EBGM values were above their respective thresholds, which means there were strong signals. Figure 5B depicts the proportion of reports per SOC. General disorders and administration site conditions accounted for the highest proportion of reports (18.02%), followed by gastrointestinal disorders (12.15%) and blood and lymphatic system disorders (10.24%). SOCs that affect the reproductive system and breast disorders occur less frequently (0.18%), while conditions that occur during pregnancy, puerperium, and perinatal life occur sporadically (0.03%).

3.3 Signal detection of preferred terms and Bonferroni-adjusted *P*-value analysis

The four algorithms combined identified a total of 70 preferred terms (PTs) associated with Abraxane, as detailed in Supplementary Table S3. Figure 6 illustrates these PTs linked with the most pronounced signal strengths, specially highlighting the top 20% of reporting odds ratios (ROR). These ROR values signify the association's strength between the administration of a specific drug and the incidence of reported adverse events. The analysis showed that biliary tract infection happened in 40 cases, with a high

Clinical characteristics with Abraxane		
	Overall (N=10230)	
Variables	Number	Proportion
Gender		
Female	4921	(48.1%)
Male	4310	(42.13%)
Unspecified	999	(9.77%)
Patient age		
<18	14	(0.14%)
18-65	3671	(35.88%)
≥65	3699	(36.16%)
Unspecified	2846	(27.82%)
Patient weight		
<50	508	(4.97%)
50-80	2595	(25.37%)
≥80	1017	(9.94%)
Unspecified	6110	(59.73%)
Reporter type		
Healthcare professional	9129	(89.24%)
Consumer	945	(9.24%)
Unspecified	156	(1.52%)
Reported Countries (Top 5)		
United States	4503	(44.02%)
Japan	1323	(12.93%)
Germany	918	(8.97%)
Canada	713	(6.97%)
Spain	382	(3.73%)

Clinical characteristics with Abraxane		
	Overall (N=10230)	
Variables	Number	Proportion
Outcomes		
Death	3671	(35.88%)
Life-Threatening	552	(5.4%)
Hospitalization	3322	(32.47%)
Disabled	95	(0.93%)
Other Outcomes	1942	(18.98%)
Unspecified	648	(6.33%)
Indications (Top 10)		
Pancreatic Cancer	4051	(39.6%)
Breast Cancer	1827	(17.86%)
Lung Cancer	1278	(12.49%)
Gastric Cancer	221	(2.16%)
Ovarian Cancer	140	(1.37%)
Head And Neck Cancer	80	(0.78%)
Cholangiocarcinoma	71	(0.69%)
Melanoma	49	(0.48%)
Oropharyngeal Cancer	46	(0.45%)
Cervix Cancer	37	(0.36%)

FIGURE 3
Clinical profile of ADEs associated with Abraxane in the FAERS database.

ROR of 170.2 (95% CI: 123.21–235.12), which means that there is a strong signal for this particular adverse event. Furthermore, the study documented 128 instances of cholangitis, with an ROR of 54.53 (95% CI: 45.73–65.02), and 115 instances of peripheral sensory neuropathy, with an ROR of 49.63 (95% CI: 41.23–59.74). There were 412 reports of febrile neutropenia, which is another serious side effect, with an ROR of 15.51 (95% CI: 14.07–17.11). Other adverse events with noteworthy signal strengths included a decreased neutrophil count (213 cases, ROR 12.94) and embolism (47 cases, ROR 12.83). After applying the Bonferroni correction to account for multiple testing, the associations remained highly significant (adj. $P < 0.001$), confirming the robustness of the safety signals detected for these adverse events. The spectrum of significant AEs identified through our data mining extends beyond those explicitly listed in the product label for albumin-bound paclitaxel, thus contributing to a more comprehensive understanding of the drug's safety profile.

3.4 Onset time of Nab-paclitaxel associated AEs

We conducted a temporal analysis of adverse events associated with albumin-bound paclitaxel, and Figure 7 depicts the results. With the exclusion of reports that contained unspecified or inaccurate information concerning the timing of onset, a total of 4,722 adverse events were documented, representing 46.16% of the

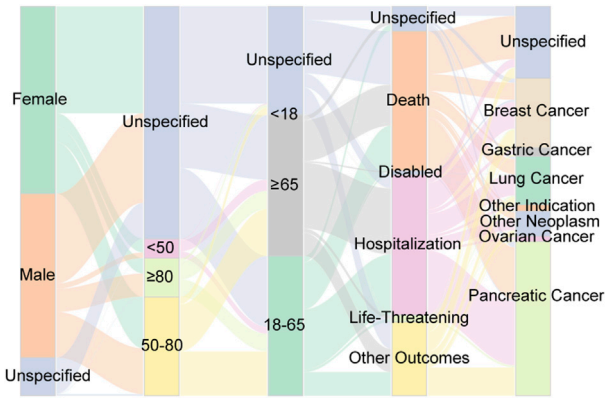


FIGURE 4
Distribution of some clinical characteristic associated with ADEs from Abraxane, including gender, age, weight, outcome and tumor type. The varying widths of the flows within the diagram quantify the volume of reports, thereby highlighting prevalent trends in the dataset.

cases where data were accessible (4,722 out of 10,230 total reports). The median duration until the onset of the event was 41 days, and the interquartile range (IQR) was between 11 and 97 days. The data collected during the study period revealed that 43.5% of adverse events (AEs) occurred within the first 30 days following treatment initiation. The occurrence of adverse events (AEs) gradually decreased over time, with subsequent intervals of 61–90 days and 31–60 days accounting for 17.2% and 11.2% of the cases, respectively. The period spanning from 91 to 180 days exhibited a consistent decline, comprising 16.4% of the total reports. Extended adverse events (AEs) occurred with reduced frequency. Specifically, 7.8% of AEs occurred between 181 and 360 days after treatment initiation, and only a minority (3.5%) occurred after 360 days had passed.

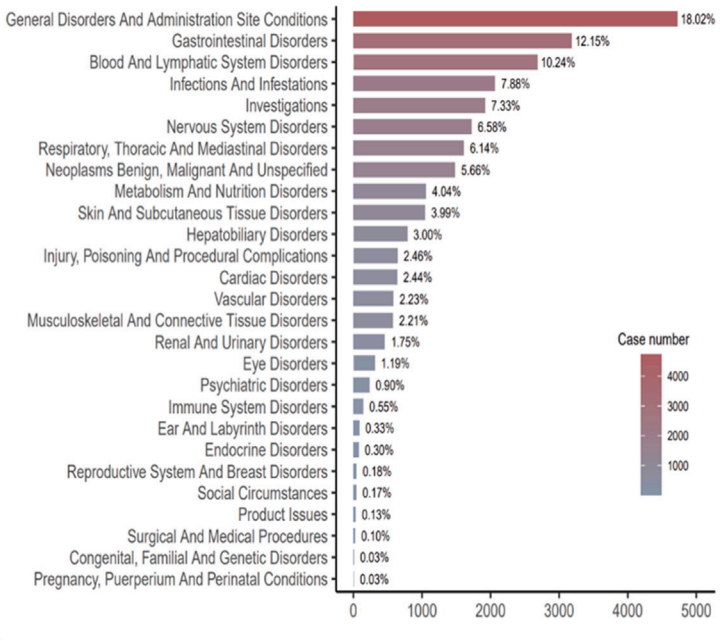
3.5 Sigal of preferred terms gender difference risk

After examining the FAERS database for adverse event signal strengths related to the use of albumin-bound paclitaxel, our analysis revealed gender-specific differences at the preferred term (PT) level (Figure 8A). In females, there is a notably higher incidence of adverse events such as nausea, vomiting, chest discomfort, bone pain, rash, erythema, and hypertension. Substantial reporting odds ratios (ROR) underscore these events, with conditions like bone pain exhibiting an ROR of 7.89 (95% CI: 2.41–25.81), indicating a markedly increased reporting frequency when compared to males. On the other hand, the study shows that males have stronger signals for bad events like febrile neutropenia, disseminated intravascular coagulation, upper gastrointestinal bleeding, and interstitial lung disease. Specifically, cholangitis and immune-mediated hepatitis have lower ROR values in females (0.40 and 0.12, respectively), suggesting a more pronounced risk profile in the male population.

Signal strength reports of Abraxane at the SOC level

		ROR		PRR		BCPNN		MGPS	
SOC	N	ROR	ROR_CI	PRR	XX	IC	IC025	EBGM	EB05
General Disorders And Administration Site Conditions	4724	**1.04**	**(1.01-1.07)**	1.03	(6.31)	0.05	(-1.62)	1.03	(1)
Gastrointestinal Disorders	3186	**1.49**	**(1.43-1.54)**	1.43	(443.68)	0.51	(-1.15)	1.43	(1.37)
Blood And Lymphatic System Disorders	2684	**6.67**	**(6.41-6.94)**	**6.09**	**(11579.81)**	**2.60**	**(0.94)**	**6.07**	**(5.84)**
Infections And Infestations	2066	**1.55**	**(1.48-1.62)**	1.51	(372.21)	0.59	(-1.07)	1.51	(1.44)
Investigations	1922	**1.20**	**(1.14-1.25)**	1.18	(57.64)	0.24	(-1.42)	1.18	(1.13)
Nervous System Disorders	1726	0.75	(0.72-0.79)	0.77	(129.06)	-0.38	(-2.04)	0.77	(0.73)
Respiratory, Thoracic And Mediastinal Disorders	1611	**1.33**	**(1.26-1.39)**	1.31	(120.58)	0.38	(-1.28)	1.31	(1.24)
Neoplasms Benign, Malignant And Unspecified	1483	**2.18**	**(2.07-2.3)**	**2.11**	**(890.65)**	1.08	(-0.59)	**2.11**	**(2)**
Metabolism And Nutrition Disorders	1060	**1.90**	**(1.78-2.02)**	1.86	(431.11)	0.90	(-0.77)	1.86	(1.75)
Skin And Subcutaneous Tissue Disorders	1045	0.73	(0.69-0.78)	0.74	(98.42)	-0.43	(-2.09)	0.74	(0.7)
Hepatobiliary Disorders	786	**3.36**	**(3.13-3.61)**	**3.29**	**(1262.83)**	**1.72**	**(0.05)**	**3.29**	**(3.06)**
Injury, Poisoning And Procedural Complications	644	0.22	(0.21-0.24)	0.24	(1691.3)	-2.04	(-3.71)	0.24	(0.22)
Cardiac Disorders	639	0.91	(0.85-0.99)	0.92	(4.94)	-0.13	(-1.79)	0.92	(0.85)
Vascular Disorders	584	1.04	(0.95-1.12)	1.03	(0.69)	0.05	(-1.62)	1.03	(0.95)
Musculoskeletal And Connective Tissue Disorders	579	0.41	(0.38-0.44)	0.42	(487.53)	-1.25	(-2.91)	0.42	(0.39)
Renal And Urinary Disorders	459	0.91	(0.83-0.99)	0.91	(4.43)	-0.14	(-1.81)	0.91	(0.83)
Eye Disorders	311	0.60	(0.53-0.67)	0.60	(83.72)	-0.73	(-2.4)	0.60	(0.54)
Psychiatric Disorders	235	0.15	(0.13-0.17)	0.16	(1127.26)	-2.67	(-4.34)	0.16	(0.14)
Immune System Disorders	144	0.50	(0.42-0.59)	0.50	(73.05)	-1.00	(-2.67)	0.50	(0.42)
Ear And Labyrinth Disorders	87	0.76	(0.62-0.94)	0.76	(6.57)	-0.39	(-2.06)	0.76	(0.62)
Endocrine Disorders	78	1.18	(0.94-1.47)	1.18	(2.1)	0.24	(-1.43)	1.18	(0.94)
Reproductive System And Breast Disorders	46	0.19	(0.14-0.26)	0.19	(154.52)	-2.36	(-4.03)	0.19	(0.15)
Social Circumstances	44	0.36	(0.27-0.49)	0.36	(49.65)	-1.46	(-3.13)	0.36	(0.27)
Product Issues	34	0.08	(0.06-0.11)	0.08	(350.21)	-3.59	(-5.26)	0.08	(0.06)
Surgical And Medical Procedures	26	0.07	(0.05-0.11)	0.08	(297.99)	-3.73	(-5.39)	0.08	(0.05)
Congenital, Familial And Genetic Disorders	9	0.11	(0.06-0.21)	0.11	(66.16)	-3.20	(-4.87)	0.11	(0.06)
Pregnancy, Puerperium And Perinatal Conditions	7	0.06	(0.03-0.13)	0.06	(100.98)	-4.03	(-5.69)	0.06	(0.03)

A



B

FIGURE 5
Distribution and signal strength of ADEs for Abraxane by system organ class (SOC). **(A)** Reports of Abraxane signal strength at the SOC level. **(B)** Proportional distribution of ADEs reports by SOC, detailing the percentage and total case count for each category.

SOC	PT	N	ROR(95% CI)	adj.P (Bonferroni correction)
Infections And Infestations	Biliary Tract Infection	40	170.2 (123.21-235.12)	<0.001
Hepatobiliary Disorders	Cholangitis	128	54.53 (45.73-65.02)	<0.001
Infections And Infestations	Enterocolitis Infectious	22	52.12 (34.13-79.6)	<0.001
Nervous System Disorders	Peripheral Sensory Neuropathy	115	49.63 (41.23-59.74)	<0.001
Hepatobiliary Disorders	Bile Duct Stenosis	24	48.39 (32.27-72.56)	<0.001
Hepatobiliary Disorders	Immune-Mediated Hepatitis	22	41.11 (26.95-62.71)	<0.001
Nervous System Disorders	Peripheral Motor Neuropathy	22	37.01 (24.27-56.43)	<0.001
Eye Disorders	Macular Oedema	63	26.86 (20.94-34.45)	<0.001
Infections And Infestations	Liver Abscess	34	25.64 (18.28-35.97)	<0.001
Hepatobiliary Disorders	Biliary Obstruction	25	19.18 (12.93-28.44)	<0.001
Blood And Lymphatic System Disorders	Haematotoxicity	64	18.45 (14.42-23.6)	<0.001
Blood And Lymphatic System Disorders	Febrile Neutropenia	412	15.51 (14.07-17.11)	<0.001
Nervous System Disorders	Neurotoxicity	97	14.39 (11.78-17.57)	<0.001
Investigations	Neutrophil Count Decreased	213	12.94 (11.3-14.81)	<0.001
Vascular Disorders	Embolism	47	12.83 (9.63-17.1)	<0.001

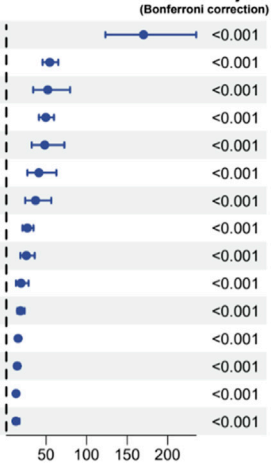


FIGURE 6
Signal strength reports of Abraxane at the preferred terms level in the FAERS database.

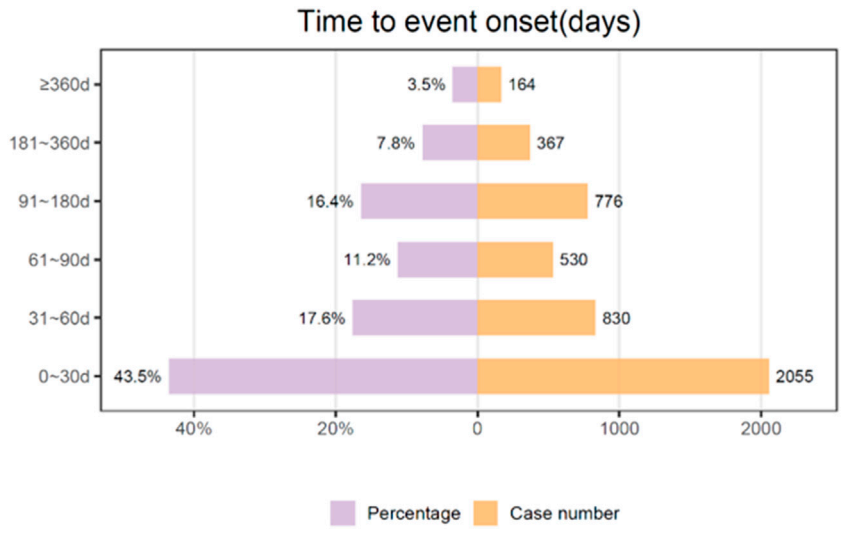


FIGURE 7
Time to onset of Abraxane associated AEs collected from the FAERS database.

The volcano plot (Figure 8B) distinctively visualizes the adverse drug events associated with albumin-bound paclitaxel that are specific to male and female patients. This makes it easy to find differences that are statistically significant between the two groups of patients. This graph plots the negative logarithm of the *p*-value against the log reporting odds ratio (log ROR), which pinpoints notable gender-specific signals. Events above the threshold line indicate a significant disparity in ADR reporting between genders. Specifically, orange dots represent potential ADE signals in males, while purple dots indicate those in females. Noteworthy ADEs, such as "pneumonia" and "interstitial lung disease" in males, stand out with high negative log10 *p*-values and substantial log ROR values, reflecting significant gender-based differences in their reporting. The visualization highlights the critical need to scrutinize ADEs along gender lines, as it is essential for discerning the varying risk profiles presented by pharmacotherapy across different patient groups. The emergent patterns underscore the imperative of considering gender-based variances in the safety and surveillance of albumin-bound paclitaxel, as these differences could affect clinical decision-making and patient care.

4 Discussion

Pharmacovigilance analysis of adverse drug reactions is of the utmost importance in order to optimize and update information regarding drug usage. It allows us to effectively address emerging risks and intricate scenarios that may arise in our ever-changing clinical practice. As clinical practice evolves, continuous monitoring

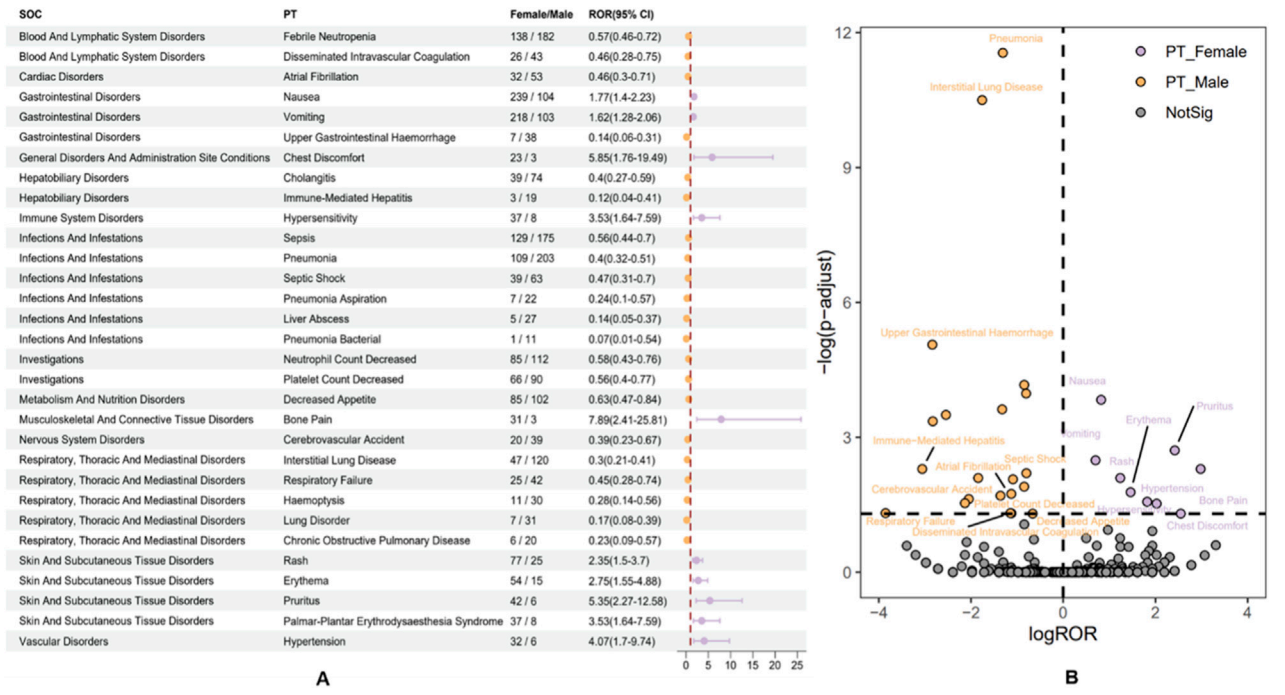


FIGURE 8
Subgroup analysis of gender differences in adverse events to Abraxane. **(A)** The various gender-specific ADEs associated with nab-paclitaxel are categorized by system organ class (SOC) and preferred term (PT), each accompanied by the corresponding ROR and 95% CI. **(B)** A volcano plot illustrates the distribution of gender differences in ADEs, highlighting significant signals with orange dots for males and purple dots for females.

is critical for addressing emergent risks and complexities in clinical practice. This endeavor is crucial to detecting potential risks and adverse effects that may emerge when administering the medication to a wider and more heterogeneous group of patients in the future. It is imperative to recognize that the conditions of clinical trials may not consistently mirror the intricacies of the real world, such as a heterogeneous patient population and a multitude of comorbidities (Bielefeldt, 2017). This underscores the importance of continuous safety surveillance and data collection in order to gain a more comprehensive understanding of the drug's efficacy and potential hazards in a real-world context. Changes in clinical use, reporting protocols, or pharmacovigilance approaches may lead to the observed dual-peak pattern in adverse event reporting for Abraxane (Figure 2). This means that there needs to be a thorough investigation to find the main causes of these changes, as well as what effects they might have on patients' safety and the drug's effectiveness. This study employs the FAERS database to provide the most comprehensive pharmacovigilance review of all adverse events associated with albumin-bound paclitaxel to date. By conducting an exhaustive and methodical examination of worldwide reports concerning the medication's detrimental impacts, this resource empowers medical practitioners to enhance clinical protocols and refine judgments. This improves patient outcomes and strengthens public trust in the drug's long-term safety.

In the current study, we extracted 10,230 ADE reports related to albumin-bound paclitaxel from the FAERS database and analyzed their clinical characteristics (Figures 3, 4). Although some reports failed to specify gender, the data indicated a greater frequency of adverse reactions in female patients compared to their male counterparts. This observation may reflect the drug's primary application in treating cancers prevalent in females, such as breast, ovarian, and cervical cancers (Yardley, 2013; Cortes et al., 2020; Sibaud et al., 2016). The age distribution of the reports, primarily adults aged 18-65 and elder over 65, aligns with the drug's target demographic. Notably, healthcare personnel submitted the majority of ADE reports, which lends credence to the data's reliability. However, the predominance of reports from Western countries introduces a potential geographic bias, underrepresenting data from Asian regions. Approximately 70% of the reports noted severe adverse drug events, such as death or prolonged hospital admissions, indicating that underlying comorbidities may influence these outcomes. These findings underscore the necessity for diligent supervision and thorough risk-benefit evaluations during treatment with albumin-bound paclitaxel, particularly in individuals with multiple comorbidities. It is crucial to approach the interpretation of these data with an understanding of the inherent limitations of the FAERS database, including incomplete data capture and potential reporting biases (Noguchi et al., 2021; Noguchi and Yoshimura, 2024). Our analysis highlights the need for ongoing monitoring and further research to better understand the correlation between the medication and severe ADEs, to mitigate risks and ensure patient safety.

In our investigation of adverse events (AEs) associated with albumin-bound paclitaxel, we examined signals across 27 system organ classes (SOCs) using four pharmacovigilance algorithms—ROR, PRR, BCPNN, and MGPS—as illustrated in Figure 5. The algorithms consistently identified robust signals for hematologic and hepatobiliary disorders, indicating a significant

association with increased risk when using this chemotherapy agent. These findings align with the data reported in the package insert and highlight the necessity for vigilant monitoring of these particular adverse effects. Specifically, the most frequently reported adverse events (AEs) were general disorders and administration site conditions, which accounted for 18.02% of all AEs and primarily manifested as fever, fatigue, pain, and swelling at the injection site. These reactions underline the importance of meticulous administration and storage of the medication. Gastrointestinal reactions posed significant challenges, affecting 12.15% of patients with symptoms like nausea, vomiting, diarrhea, and mucositis, severely impacting their quality of life. Adverse events in the blood and lymphatic systems were also notably prevalent, constituting 10.24% of the reports. We observed serious conditions such as anemia, bone marrow suppression, leukopenia, and thrombocytopenia, which could increase infection risks and bleeding tendencies, sometimes requiring treatment adjustments. Other notable adverse effects involved infection and infestations (7.88%), investigations (7.33%), and nervous system disorders (6.58%), reflecting the drug's extensive impact on multiple organ systems. This comprehensive profile necessitates a multidisciplinary approach to patient care, emphasizing the need for continuous assessment and management of these risks to ensure the safety and effectiveness of therapy. Overall, the consistency of strong signals in the blood and lymphatic system, along with hepatobiliary and neoplastic disorders, calls for enhanced scrutiny and further research to better understand the underlying mechanisms and optimize patient management strategies.

This study covers most of the ADE signals and SOC categories for albumin-bound paclitaxel, which is in line with the common side effects listed on the product label (Supplementary Table S3; Figure 6). Recently, the hematological and neurological toxicities caused by this drug have garnered attention. Studies show that albumin-bound paclitaxel mainly suppresses bone marrow. This usually happens 8–10 days after chemotherapy, which means that treatment may have to be delayed or stopped, which can affect how well it works and how long the patient lives (Higuchi et al., 2017). Other studies have demonstrated the reversibility of damage to immature hematopoietic cells and the potential mitigation of bone marrow suppression by granulocyte colony-stimulating agents (Nieuweboer et al., 2015), despite the recommendation against their routine use. Therefore, we still need effective strategies to control the incidence of neutropenia and leukopenia. Notably, this study demonstrated a significant association between albumin-bound paclitaxel and peripheral neuropathy, with a reporting odds ratio (ROR) for peripheral sensory neuropathy as high as 37.01 (95% CI: 24.271–56.43). These findings align with the adverse event data observed in clinical trials. Based on a study of 4,613 patients, this drug greatly raises the risk of grade 3 sensory neuropathy in people with non-small cell lung cancer. When used with gemcitabine for pancreatic cancer treatment, the rate of neuropathy was higher (17% vs. 1%) compared to when used alone (Tan et al., 2019). The specific mechanisms behind the neurotoxicity induced by albumin-bound paclitaxel are still unclear, but they may relate to the dose limitations of taxane drugs and the long-term adverse effects causing abnormal microtubule accumulations in axons and Schwann cells (Bae et al., 2021; Hu et al., 2019). These accumulations can interfere with normal neuronal functions, leading to pain, numbness, and other neurologically related symptoms. Currently, there are no effective preventative medications, and symptomatic treatments such as mecobalamin and the use of ice gloves and booties can somewhat alleviate these symptoms during chemotherapy. Recent studies have shown that elevated levels of interleukin-20 (IL-20) in patients during chemotherapy are closely associated with the risk of peripheral neurotoxicity (Chen et al., 2020). Inhibiting the activity of IL-20 can prevent sensory neurotoxicity without affecting the therapeutic effects of the drugs, offering new directions for future treatments. However, translating these findings into clinical practice requires further clinical trials to provide evidence-based support. These studies and their outcomes will provide more effective methods for managing neurotoxicity and improving patient quality of life.

The results of this study differ somewhat from the information on the product label. For instance, our study frequently reported macular edema, or cystoid macular edema, which is considered rare under the eye disorders category. In order to increase confidence, we further corrected the correlation statistically. When performing multiple pairwise tests on a single set of data, the Bonferroni correction, a conservative method, reduces the chances of obtaining false-positive results (Type I errors). In the context of this table, cystoid macular edema has an adjusted p-value of <0.001, indicating that after adjusting for multiple comparisons, the signals associated with the AE are still statistically significant. Moreover, there have been sporadic reports of cystoid macular edema associated with albumin-bound paclitaxel in recent years (Yamane et al., 2023; Ye et al., 2021). This also corroborates the reliability of our research findings to a certain extent. Consequently, regular ophthalmologic exams are necessary during the clinical use of the drug, especially if changes in visual acuity or visual field occur, with optical coherence tomography needed for early detection and timely intervention. Furthermore, this study revealed high ROR values for cholangitis, bile duct stenosis, and pseudocirrhosis under the hepatobiliary disorders category, small intestine colonitis infections under the infections and infestations category, and duodenal obstruction under gastrointestinal disorders, indicating a higher risk of these ADEs and highlighting the importance of monitoring the hepatobiliary and gastrointestinal systems. Given the significant risk associated with these ADEs, future research should focus more on understanding their mechanisms and risk factors, as well as developing appropriate management strategies.

The temporal distribution of adverse events (AEs) associated with albumin-bound paclitaxel, as depicted in Figure 7, offers significant insights into the drug's safety profile. Notably, the highest frequency of AEs occurs within the first 30 days of treatment initiation, accounting for 43.5% of the cases. This initial period may be critical for patient monitoring and could reflect the drug's immediate pharmacological impacts on the body. The reduction in AE occurrence over time, with 17.6% of cases reported between 31 and 60 days and 11.2% between 61 and 90 days, suggests a diminishing acute toxic effect or the possible emergence of tolerance to the drug. However, the relatively sustained percentage of AEs occurring in the 91- to 180-day range (16.4%) signals the need for ongoing vigilance beyond the acute treatment phase. This might be indicative of cumulative toxicity or delayed effects of the medication that become evident

only after prolonged exposure. The fact that 7.8% of AEs were reported between 181 and 360 days and a minority of 3.5% after 1 year could be associated with long-term treatment effects or late-onset toxicity, which are often overlooked in early post-marketing surveillance. It is also possible that these extended AEs are due to persistent use of the drug in a chronic setting or indicate late-emerging sequelae from earlier treatment periods. The data underscores the necessity for a comprehensive pharmacovigilance approach that extends well beyond the initial treatment window and calls for sustained patient follow-up. Additionally, the significant drop in AEs after the first month suggests that initial dosing and patient adjustment to treatment are critical factors in managing adverse outcomes. However, the non-negligible incidence of AEs after the acute phase suggests that we should not underestimate long-term side effects. Clinicians should remain aware of the potential for both acute and delayed AEs with albumin-bound paclitaxel. This study's temporal analysis reinforces the importance of educating patients about the possibility of late-onset AEs and the need for regular monitoring, even after the initial period of highest risk has passed. These results can also help make albumin-bound paclitaxel therapy safer by guiding risk reduction strategies like changing the dose and implementing supportive care protocols.

Our analysis of the FAERS database to investigate the gender differences in adverse event (AE) reporting for albumin-bound paclitaxel has elucidated distinct patterns in drug tolerance and safety profiles between males and females. The gender-specific differences at the preferred term (PT) level, as depicted in Figure 8A, indicate that females have a significantly higher incidence of AEs such as nausea, vomiting, chest discomfort, bone pain, rash, erythema, and hypertension. Notably, bone pain showed a remarkably high reporting odds ratio (ROR) of 7.89 (95% CI: 2.41–25.81) in females. These findings suggest that gender-related biological factors, differences in drug exposure, or reporting behavior may make women more susceptible to certain AEs or more likely to report these events. In contrast, males showed stronger signals for severe conditions such as febrile neutropenia, disseminated intravascular coagulation, upper gastrointestinal hemorrhage, and interstitial lung disease. On the other hand, females showed lower RORs for conditions like cholangitis and immune-mediated hepatitis, suggesting that males are more likely to experience these side effects. This divergence in AE profiles necessitates a gender-stratified approach in clinical practice and drug surveillance.

The volcano plot (Figure 8B) further elucidates these disparities, with a clear demarcation between statistically significant ADRs in male and female patients. Log ROR and negative log10 p-values effectively highlight the significantly more frequently reported ADRs in one gender compared to the other. For instance, the substantial log ROR values for "pneumonia" and "interstitial lung disease" in males emphasize the importance of considering gender when assessing ADR risk profiles. These findings have a multitude of implications. Clinically, they call for heightened awareness and potentially differential monitoring strategies for male and female patients undergoing treatment with albumin-bound paclitaxel. The pronounced gender-specific AEs identified in this study could influence treatment decisions, such as dosing regimens, supportive care measures, and even the choice of therapeutic agents. Furthermore, the results reinforce the need for gender-specific analysis in pharmacovigilance studies to accurately capture and address the drug safety concerns for each patient demographic. These findings raise questions about the underlying mechanisms that contribute to gender-specific AEs from a research perspective. Further investigation into pharmacokinetics and pharmacodynamics, hormone-drug interactions, genetic factors, and even psychosocial elements could provide a deeper understanding of the observed differences. This knowledge could pave the way for personalized medicine approaches that tailor treatments to the unique risk profiles of male and female patients, ultimately improving patient care and therapeutic outcomes. It is worth noting that the previous study employed only two algorithms for the pharmacovigilance analysis of albumin-bound paclitaxel, and the data cutoff for adverse events was in 2021 (Wang and Liu, 2023). In our current study, we further analyzed the adverse events of albumin-bound paclitaxel by utilizing four algorithms, along with the Bonferroni correction, to ensure more robust signal detection and interpretation of the results. This provides a more comprehensive analysis and enhances the reliability of our findings compared to the prior study.

We used the FAERS database, an observational and spontaneous reporting system, to gather data on drug-related adverse AEs in real-world clinical settings. Given the observational nature of this dataset, disproportionality analysis methods, such as the reporting odds ratio (ROR), do not aim to establish direct causal relationships between a drug and AEs. Instead, these methods compare the frequency of reported AEs for a specific drug with the overall frequency in the entire database to identify potential associations or signals. Using the FAERS database as an internal control system, we consider the background population (all other drugs) as a comparative baseline. This approach allows us to detect disproportionality, indicating that albumin-bound paclitaxel may be associated with a higher reporting rate for certain AEs. However, the presence of a signal indicates an association rather than direct causality. Future research should focus on conducting more in-depth sensitivity analyses that compare the frequency of AEs linked to Abraxane with those of other anticancer drugs, particularly other taxanes such as docetaxel and paclitaxel. Additionally, restricting the analysis to patients with specific tumor indications would further minimize indication bias.

The FAERS database, being a spontaneous reporting system, inherently suffers from issues like underreporting and missing information, which can distort the true frequency and severity of adverse drug events (ADEs). As highlighted in research Noguchi et al. (2021), these systems provide critical safety signals but require cautious interpretation due to their non-systematic data collection processes. The variability introduced by reports from different sources—patients, healthcare providers, and pharmaceutical companies—can lead to reporting bias, affecting the reliability of the data and the statistical signals detected. Although this study utilized advanced signal detection algorithms like ROR, PRR, BCPNN, and MGPS to enhance the robustness of our findings, these methods primarily detect signals rather than establish causality. As noted in study Noguchi and Yoshimura (2024), applying these algorithms necessitates careful consideration of data discrepancies and potential confounders. The identification of ADE signals indicates statistical associations, not causality, pointing to the need for further clinical research to validate these

findings. Future research should integrate broader datasets, such as electronic health records or longitudinal studies, to provide a more detailed assessment of drug safety. Despite its limitations, this study contributes new insights into the safety of albumin-bound paclitaxel, paving the way for further investigations and emphasizing the importance of continuous safety monitoring.

5 Conclusion

This study utilized the FAERS database to conduct an extensive investigation and analysis of the real-world adverse reaction signals associated with albumin-bound paclitaxel, primarily aligned with the information on the drug's label. Clinicians should be cautious not only about typical adverse events such as bone marrow suppression and neurotoxicity, but also about ocular symptoms during clinical treatment. When deemed appropriate, employ pharmacological monitoring to facilitate the judicious utilization of medications in the therapeutic environment.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.fda.gov/.

Author contributions

YD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–original draft. YW: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing–original draft. SL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Project administration, Software, Writing–original draft. MZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Writing–original draft. LL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing–original draft. QD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing–original draft. RY: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The Scientific Research Project of Cadre Healthcare in Sichuan Province (2023-1702), "Study on the Diversity of TCR in Peripheral Blood of Women with Different Cervical Cancer," and the "Key Project" of the Sichuan Provincial Department of Science and Technology (2019YFS0532), "Study on the Key Factors Affecting the Diagnosis and Treatment of Major Diseases in Obstetrics and Gynecology" (2021229), provided support for this research. The Chongqing Natural Science Foundation (Grant No. CSTB2023NSCQ-MSX0283 and CSTB2023NSCQ-MSX0642), the National Natural Science Foundation of China (Grant No. 31800690), and the Central-Guided Local Science and Technology Development Foundation (Grant No. 2023ZYD0060) provided funding for this research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1448144/full#supplementary-material

References

Anand, K., Ensor, J., Trachtenberg, B., and Bernicker, E. H. (2019). Osimertinib-induced cardiotoxicity: a retrospective review of the FDA adverse events reporting system (FAERS). *JACC. CardioOncology* 1 (2), 172–178. doi:10.1016/j.jaccao.2019.10.006

Bae, E. H., Greenwald, M. K., and Schwartz, A. G. (2021). Chemotherapy-induced peripheral neuropathy: mechanisms and therapeutic avenues. *Neurother* 18 (4), 2384–2396. doi:10.1007/s13311-021-01142-2

Bielefeldt, K. (2017). From harmful treatment to secondary gain: adverse event reporting in dyspepsia and gastroparesis. *Dig. Dis. Sci.* 62 (11), 2999–3013. doi:10.1007/s10620-017-4633-8

Chen, L. H., Yeh, Y. M., Chen, Y. F., Hsu, Y. H., Wang, H. H., Lin, P. C., et al. (2020). Targeting interleukin-20 alleviates paclitaxel-induced peripheral neuropathy. *Pain* 161 (6), 1237–1254. doi:10.1097/j.pain.0000000000001831

Cortes, J., Cescon, D. W., Rugo, H. S., Nowecki, Z., Im, S. A., Yusof, M. M., et al. (2020). Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet (London, England)* 396 (10265), 1817–1828. doi:10.1016/s0140-6736(20)32531-9

Friberg, L. E., Henningsson, A., Maas, H., Nguyen, L., and Karlsson, M. O. (2002). Model of chemotherapy-induced myelosuppression with parameter

consistency across drugs. *J. Clin. Oncol.* 20 (24), 4713–4721. doi:10.1200/JCO.2002.02.140

Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., et al. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J. Clin. Oncol.* 23 (31), 7794–7803. doi:10.1200/JCO.2005.04.937

Gu, T., Jiang, A., Zhou, C., Lin, A., Cheng, Q., Liu, Z., et al. (2023). Adverse reactions associated with immune checkpoint inhibitors and bevacizumab: a pharmacovigilance analysis. *Int. J. Cancer* 152 (3), 480–495. doi:10.1002/ijc.34332

Hellerstedt-Börjesson, S., Nordin, K., Fjällskog, M. L., Rissanen, R., Peterson, M., and Arving, C. (2018). Colored body images reveal the perceived intensity and distribution of pain in women with breast cancer treated with adjuvant taxanes: a prospective multi-method study of pain experiences. *Scand. J. pain* 18 (4), 581–591. doi:10.1515/sjpain-2018-0050

Higuchi, M., Takagi, H., Owada, Y., Inoue, T., Watanabe, Y., Yamaura, T., et al. (2017). Efficacy and tolerability of nanoparticle albumin-bound paclitaxel in combination with carboplatin as a late-phase chemotherapy for recurrent and advanced non-small-cell lung cancer: a multi-center study of the Fukushima lung cancer association group of surgeons. *Oncol. Lett.* 13 (6), 4315–4321. doi:10.3892/ol.2017.5998

Higuchi, T., Kawaguchi, K., Miyake, K., Oshiro, H., Zhang, Z., Razmjooei, S., et al. (2019). The combination of gemcitabine and nab-paclitaxel as a novel effective treatment strategy for undifferentiated soft-tissue sarcoma in a patient-derived orthotopic xenograft (PDOX) nude-mouse model. *Biomed. & Pharmacother.* 111, 835–840. doi:10.1016/j.biopha.2018.12.110

Hu, L. Y., Mi, W. L., Wu, G. C., Wang, Y. Q., and Mao-Ying, Q. L. (2019). Prevention and treatment for chemotherapy-induced peripheral neuropathy: therapies based on CIPN mechanisms. *Curr. Neuropharmacol.* 17 (2), 184–196. doi:10.2174/1570159X15666170915143217

Ibrahim, N. K., Desai, N., Legha, S., Soon-Shiong, P., Theriault, R. L., Rivera, E., et al. (2002). Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin. cancer Res.* 8 (5), 1038–1044.

Joerger, M. (2012). Prevention and handling of acute allergic and infusion reactions in oncology. *Ann. Oncol.* 23 (Suppl. 10), x313–x319. doi:10.1093/annonc/mds314

Lobo, C., Lopes, G., Silva, O., and Gluck, S. (2007). Paclitaxel albumin-bound particles (abraxane) in combination with bevacizumab with or without gemcitabine: early experience at the University of Miami/Braman Family Breast Cancer Institute. *Biomed. & Pharmacother.* 61 (9), 531–533. doi:10.1016/j.biopha.2007.08.008

Mamounas, E. P., Bryant, J., Lembersky, B., Fehrenbacher, L., Sedlacek, S. M., Fisher, B., et al. (2005). Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J. Clin. Oncol.* 23 (16), 3686–3696. doi:10.1200/JCO.2005.10.517

Mosca, L., Ilari, A., Fazi, F., Assaraf, Y. G., and Colotti, G. (2021). Taxanes in cancer treatment: activity, chemoresistance and its overcoming. *Drug Resist. Updat.* 54, 100742. doi:10.1016/j.drup.2020.100742

Nieuweboer, A. J., Smid, M., de Graan, A. J., Elbouazzaoui, S., de Bruijn, P., Martens, J. W., et al. (2015). Predicting paclitaxel-induced neutropenia using the DMET platform. *Pharmacogenomics* 16 (11), 1231–1241. doi:10.2217/pgs.15.68

Noguchi, Y., Tachi, T., and Teramachi, H. (2021). Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Briefings Bioinforma.* 22 (6), bbab347. doi:10.1093/bib/bbab347

Noguchi, Y., and Yoshimura, T. (2024). Detection algorithms for simple two-group comparisons using spontaneous reporting systems. *Drug Saf.* 47 (6), 535–543. doi:10.1007/s40264-024-01404-w

Nyman, D. W., Campbell, K. J., Hersh, E., Long, K., Richardson, K., Trieu, V., et al. (2005). Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J. Clin. Oncol.* 23 (31), 7785–7793. doi:10.1200/JCO.2004.00.6148

Schiff, P. B., and Horwitz, S. B. (1980). Taxol stabilizes microtubules in mouse fibroblast cells. *Proc. Natl. Acad. Sci. U. S. A.* 77 (3), 1561–1565. doi:10.1073/pnas.77.3.1561

Shepherd, F. A., Dancey, J., Ramlau, R., Mattson, K., Gralla, R., O'Rourke, M., et al. (2000). Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J. Clin. Oncol.* 18 (10), 2095–2103. doi:10.1200/JCO.2000.18.10.2095

Shin, G. J., Pero, M. E., Hammond, L. A., Burgos, A., Kumar, A., Galindo, S. E., et al. (2021). Integrins protect sensory neurons in models of paclitaxel-induced peripheral sensory neuropathy. *Proc. Natl. Acad. Sci. U. S. A.* 118 (15), e2006050118. doi:10.1073/pnas.2006050118

Sibaud, V., Lebœuf, N. R., Roche, H., Belum, V. R., Gladieff, L., Deslandres, M., et al. (2016). Dermatological adverse events with taxane chemotherapy. *Eur. J. dermatology* 26 (5), 427–443. doi:10.1684/ejd.2016.2833

Swain, S. M. (2011). Chemotherapy: updates and new perspectives. *Oncol.* 16 (Suppl. 1), 30–39. doi:10.1634/theoncologist.2011-S1-30

Tan, H., Hu, J., and Liu, S. (2019). Efficacy and safety of nanoparticle albumin-bound paclitaxel in non-small cell lung cancer: a systematic review and meta-analysis. *Artif. cells, nanomedicine, Biotechnol.* 47 (1), 268–277. doi:10.1080/21691401.2018.1552595

Wang, Y., and Liu, X. (2023). Safety signals of albumin-bound paclitaxel: data mining of the Food and Drug Administration adverse event reporting system. *Indian J. Pharmacol.* 55 (3), 167–173. doi:10.4103/ijp.ijp_640_22

Yamane, H., Itagaki, T., Kajitani, K., Koura, Y., Kawabuchi, Y., and Ohara, M. (2023). Cystoid macular edema following treatment with nanoparticle albumin-bound paclitaxel and atezolizumab for metastatic breast cancer. *Case Rep. Oncol.* 16 (1), 1121–1128. doi:10.1159/000533999

Yang, H., Wan, Z., Chen, M., Zhang, X., Cui, W., and Zhao, B. (2023). A real-world data analysis of topotecan in the FDA Adverse Event Reporting System (FAERS) database. *Expert Opin. Drug Metab. Toxicol.* 19 (4), 217–223. doi:10.1080/17425255.2023.2219390

Yardley, D. A. (2013). nab-Paclitaxel mechanisms of action and delivery. *J. Control. release* 170 (3), 365–372. doi:10.1016/j.jconrel.2013.05.041

Ye, S., Fang, Q., Yao, J., Xing, J., Tang, S., and Ma, J. H. (2021). Intravitreal ranibizumab had limited effect on cystoid macular edema due to albumin-bound paclitaxel: a case report and literature review. *Front. Oncol.* 11, 773540. doi:10.3389/fonc.2021.773540

Yoneshima, Y., Morita, S., Ando, M., Nakamura, A., Iwasawa, S., Yoshioka, H., et al. (2021). Phase 3 trial comparing nanoparticle albumin-bound paclitaxel with docetaxel for previously treated advanced NSCLC. *J. Thorac. Oncol.* 16 (9), 1523–1532. doi:10.1016/j.jtho.2021.03.027

Yu, R. J., Krantz, M. S., Phillips, E. J., and Stone, C. A., Jr. (2021). Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA adverse event reporting system (FAERS). *J. allergy Clin. Immunol.* 9 (2), 819–829.e2. doi:10.1016/j.jaip.2020.09.021

Zhao, H., Li, J. M., Li, Z. R., Zhang, Q., Zhong, M. K., Yan, M. M., et al. (2023). Major adverse cardiovascular events associated with testosterone treatment: a pharmacovigilance study of the FAERS database. *Front. Pharmacol.* 14, 1182113. doi:10.3389/fphar.2023.1182113

Zhou, C., Peng, S., Lin, A., Jiang, A., Peng, Y., Gu, T., et al. (2023). Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *EClinicalMedicine* 59, 101967. doi:10.1016/j.eclinm.2023.101967

Zierhut, C., Yamaguchi, N., Paredes, M., Luo, J. D., Carroll, T., and Funabiki, H. (2019). The cytoplasmic DNA sensor cGAS promotes mitotic cell death. *Cell* 178 (2), 302–315. doi:10.1016/j.cell.2019.05.035

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 21 November 2024
DOI 10.3389/fphar.2024.1510220

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Lin Song,
Chongqing Medical University, China
Yao Liu,
Daping Hospital, China

*CORRESPONDENCE
Yinglan Zhao,
zhaoyinglan@scu.edu.cn

RECEIVED 12 October 2024
ACCEPTED 11 November 2024
PUBLISHED 21 November 2024

CITATION
Su N, Tang R, Zhang Y, Ni J, Huang Y, Liu C, Xiao Y, Zhu B and Zhao Y (2024) Using machine learning to identify risk factors for pancreatic cancer: a retrospective cohort study of real-world data.
Front. Pharmacol. 15:1510220.
doi: 10.3389/fphar.2024.1510220

Using machine learning to identify risk factors for pancreatic cancer: a retrospective cohort study of real-world data

Na Su[1,2,3], Rui Tang[4], Yice Zhang[1], Jiaqi Ni[1], Yimei Huang[5], Chunqi Liu[3,6], Yuzhou Xiao[3,6], Baoting Zhu[1] and Yinglan Zhao[3,6]*

[1]West China School of Pharmacy, Sichuan University, Chengdu, China, [2]Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Biotherapy, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China, [4]Institute of Medical Information, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, China, [5]University of Florida Health Shands Hospital, Gainesville, FL, United States, [6]National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Objectives: This study aimed to identify the risk factors for pancreatic cancer through machine learning.

Methods: We investigated the relationships between different risk factors and pancreatic cancer using a real-world retrospective cohort study conducted at West China Hospital of Sichuan University. Multivariable logistic regression, with pancreatic cancer as the outcome, was used to identify covariates associated with pancreatic cancer. The machine learning model extreme gradient boosting (XGBoost) was adopted as the final model for its high performance. Shapley additive explanations (SHAPs) were utilized to visualize the relationships between these potential risk factors and pancreatic cancer.

Results: The cohort included 1,982 patients. The median ages for pancreatic cancer and nonpancreatic cancer groups were 58.1 years (IQR: 51.3–64.4) and 57.5 years (IQR: 49.5–64.9), respectively. Multivariable logistic regression indicated that kirsten rats arcomaviral oncogene homolog (KRAS) gene mutation, hyperlipidaemia, pancreatitis, and pancreatic cysts are significantly correlated with an increased risk of pancreatic cancer. The five most highly ranked features in the XGBoost model were KRAS gene mutation status, age, alcohol consumption status, pancreatitis status, and hyperlipidaemia status.

Conclusion: Machine learning algorithms confirmed that KRAS gene mutation, hyperlipidaemia, and pancreatitis are potential risk factors for pancreatic cancer. Additionally, the coexistence of KRAS gene mutation and pancreatitis, as well as KRAS gene mutation and pancreatic cysts, is associated with an increased risk of pancreatic cancer. Our findings offered valuable implications for public health strategies targeting the prevention and early detection of pancreatic cancer.

KEYWORDS

pancreatic cancer, machine learning, multivariable logistic regression, risk factors, KRAS gene mutation

1 Introduction

Pancreatic cancer (PC) is a leading cause of cancer-related death globally, with a 5-year survival rate of approximately 13% (Siegel et al., 2024; Pourshams et al., 2019). PC has an increasing mortality rate and often results in metastasis due to its subtle early symptoms, so most patients are diagnosed at an advanced stage, which limits treatment options (Park et al., 2021). Although computerized tomography (CT) and magnetic resonance imaging (MRI) are effective at diagnosing pancreatic cancer, the cost of these two techniques is relatively high, which limits their wide use (Yang et al., 2021; Diehl et al., 1998; Lu et al., 1997; Sandrasegaran et al., 2013). Seeking potential risk factors could be conducive to early diagnosis and intervention in the risk population.

Generally, risk factors can be categorized into genetic and hereditary factors, environmental factors, medical conditions, and demographic Factors. Genetic factors play a significant role in developing pancreatic cancer with about 10% of pancreatic cancer cases attributed to inherited genetic mutations (Mario et al., 2018). In addition, previous studies indicated that smoking, obesity, and alcohol consumption are responsible for pancreatic cancer (Mario et al., 2018). There is also compelling evidence that factors like chronic pancreatitis and age are associated with pancreatic cancer (Mario et al., 2018; Yuan et al., 2022). Kirsten rat sarcoma viral oncogene homolog (KRAS) may influence pancreatic cancer development through various metabolic alterations. These alterations include enhanced glucose uptake, differential channeling of glucose intermediates, reprogramming of glutamine metabolism, increased autophagy, and macropinocytosis (Bryant et al., 2014). Current knowledge about risk factors for developing pancreatic cancer is focused mainly on the impact of specific risk factors (Yuan et al., 2022; Maisonneuve and Lowenfels, 2015; Kirkegård et al., 2017). However, PC is caused by multiple factors, and little is known regarding the relative predictive power of different risk factors. Traditional methods for identifying risk factors rely on case-control studies and logistic regression models. However, logistic regression models have limitations in data processing, particularly when dealing with large-scale high-dimensional clinical data (Oosterhoff et al., 2022; Song et al., 2021). To address these limitations, we designed a retrospective cohort study to reveal the relationships between different risk factors and pancreatic cancer based on machine learning.

2 Methods

2.1 Study setting and data source

A retrospective cohort study was conducted using electronic medical records (EMR) from 1 January 2010, and 31 December 2023, at West China Hospital (WCH), Sichuan University (Chengdu, China). All data were extracted from the hospital EMR. The EMR contains information stored in structured or semistructured formats (e.g., patient demographics, physical examination, laboratory tests, medications, and diagnoses). This study was approved by the Institutional Review Board of WCH in May 2021 (WCH 2021-590), and patient consent was waived.

2.2 Study population

We included 1,982 patients who had a kirsten rats arcomaviral oncogene homolog (KRAS) gene testing in WCH between 1 January 2010, and 31 December 2023. Patients who met any of the following criteria were excluded: had a history of other malignancies, had incomplete data or missing important information, or had serious complications or illness. Following inclusion, data loss was minimal due to the low rate of missingness in our data source. Given this low rate, statistical methods for handling missing data were not applied.

2.3 Definition of pancreatic cancer

Patients with pancreatic cancer were defined as individuals who met the diagnostic criteria for pancreatic cancer and had a confirmed diagnosis at West China Hospital. The diagnostic criteria included clinical symptoms (such as abdominal pain and jaundice), radiological assessments (CT and MRI), histopathological examination, and blood tests (serum CA19-9>39 U/mL) (Chan et al., 2014; Goonetilleke and Siriwardena, 2007; Ni et al., 2005). These factors were analyzed comprehensively to establish the diagnosis by the doctor.

2.4 Independent variable

Previous studies identified some potential risk factors for pancreatic cancer. Based on clinical evidence and biological rationale (Kamisawa et al., 2016; McGuigan et al., 2018), we compiled an extensive list of variables to identify potential risk factors, classifying them into four groups: demographic characteristics (age and sex), living habits (smoking and drinking), non-pancreatic comorbidities (hypertension, diabetes, uarthritis/hyperuricemia, overweight/obesity and hyperlipidemia) and pancreatic-related diseases (pancreatic cysts and pancreatitis). For statistical analysis, chi-square tests were used for normally distributed categorical variables, while Wilcoxon rank-sum tests were used for continuous variables that did not conform to a normal distribution. A p-value of ≤ 0.05 was considered statistically significant.

2.5 Multivariable logistic regression

Multivariable logistic regression analyses were performed to calculate the z-value and p-value of the association between each covariate and pancreatic cancer. This initial screening aimed to identify independent variables significantly associated with the disease ($p < 0.05$).

Significant variables were then included in the multivariable logistic regression model to further evaluate their effects while

TABLE 1 Baseline characteristics of the patients.

Variables	Contents	Groups (N = 1982)		χ2/W	P value
		Pancreatic cancer (N = 129)	Nonpancreatic cancer (N = 1853)		
Sex	Male	67	1,178	9.34	0.0022
	Female	62	675		
Age (y)	Mean	58.1 (51.3,64.4)	57.5 (49.5,64.9)		
	(0, 20)	0	5	98,969(W)	0.6427
	(20, 40)	7	154		
	(40, 60)	70	909		
	(60, 80)	51	772		
	(80, 100)	1	13		
Histology	Ductal adenocarcinoma	103	0	-	-
	Not performed	26	0	-	-
BMI (kg/m^2)	Mean	22.58 (20.70,24.07)	23.34 (20.90,25.39)		
	<24	95	1,182	116,701(W)	0.0045
	28>BMI≥24	32	560		
	≥28	2	111		
Smoking (n)	Yes	38	754	7.86	0.0051
	No	91	1,099		
Drinking (n)	Yes	38	754	2.11	0.3475
	No	91	1,099		
KRAS gene	Mutant	108	951	79.35	<0.001
	Wild	21	902		
Metabolic disease (n)	Yes	54	831	5.31	0.0211
	No	75	1,022		
Overweight/Obesity (n)	Yes	34	671	12.39	0.0004
	No	95	1,182		
Diabetes (n)	Yes	21	230	0.15	0.703
	No	108	1,623		
Hypertension (n)	Yes	28	448	0.67	0.4144
	No	101	1,405		
Hyperlipidemia (n)	Yes	13	63	8.93	0.0028
	No	116	1790		
Uarthritis/Hyperuricemia (n)	Yes	6	45	0.77	0.3799
	No	123	1808		
Pancreatitis (n)	Yes	24	16	153.12	<0.001
	No	105	1837		
Pancreatic cyst (n)	Yes	8	4	58.05	<0.001
	No	121	1849		

accounting for potential confounders. The z-value and p-value were computed to estimate the relationship between each variable and pancreatic cancer within the model. Additionally, we performed pairwise multivariable regression with generalized linear models to assess the synergistic effects of KRAS gene mutation and other factors on pancreatic cancer. All statistical analyses were performed using R (version 4.1.3).

2.6 Model construction and shapley additive explanations (SHAP)

All the covariates were included in the machine learning models. Twelve machine-learning methods were tested: extreme gradient boosting (XGBoost), random forest (RF), classification and regression tree (CART), support vector classifier (SVC), adaptive boosting (AdaBoost), gradient boosting, neural network (NN), extremely randomized trees (ExtraTrees), balanced bagging classifier, balanced random forest classifier (BalancedRF), random undersampling boosting (RUSBoost) and easyensemble. All variables were included in these models. A training: testing (80:20) approach was used to compute the final set of model-fit-parameters. RandomizedSearchCV was used to search for the optimal hyperparameters for the 12 models. All machine learning models were constructed using 5-fold cross-validation. The accuracy, precision, F1 score, recall, and area under the receiver operating characteristic (AUROC) curve were used to evaluate model performance. Additionally, SHAP values are a powerful tool for interpreting the predictive outcomes of machine learning models by quantifying the impact of each feature on the model's predictions. In this study, the SHAP technique was utilized to visualize the relationships between these potential risk factors and pancreatic cancer. We included only positive SHAP values, as our goal was to identify potential risk factors for pancreatic cancer. Positive SHAP values specifically indicate contributions toward an increased risk of pancreatic cancer, aligning with our study's focus.

3 Results

3.1 Basic characteristics of the study population

The study involved 1,982 patients in the cohort during the study period. As shown in Table 1, we divided the patients into two groups: a pancreatic cancer group and a nonpancreatic cancer group. The median ages for pancreatic cancer and nonpancreatic cancer groups were 58.1 years (IQR: 51.3–64.4) and 57.5 years (IQR: 49.5–64.9), respectively. The gender imbalance observed in this study was statistically significant (p = 0.002), with a greater proportion of males being found in the nonpancreatic group. Additionally, the pancreatic cancer group exhibited a significantly lower median body mass index (BMI) (22.58, IQR: 20.70–24.07) compared to the nonpancreatic cancer group (23.34, IQR: 20.90–25.39) (p = 0.004507). We also found a greater prevalence of smoking in the nonpancreatic cancer group, whereas alcohol consumption did not differ significantly between the groups. Notably, the pancreatic cancer group had a greater frequency of KRAS gene mutation (83.7% vs. 51.3%, $p < 0.001$) and a greater prevalence of pancreatitis (18.6% vs. 0.9%, $p < 0.001$) and pancreatic cysts (6.2% vs. 0.2%, $p < 0.001$) compared to the nonpancreatic cancer group.

3.2 Multivariable logistic regression

Table 2 presents the results of multivariable logistic regression analyses assessing the associations between baseline variables and pancreatic cancer status. The receiver operating characteristic (ROC) curve of the multivariable logistic regression model revealed that the AUC of the integrated factors was 0.829 (Supplementary Figure S1). KRAS gene mutation (OR = 9.09, 95% CI: 5.50–15.75, p < 0.001), hyperlipidaemia (OR = 3.37, 95% CI: 1.35–7.86, p = 0.006), pancreatitis (OR = 29.97, 95% CI: 12.93–72.27, p < 0.001), and pancreatic cysts (OR = 17.29, 95% CI: 3.85–97.69, p < 0.001) were significantly correlated with an increased risk of pancreatic cancer. After the screening, KRAS gene mutation, hyperlipidaemia, pancreatitis, and pancreatic cysts were entered into the model as independent variables, and KRAS gene mutation (OR = 8.99, 95% CI: 5.48–15.46, p < 0.001), hyperlipidaemia (OR = 3.46, 95% CI: 1.45–7.65, p = 0.003), pancreatitis (OR = 25.30, 95% CI: 11.46–57.79 p < 0.001), and pancreatic cysts (OR = 21.12, 95% CI: 4.71–119.03, p = 0.0001) were significantly associated with the risk of developing pancreatic cancer (Supplementary Table S1).

3.3 Machine learning algorithm

In this study, we developed 12 machine-learning models to identify risk factors for pancreatic cancer (Supplementary Table S2). Five-fold cross-validation was used to evaluate the performance of the constructed models, and we found that RF, CART, and XGBoost outperformed models of data imbalance processing technology (BalanceBagging, BalanceRF, RUSBoost, and EasyEnsemble) (Supplementary Figure S2). We also assessed their performance using metrics such as the area under the curve (AUC), accuracy, precision, recall, and F1 score. As shown in Supplementary Table S3, XGBoost was the best-performing model (AUC = 0.999, accuracy = 0.994, precision = 1.000, recall = 0.909, F1 score = 0.952). The recall and precision scores of RF and CART models are low, as these models often prioritize achieving higher accuracy by classifying the majority of samples as negative cases. According to the above assessment, XGBoost was chosen as the final machine learning model.

SHAP values indicate the importance of each feature to the prediction of individual instances. We assessed the contributions of different factors in the XGBoost models using SHAP values. Figure 1 displays the importance scores of the different factors. The study identified KRAS gene mutation, age, alcohol consumption status, pancreatitis status, and hyperlipidaemia status as the five most common potential risk factors.

TABLE 2 Multivariable logistic regression.

Intercept	Estimate	Standard error	z value	P	OR	Confidence interval, CI	
						Lower	Upper
Sex	−0.13	0.28	−0.46	0.6440	0.88	0.50	1.51
Age	0.02	0.01	1.75	0.0795	1.02	1.00	1.04
Smoking	−1.05	0.33	−3.22	0.0013	0.35	0.18	0.66
Drinking	−0.22	0.41	−0.53	0.5973	0.81	0.37	1.83
KRAS gene	−2.21	0.27	−8.26	<0.001	9.09	5.50	15.75
Metabolic disease	−1.09	0.44	−2.45	0.0142	0.34	0.14	0.80
Overweight/Obesity	−0.07	0.40	−0.19	0.8508	0.93	0.43	2.05
Diabetes	0.28	0.37	0.75	0.4511	1.33	0.63	2.73
Hypertension	−0.51	0.28	−1.86	0.0624	0.60	0.34	1.01
Hyperlipidemia	1.22	0.45	2.72	0.0065	3.37	1.35	7.86
Uarthritis/Hyperuricemia	0.84	0.51	1.65	0.0988	2.31	0.78	5.88
Pancreatitis	3.40	0.44	7.78	<0.001	29.97	12.93	72.27
Pancreatic cyst	2.85	0.80	3.55	0.0004	17.29	3.85	97.69

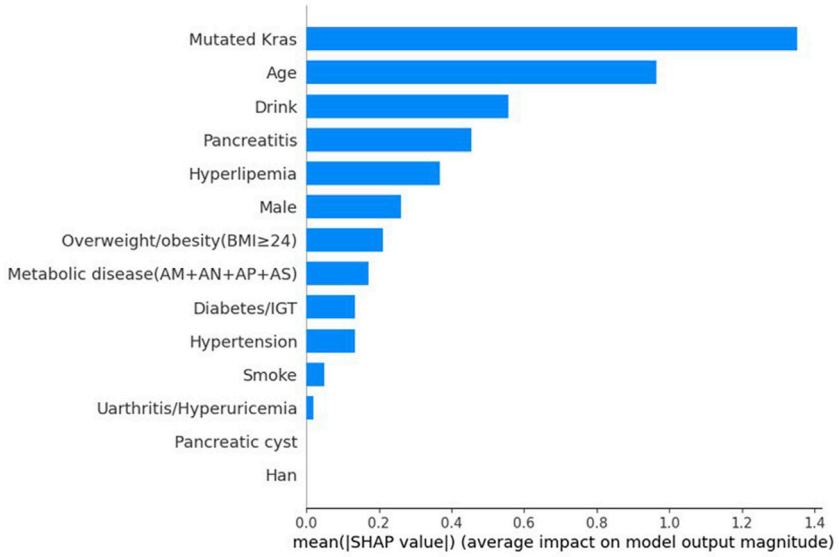


FIGURE 1
SHAP explanations.

3.4 Synergistic effects of KRAS gene mutation and other factors

Pairwise multivariable regression analyses were conducted to investigate the synergistic effects of KRAS gene mutation and other factors. We found a significant association between the coexistence of KRAS gene mutation and pancreatitis (OR = 14.18, 95% CI: 2.78–105.26, P < 0.01), as well as between KRAS gene mutation and pancreatic cysts (OR = 20.62, 95% CI: 7.56–60.30, P = 0.0026), with an increased risk of pancreatic cancer (Figure 2).

4 Discussion

The results of this retrospective cohort study showed that KRAS gene mutation, hyperlipidaemia, pancreatitis, and pancreatic cysts are significantly associated with the risk of developing pancreatic

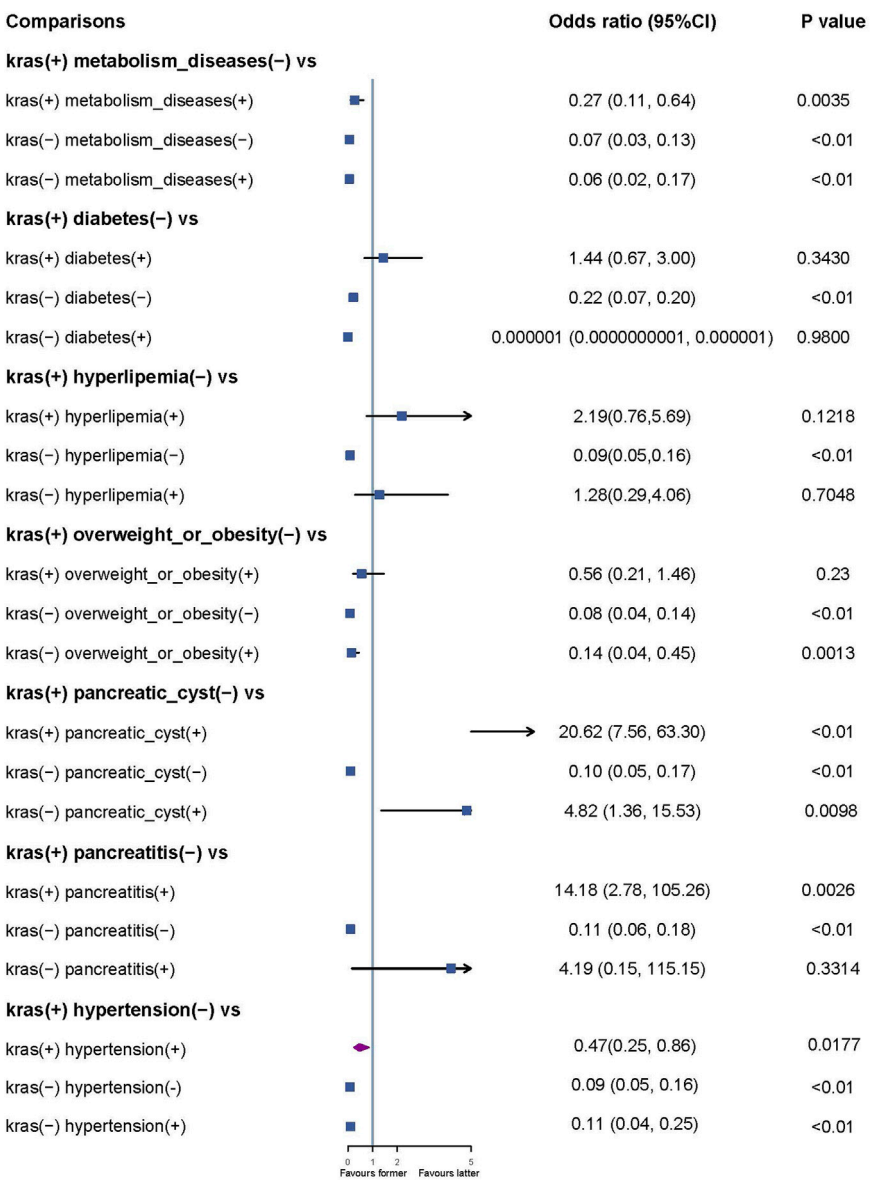


FIGURE 2
Synergistic effects of KRAS gene mutations and other factors.

cancer. A machine learning model utilizing demographic characteristics, living habits, nonpancreatic diseases, and pancreatic disease had strong predictive performance (XGBoost, AUC = 0.999). The greatest predictors for pancreatic cancer included KRAS gene mutation, age, alcohol consumption status, pancreatitis, and hyperlipidemia. Both logistic regression and machine learning confirmed that KRAS gene mutation, hyperlipidaemia and pancreatitis are potential risk factors for pancreatic cancer. Additionally, the coexistence of KRAS gene mutation and pancreatitis, as well as KRAS gene mutation and pancreatic cysts, is associated with an increased risk of pancreatic cancer.

The study is among the first to apply advanced machine learning algorithms, specifically XGBoost, to real-world clinical data for the identification of pancreatic cancer risk factors. While previous studies have relied on traditional statistical methods, such as logistic regression, the use of machine learning allows for the handling of high-dimensional data and complex interactions between variables, providing more robust risk prediction models. We also identified the synergistic effects between KRAS mutation and other risk factors, offering new insights into the genetic and biological mechanisms of pancreatic cancer development. Additionally, machine learning models trained on real-world data enable promising applications for improving pancreatic cancer risk assessment, early detection, and diagnosis. However, further validation in diverse populations and prospective clinical studies will be crucial before widespread implementation.

Bryant, Kirsten L. et al. have demonstrated that oncogenic KRAS plays a central role in regulating tumor metabolism,

orchestrating diverse metabolic changes such as enhanced glucose uptake, selective channeling of glucose intermediates, reprogrammed glutamine metabolism, increased autophagy, and macropinocytosis (Bryant et al., 2014). Several prior studies have shown similar results: KRAS mutation is related to PC and is found in almost all pancreatic ductal adenocarcinomas (PDACs) (Cox et al., 2014; Luo, 2021). Kamisawa, Terumi et al. reported that KRAS mutation and alterations in *CDKN2A* are early events in pancreatic tumorigenesis (Kamisawa et al., 2016). Bannoura SF et al. suggested that oncogenic KRAS signaling is critical for both the initiation and maintenance of pancreatic cancer; therefore, it is an ideal target for therapy (Bannoura et al., 2021). Although KRAS is a critical oncogene and therefore an important therapeutic target, its therapeutic inhibition is challenging. Recently, specific mutant KRAS inhibitors have been discovered (Bannoura et al., 2021).

Smoking is recognized as a risk factor for many types of cancer (Sasco et al., 2004; Scherübl, 2023). A review and meta-analysis concluded that cigarette smoking causes a 75% increase in the risk of pancreatic cancer compared to nonsmokers, and the risk persists for a minimum of 10 years after smoking cessation (Iodice et al., 2008). Similarly, a meta-analysis indicated that pancreatic cancer risk increases sharply with a low number of cigarettes smoked or after a 5 years of smoking and that it rapidly decreases a few years after cessation, although it takes almost 20 years to reach that of nonsmokers (Lugo et al., 2018). However, we did not find the same result, probably because of bias and the limited study population.

A growing body of evidence suggests that longstanding preexisting chronic pancreatitis is a strong risk factor for pancreatic cancer (Kamisawa et al., 2007; Dítě et al., 2010; Kudo et al., 2011). Although there is a strong link between chronic pancreatitis and pancreatic cancer, over 20 years, only approximately five percent of patients with chronic pancreatitis will develop pancreatic cancer (Raimondi et al., 2010). Lin et al. confirmed that hyperlipidaemia can promote tumor growth and subcutaneous tumor formation in mice, and Roy et al. described a two-way relationship between pancreatic cancer and diabetes, which might indicate that there is a complicated relationship between metabolic disease and pancreatic cancer (Qin et al., 2023; Roy et al., 2021).

Identifying risk factors for pancreatic cancer offers significant benefits in clinical and public health contexts. Early detection and targeted screening of high-risk populations can improve the proportion of early-stage diagnoses, which is associated with increased survival rates (Grigorescu et al., 2024). Additionally, understanding modifiable risk factors facilitates the development of targeted public health initiatives, such as lifestyle modification programs and genetic counseling, aimed at mitigating risk in susceptible populations.

A potential weakness of this study is the retrospective nature of this cohort. Since retrospective studies rely on existing records that were not originally collected for research purposes, key information is often missing or incomplete (Talari and Goyal, 2020). There may be variations in diagnostic criteria, treatment protocols, or data entry practices that are difficult to account for retrospectively. Medical records may lack detailed information on confounding variables or precise measurements necessary for robust analysis. These limitations can introduce potential biases and restrict the validity and generalizability of study conclusions. Several statistical methods were used to control for confounding factors; however, some unmeasured residual confounding factors were likely present. Furthermore, due to data inaccuracies and incomplete data, misclassification bias was not uncommon in retrospective database studies. The strength of inference on causality was thus weakened given the retrospective nature of the study. Future studies could address these limitations by implementing strategies such as improving data collection processes, refining study designs, and employing advanced analytical approaches. These enhancements may help to mitigate data gaps, reduce bias, and strengthen the reliability of study findings (Popovic and Huecker, 2024; Jager et al., 2020).

5 Conclusion

We confirmed that KRAS gene mutation, hyperlipidaemia, pancreatitis, and pancreatic cysts are significantly correlated with an increased risk of pancreatic cancer. KRAS gene mutation, age, alcohol consumption status, pancreatitis status, and hyperlipidaemia status are the strongest predictors of pancreatic cancer. Both logistic regression and machine learning algorithms confirmed that KRAS gene mutation, hyperlipidaemia and pancreatitis are potential risk factors for pancreatic cancer. Additionally, the coexistence of KRAS gene mutation and pancreatitis, as well as KRAS gene mutation and pancreatic cysts, is associated with an increased risk of pancreatic cancer.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of WCH (WCH 2021-590). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NS: Conceptualization, Formal Analysis, Methodology, Software, Writing–original draft, Writing–review and editing. RT: Formal Analysis, Software, Writing–original draft. YZ:

Conceptualization, Validation, Visualization, Writing–original draft. JN: Supervision, Writing–review and editing. YH: Supervision, Validation, Writing–review and editing. CL: Data curation, Writing–original draft. YX: Formal Analysis, Writing–original draft. BZ: Formal Analysis, Writing–original draft. YZ: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Software, Writing–original draft.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. NS was supported by grants from the Sichuan Province Science and Technology Support Program (grant number 2023JDR0243) and the Health Commission Program (grant number 2020-111). This research was supported by the National Key Clinical Specialties Construction Program.

Acknowledgments

We acknowledge support from the West China School of Pharmacy, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, and Collaborative Innovation Center for Biotherapy, Sichuan University. We also thank ZS for his contribution to the paper.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1510220/full#supplementary-material

Publisher's note

References

Bannoura, S. F., Uddin, M. H., Nagasaka, M., Fazili, F., Al-Hallak, M. N., Philip, P. A., et al. (2021). Targeting KRAS in pancreatic cancer: new drugs on the horizon. *Cancer Metastasis Rev.* 40, 819–835. doi:10.1007/s10555-021-09990-2

Bryant, K. L., Mancias, J. D., Kimmelman, A. C., and Der, C. J. (2014). KRAS: feeding pancreatic cancer proliferation. *Trends Biochem. Sci.* 39, 91–100. doi:10.1016/j.tibs.2013.12.004

Chan, A., Prassas, I., Dimitromanolakis, A., Brand, R. E., Serra, S., Diamandis, E. P., et al. (2014). Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer. *Clin. Cancer Res.* 20, 5787–5795. doi:10.1158/1078-0432.CCR-14-0289

Cox, A. D., Fesik, S. W., Kimmelman, A. C., Luo, J., and Der, C. J. (2014). Drugging the undruggable RAS: mission possible? *Nat. Rev. Drug Discov.* 13, 828–851. doi:10.1038/nrd4389

Diehl, S. J., Lehmann, K. J., Sadick, M., Lachmann, R., and Georgi, M. (1998). Pancreatic cancer: value of dual-phase helical CT in assessing resectability. *Radiology* 206, 373–378. doi:10.1148/radiology.206.2.9457188

Dítě, P., Novotný, I., Precechtělová, M., Růzicka, M., Záková, A., Hermanová, M., et al. (2010). Incidence of pancreatic carcinoma in patients with chronic pancreatitis. *Hepatogastroenterology* 57, 957–960.

Goonetilleke, K. S., and Siriwardena, A. K. (2007). Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur. J. Surg. Oncol.* 33, 266–270. doi:10.1016/j.ejso.2006.10.004

Grigorescu, R. R., Husar-Sburlan, I. A., and Gheorghe, C. (2024). Pancreatic cancer: a review of risk factors. *Life* 14, 980. doi:10.3390/life14080980

Iodice, S., Gandini, S., Maisonneuve, P., and Lowenfels, A. B. (2008). Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch. Surg.* 393, 535–545. doi:10.1007/s00423-007-0266-2

Jager, K. J., Tripepi, G., Chesnaye, N. C., Dekker, F. W., Zoccali, C., and Stel, V. S. (2020). Where to look for the most frequent biases? *Nephrol. Carlt. Vic.* 25, 435–441. doi:10.1111/nep.13706

Kamisawa, T., Tu, Y., Egawa, N., Nakajima, H., Tsuruta, K., and Okamoto, A. (2007). The incidence of pancreatic and extrapancreatic cancers in Japanese patients with chronic pancreatitis. *Hepatogastroenterology* 54, 1579–1581.

Kamisawa, T., Wood, L. D., Itoi, T., and Takaori, K. (2016). Pancreatic cancer. *Lancet* 388, 73–85. doi:10.1016/S0140-6736(16)00141-0

Kirkegård, J., Mortensen, F. V., and Cronin-Fenton, D. (2017). Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 112, 1366–1372. doi:10.1038/ajg.2017.218

Kudo, Y., Kamisawa, T., Anjiki, H., Takuma, K., and Egawa, N. (2011). Incidence of and risk factors for developing pancreatic cancer in patients with chronic pancreatitis. *Hepatogastroenterology* 58, 609–611.

Lu, D. S., Reber, H. A., Krasny, R. M., Kadell, B. M., and Sayre, J. (1997). Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am. J. Roentgenol.* 168, 1439–1443. doi:10.2214/ajr.168.6.9168704

Lugo, A., Peveri, G., Bosetti, C., Bagnardi, V., Crippa, A., Orsini, N., et al. (2018). Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: a comprehensive review and meta-analysis. *Eur. J. Cancer* 104, 117–126. doi:10.1016/j.ejca.2018.09.007

Luo, J. (2021). KRAS mutation in pancreatic cancer. *Semin. Oncol.* 48, 10–18. doi:10.1053/j.seminoncol.2021.02.003

Maisonneuve, P., and Lowenfels, A. B. (2015). Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int. J. Epidemiol.* 44, 186–198. doi:10.1093/ije/dyu240

Mario, C., Marilisa, F., Kryssia, I. R. C., Pellegrino, C., Ginevra, C., Chiara, M., et al. (2018). Epidemiology and risk factors of pancreatic cancer. *Acta Bio Medica Atenei Parm.* 89, 141–146. doi:10.23750/abm.v89i9-S.7923

McGuigan, A., Kelly, P., Turkington, R. C., Jones, C., Coleman, H. G., and McCain, R. S. (2018). Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J. Gastroenterol.* 24, 4846–4861. doi:10.3748/wjg.v24.i43.4846

Ni, X. G., Bai, X. F., Mao, Y. L., Shao, Y. F., Wu, J. X., Shan, Y., et al. (2005). The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. *Eur. J. Surg. Oncol.* 31, 164–169. doi:10.1016/j.ejso.2004.09.007

Oosterhoff, J. H. F., Gravesteijn, B. Y., Karhade, A. V., Jaarsma, R. L., Kerkhoffs, GMMJ, Ring, D., et al. (2022). Feasibility of machine learning and logistic regression algorithms to predict outcome in orthopaedic trauma surgery. *J. Bone Jt. Surg. Am.* 104, 544–551. doi:10.2106/JBJS.21.00341

Park, W., Chawla, A., and O'Reilly, E. M. (2021). Pancreatic cancer: a review. *JAMA* 326 (326), 851–862. doi:10.1001/jama.2021.13027

Popovic, A., and Huecker, M. R. (2024). "Study bias," in *StatPearls* (Treasure Island (FL): StatPearls Publishing).

Pourshams, A., Sepanlou, S. G., Ikuta, K. S., Bisignano, C., Safiri, S., Roshandel, G., et al. (2019). The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterology and Hepatology* 4 (4), 934–947. doi:10.1016/S2468-1253(19)30347-4

Qin, L., Sun, K., Shi, L., Xu, Y., and Zhang, R. (2023). High-fat mouse model to explore the relationship between abnormal lipid metabolism and enolase in pancreatic cancer. *Mediat. Inflamm.* 2023, 4965223. doi:10.1155/2023/4965223

Raimondi, S., Lowenfels, A. B., Morselli-Labate, A. M., Maisonneuve, P., and Pezzilli, R. (2010). Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best. Pract. Res. Clin. Gastroenterol.* 24, 349–358. doi:10.1016/j.bpg.2010.02.007

Roy, A., Sahoo, J., Kamalanathan, S., Naik, D., Mohan, P., and Kalayarasan, R. (2021). Diabetes and pancreatic cancer: exploring the two-way traffic. *World J. Gastroenterol.* 27, 4939–4962. doi:10.3748/wjg.v27.i30.4939

Sandrasegaran, K., Nutakki, K., Tahir, B., Dhanabal, A., Tann, M., and Cote, G. A. (2013). Use of diffusion-weighted MRI to differentiate chronic pancreatitis from pancreatic cancer. *AJR Am. J. Roentgenol.* 201, 1002–1008. doi:10.2214/AJR.12.10170

Sasco, A. J., Secretan, M. B., and Straif, K. (2004). Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer* 45 (Suppl. 2), S3–S9. doi:10.1016/j.lungcan.2004.07.998

Scherübl, H. (2023). Tobacco smoking and cancer risk. *Pneumologie* 77, 27–32. doi:10.1055/a-1916-1466

Siegel, R. L., Giaquinto, A. N., and Jemal, A. (2024). Cancer statistics, 2024. *CA Cancer J. Clin.* 74, 12–49. doi:10.3322/caac.21820

Song, X., Liu, X., Liu, F., and Wang, C. (2021). Comparison of machine learning and logistic regression models in predicting acute kidney injury: a systematic review and meta-analysis. *Int. J. Med. Inf.* 151, 104484. doi:10.1016/j.ijmedinf.2021.104484

Talari, K., and Goyal, M. (2020). Retrospective studies - utility and caveats. *J. R. Coll. Physicians Edinb* 50, 398–402. doi:10.4997/JRCPE.2020.409

Yang, J., Xu, R., Wang, C., Qiu, J., Ren, B., and You, L. (2021). Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. *Cancer Commun. (Lond).* 41, 1257–1274. doi:10.1002/cac2.12204

Yuan, C., Kim, J., Wang, Q. L., Lee, A. A., Babic, A., et al. (2022). The age-dependent association of risk factors with pancreatic cancer. *Ann. Oncol.* 33, 693–701. doi:10.1016/j.annonc.2022.03.276

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 06 December 2024
DOI 10.3389/fphar.2024.1439586

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Suodi Zhai,
Peking University Third Hospital, China
Khalid Waleed Taher,
King Faisal Specialist Hospital and Research Centre, Saudi Arabia

*CORRESPONDENCE
Zhiqiang Lin,
lin-zhiqiang@163.com

RECEIVED 28 May 2024
ACCEPTED 12 November 2024
PUBLISHED 06 December 2024

CITATION
Jiang L and Lin Z (2024) Voriconazole: a review of adjustment programs guided by therapeutic drug monitoring.
Front. Pharmacol. 15:1439586.
doi: 10.3389/fphar.2024.1439586

Voriconazole: a review of adjustment programs guided by therapeutic drug monitoring

Li Jiang and Zhiqiang Lin*

Department of Pharmacy, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, Fujian Province, China

Objectives: Exploring adjustments to the voriconazole dosing program based on therapeutic drug monitoring results to implement individualized therapy.

Methods: PubMed and Embase were systematically searched to obtain study about voriconazole dose adjustment program guided by therapeutic drug monitoring. Quality evaluation and summarization of the obtained studies were performed to obtain program adjustments for voriconazole under therapeutic drug monitoring.

Results: A total of 1,356 and 2,979 studies were searched on PubMed and Embase, respectively, and after removing irrelevant and duplicated studies, a total of 25 studies were included. A loading dose of 5 mg/kg q12 h or 200 mg q12 h and a maintenance dose of 50 mg q12 h or 100 mg q24 h is recommended for patients with Child-Pugh C. And in patients with Child-Pugh C, CYP2C19 genotype had no significant effect on voriconazole blood concentrations. Recommendations for presenting dosing programs based on different CYP2C19 genotypes are inconsistent, and genetic testing is not routinely recommended prior to dosing from a pharmacoeconomic perspective. Additionally, in adult patients, if the voriconazole trough concentration is subtherapeutic, the voriconazole dose should be increased by 25%~50%. If the voriconazole trough concentration is supratherapeutic,the voriconazole dose should be decreased by 25%~50%. If a drug-related adverse event occurs, hold 1 dose, decrease subsequent dose by 50%.In pediatric patients, if the voriconazole trough concentration is subtherapeutic, increase the voriconazole dose by 1~2 mg/kg or increase the voriconazole dose by 50%. If the voriconazole trough concentration is supratherapeutic, reduce the voriconazole dose by 1 mg/kg or hold 1 dose, and decrease the subsequent dose by 25%.

Conclusion: It is recommended that all patients on voriconazole should have their initial dosing program selected on the basis of their hepatic function or other influencing factors (e.g., pathogens, infections, C-reactive protein, albumin, or

Abbreviations: q12 h, every 12 h; q.d, once daily; Iv, intravenously; Po, orally; TBIL, total bilirubin; PTA, Probability of target attainment; CYP2C19, cytochrome P2C19; UMs, ultrarapid metabolizers; RMs, rapid metabolizers; NMs, normal metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers; SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicentre retrospective; RCT, randomized controlled trial; ULN, upper limit of normal; AML, acute myeloid leukemia; ALB, albumin; CFR, cumulative fraction of response; AdjBW, adjusted body weight; TBW, total body weight; CRP, c-reactive protein; TDM, therapeutic drug monitoring; CAP, chronic pulmonary aspergillosis; HSCT, hematopoietic stem cell transplantation; NR, no reference; MIPD, model-informed precision dosing; NLME, nonlinear mixed-effects; CNS, central nervous system.

obesity), and that therapeutic concentrations should be achieved through appropriate dosage adjustments guided by therapeutic drug monitoring. Routine genetic testing for voriconazole application in patients is not considered necessary at this time. However, there has been a great deal of research and partial consensus on individualized dosing of voriconazole, but there are still some critical issues that have not been resolved.

KEYWORDS

voriconazole, therapeutic drug monitoring, dose adjustment, individualized medication, concentration range

1 Introduction

Voriconazole is a second-generation triazole antifungal drug with broad-spectrum antifungal activity, which is commonly used to treat invasive fungal disease in clinic, and is the first-line drug for invasive aspergillosis. The voriconazole trough concentration has been proved to be related to efficacy and toxicity, but there are still uncertainties in the process of voriconazole therapeutic drug monitoring (TDM) and individualized dosing (Perreault et al., 2019). Yi WM conducted the study in 151 adult patients, 68/151 (45.0%) of whom were critically ill. The study showed that voriconazole blood concentration monitoring is within the target concentration range (1.0~5.5 mg/L) in only 134/250 (53.6%) of patients, <1.0 mg/L in 65/250 (26.0%), and >5.5 mg/L in 51/250 (20.4%), which suggests that voriconazole blood concentrations were not within the target concentration range in 116/250 (46.4%) of patients (Yi et al., 2017). Moreover, the probability that the trough concentration was within the target concentration range was increased two-fold compared to no dose adjustment when patients outside the target concentration range were dose-adjusted and the trough concentration was later reviewed (Yi et al., 2017). Sarah Perreault conducted a study in 128 adults with hematologic malignancies. The study showed that after 2 dose adjustments, 80% of patients were able to achieve the target concentration range (Perreault et al., 2019). One study based on pediatric patients (1.2~18.5 years) showed that 55% of patients had voriconazole steady-state trough concentrations outside of the therapeutic concentration range, and 82% of these patients were able to achieve the therapeutic concentration range after dose adjustment (Lempers et al., 2019). Voriconazole exhibits nonlinear pharmacokinetics *in vivo* when administered at doses recommended in the drug insert for the treatment of invasive Aspergillus infections in adults or pediatrics. Numerous studies have been conducted on the individualized administration of voriconazole, but there are still some key unanswered questions regarding its clinical application. There are also current studies using Model-informed precision dosing (MIPD) to predict and optimize treatment outcomes based on patient characteristics and therapeutic drug monitoring data. In order to improve the clinical efficacy of voriconazole and to achieve individualized dosing of voriconazole, this study explored several aspects of the initial dosing program, the therapeutic concentration range, and the dose-adjustment program to provide a reference for obtaining the optimal clinical treatment program.

2 Materials and quality assessment

2.1 Data sources and searches

The study searched the literatures for voriconazole administered under the guidance of therapeutic drug monitoring. The literatures covered program adjustments or made dose adjustments based on the patient's liver function profile, genotyping, and body weight. Two researchers independently searched 2 databases (PubMed and Embase) from January 2002 to March 2024 to identify studies on voriconazole dose adjustment program guided by therapeutic drug monitoring (Figure 1). Once duplicates had been removed, the researchers identified studies eligible for analysis by examining titles and abstracts of every record, followed by full-text reviews. Any disagreement between reviewers was resolved by discussion, with arbitration by a third reviewer when required. The search strategy was:

("voriconazole" OR "VRZ" OR "VRC" OR "VCZ") AND ("dose adjustment" OR "dosage regimens" OR "dose modification")
("voriconazole" OR "VRZ" OR "VRC" OR "VCZ") AND ("liver failure" OR "liver cirrhosis" OR "liver dysfunction")
("voriconazole" OR "VRZ" OR "VRC" OR "VCZ") AND ("CYP2C19")
("voriconazole" OR "VRZ" OR "VRC" OR "VCZ") AND ("obese" OR "obesity" OR "higher weight" OR "BMI" OR "body mass index")
("voriconazole" OR "VRZ" OR "VRC" OR "VCZ") AND ("software")

2.2 Inclusion and exclusion criteria

Inclusion criteria were decided according to PICOS. Participants (P): 1) patients were administered voriconazole, therapeutic drug monitoring was performed, and a target concentration range for voriconazole was specified, 2) inclusion of pediatric and adult populations. Intervention (I): propose an initial dosing program for special populations, or propose a dosage adjustment program based on a standard dosing program (For patients 12–14 years old and weighing >50 kg or patients ≥15 years old, the loading dose is 400 mg q12 h iv/po, and the maintenance dose is 200 mg q12 h iv/po. For patients aged 2–12 years old or younger, the loading dose is 9 mg/kg q12 h iv/po, and the maintenance dose is 8 mg/kg q12 h iv/po.). Control (C): The initial dosing program for special populations was compared with the standard dosing program, or dose-adjusted was compared with no dose adjustment. Outcome (O): Probability

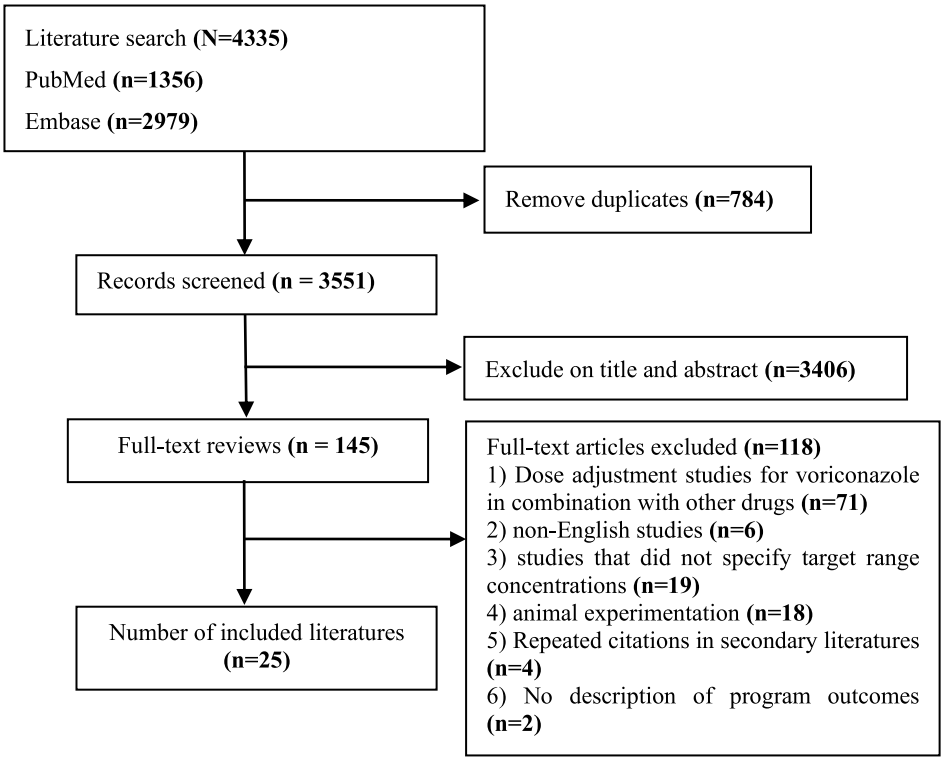


FIGURE 1
PRISMA flowchart.

of target attainment (PTA). Study design (S): 1) human study, 2) inclusion of experimental studies (randomized controlled and non-randomized controlled studies), analytical studies (cohort and case-control studies) and pharmacokinetic modeling studies, 3) the study was available in English. Studies have also elaborated on the voriconazole guidelines.

The following studies were excluded: 1) dose adjustment studies for voriconazole in combination with other drugs, 2) studies that did not specify target range concentrations, 3) animal experimentation and laboratory study, 4) non-English studies.

Studies that excluded studies involving switching between different routes of administration were not performed but are labeled in the text.

2.3 Quality assessment

This study used the Newcastle-Ottawa Scale (NOS) (GA Wells et al., 2013) for quality assessment of case-control and cohort studies, MINORS (Slim et al., 2003) for quality assessment of non-randomized controlled interventional studies, and Jadad (Jadad et al., 1996) for quality assessment of randomized controlled interventional studies. For quality evaluation methods of pharmacokinetic modeling studies refer to Niu Wanjie et al. (2018).

The included studies are qualitatively described based on recommendations for initial dosing in specific populations, the implementation of TDM (target concentration ranges, dose recommendations following TDM, timing of repeat TDM), and MIPD.

After a literature search and quality assessment, the contents of the literature were categorized and discussed to derive recommendations for special populations (Child-Pugh C patients, patients with different CYP2C19 genotypes or other special populations) and dose adjustments.

3 Result

3.1 Literature search

A total of 1,356 and 2,979 studies were searched on PubMed and Embase, respectively, and after removing irrelevant and duplicated studies, a total of 25 studies were included in this paper, of which 4 studies were case-control studies, 4 were cohort studies, 5 were non-randomized controlled studies, 1 was a randomized controlled study and 11 used a modeling program, of which 9 were Population pharmacokinetics (Pop PK), and 3 were Physiologically based pharmacokinetics (PBPK). The study was also described for 5 voriconazole guidelines (Britain, Canada, China, Australia, Japan) (Ashbee et al., 2014; Laverdiere et al., 2014; Chen et al., 2018; Chau et al., 2021; Takesue et al., 2022).

3.2 Evaluation of the quality of literatures

Of the 25 studies, 4 studies (Zhou et al., 2020; Diller et al., 2021; Zembles et al., 2023; Zhang et al., 2023) were case-control studies and 4 (Yamada et al., 2018; Chaudhri et al., 2020; Tang et al., 2021;

TABLE 1 The newcastle-ottawa scale (NOS).

First Author(Year)	Case-control studies/Cohort studies	The Newcastle-Ottawa Scale			
		Selection	Comparability	Exposure/ Outcome	NOS Score
Yamada et al. (2018)	Cohort studies	4	2	1	7
Chaudhri et al. (2020)	Cohort studies	4	2	1	7
Zhou et al. (2020)	Case-control studies	4	2	2	8
Diller et al. (2021)	Case-control studies	4	2	1	7
Zhao Y. C. et al. (2021)	Cohort studies	4	2	1	7
Tang et al. (2021)	Cohort studies	4	2	1	7
Zhang et al. (2023)	Case-control studies	4	2	2	8
Zembles et al. (2023)	Case-control studies	4	2	2	8

TABLE 2 MINORS and jadad.

First Author(Year)	Park et al. (2012)	Gao et al. (2018)	Perreault et al. (2019)	Hope et al. (2019)	Hicks et al. (2020)	Wang et al. (2021)
MINORS	No	Yes	Yes	Yes	Yes	Yes
1. A stated aim of the study		2	2	2	2	2
2. Inclusion of consecutive patients		2	2	2	2	2
3. Prospective collection of data		2	2	2	2	2
4. Endpoint appropriate to the study aim		2	2	2	2	2
5. Unbiased evaluation of endpoints		2	2	2	2	2
6. Follow-up period appropriate to the major endpoint		0	0	0	0	0
7. Loss to follow up not exceeding 5%		1	1	1	1	1
8. Prospective calculation of the sample size		0	0	0	0	0
And in the case of comparative studies						
9. A control group having the gold standard intervention		1	2	2	2	2
10. Contemporary groups		1	2	2	2	2
11. Baseline equivalence of groups		0	1	1	1	1
12. Statistical analyses adapted to the study design		1	2	2	2	2
MINORS score		14	18	18	18	18
Jadad	Yes	No	No	No	No	No
Randomized	2					
Random allocation	2					
Blinding	1					
Withdrawals and drop outs	1					
Jadad score	6					

Zhao Y. C. et al., 2021) were cohort studies, all of which were evaluated for quality using the NOS (GA Wells et al., 2013), with 5 of them having 7"*" and 3 of them having 8"*". 5 studies (Perreault et al., 2019; Gao et al., 2018; Hope et al., 2019; Hicks et al., 2020; Wang et al., 2021) were non-randomized controlled interventional studies and were evaluated for quality using MINORS (Slim et al., 2003), with four being moderate-quality literatures (scores of 13~18) and two being high-quality literatures (scores of 19~24). 1 study (Park et al., 2012) was a randomized controlled interventional study with quality assessment using Jadad (Jadad et al., 1996), which is a high-quality literature (scores of 4~7). 11 studies (Pascual et al., 2012; Hope et al., 2013; Wang et al., 2014; Neely et al., 2015; Lin et al., 2018; Li et al., 2020; Li et al., 2021; Zubiaur et al., 2021; Jiang et al., 2022; Lin et al., 2022; Wang et al., 2024) applied the method of model simulation, and the quality evaluation method was referred to the study of Niu Wanjie et al. (2018). A total of 4 studies scored 77~80, and a total of 7 studies scored 81~86. Details are provided in Tables 1– 3.

TABLE 3 Model-related study scores.

First author(Year)	Title and abstract	Introduction	Methods	Results	Discussion and Conclusions	Others	Total scare
Pascual et al. (2012)	100	33	64	75	100	100	79
Hope et al. (2013)	86	66	56	75	100	100	81
Wang et al. (2014)	100	66	68	88	80	100	84
Neely et al. (2015)	86	66	60	75	100	100	81
Lin et al. (2018)	100	33	56	75	100	100	77
Li et al. (2020)	86	100	56	75	100	100	86
Zubiaur et al. (2021)	71	100	48	75	80	100	79
Lin et al. (2022)	100	67	68	75	100	100	85
Li et al. (2021)	86	100	80	75	100	50	82
Jiang et al. (2022)	86	33	84	75	100	100	80
Wang et al. (2024)	100	66	68	63	100	100	83

3.3 Initial dosing program for special populations

From 2013 to 2022, the relevant guidelines for drug monitoring for voriconazole therapy have been published or updated in Britain (Ashbee et al., 2014), Canada (Laverdiere et al., 2014), China (Chen et al., 2018), Australia (Chau et al., 2021) and Japan (Takesue et al., 2022), and many studies have also put forward suggestions on the initial dosage program for patients of different ages, Child-Pugh C, CYP2C19 genotype, race and Body Mass Index (BMI). Of the five guidelines, only the Britain and Japanese guidelines recommend an initial dosing program, with the British guideline recommending the same initial dosing program as the program in the specification (loading dose of 6 mg/kg q12 h iv or 400 mg q12 h po, and maintenance dose of 4 mg/kg q12 h iv or 200 mg q12 h po). The Japanese guidelines recommend the loading dose to be the same as the instructions, and the maintenance dose to be divided according to different populations and disease types. The maintenance dose is 4 mg/kg q12 h iv for non-Asian populations and 3 mg/kg q12 h iv for Asian populations. The maintenance dose for patients with *Candida* infections (except for *Candida* glabrata and *Candida* krusei) is 200 mg q12 h, and for patients with Aspergillus infections is 300 mg q12 h.

There were 7 studies on Child-Pugh C patients, 3 were prospectives and 4 were retrospectives, and of these 7 studies, 1 was conducted using the pop PK model, in which a loading dose of 5 mg/kg q12 h and a maintenance dose of 50 mg q12 h or 100 mg q24 h were recommended for Child-Pugh C patients (Lin et al., 2022). Of the remaining 6 studies, 2 studies suggested that the maintenance dose of voriconazole in Child-Pugh patients should be reduced to one-third of the standard dose (Zhang et al., 2023; Yamada et al., 2018). 2 studies recommended a loading dose of voriconazole of 200 mg q12 h (Gao et al., 2018; Wang et al., 2021), 1 study recommended 200 mg q24 h (Zhao Y. et al., 2021) and all three recommended a maintenance dose of 50 mg q12 h or 100 mg q24 h. In addition, 1 study was a stratified study using Total Bilirubin (TBIL) to determine the dosing program based on patients' TBIL values (Tang et al., 2021). The specific studies are presented in Table 4.

A total of 5 studies, 4 prospective and 1 retrospective, were conducted in patients with different CYP2C19 genotypes. The recommendations of these 5 studies varied, with only the patients with intermediate metabolizers (IM) being more consistent, with 4 studies (Hicks et al., 2020; Lin et al., 2018; Li et al., 2020; Zubiaur et al., 2021) suggesting that standard treatment programs could be used. Modeling methods were used in 4 of these 5 studies (2 for pop PK and 2 for PBPK).For patients with ultrarapid metabolizers (UMs), switching or using the program 500 mg q6 h for 48h, followed by 500 mg q8 h was recommended. For patients with rapid metabolizers (RMs), the maintenance dose was recommended to be 400 mg q12 h or using the program 400 mg q8 h for 24 h, followed by 500 mg q12 h. For patients with normal metabolizers (NMs) For patients with NMs, the recommended maintenance dose is 325–400 mg q12 h po or 200–300 mg q12 h iv or using program 400 mg q6h for 24 h, followed by 200 mg q12 h. For patients with IMs, 3 studies recommend using the standard dose, and 1 study suggests the maintenance dose of 275 mg q12 h or 175 mg t.i.d. For patients with poor metabolizers (PMs), 150~200 mg q12 h iv or 225~250 mg q12 h po is recommended, as well as the program 200 mg q12 h for 24 h, followed by 100 mg q24 h for a maximum of 2 weeks, followed by 50 mg q24 h for a maximum of 2 months. The remaining 1 study (Hicks et al., 2020) recommended that voriconazole be avoided in patients with the UMs phenotype, that the maintenance dose for patients with the RMs phenotype could be 300 mg bid po, and that patients with the remaining genotypes could be treated with the standard treatment program. These specific studies are listed in Table 5.

In addition, for overweight and obese patients, the Canadian guideline indicates that dosing based on true body weight (TBW) in obese patients (BMI ≥ 35 kg/m^2) may increase the risk of overexposure and toxicity, and therefore recommends that intravenous and oral voriconazole dosing in obese patients should be based on ideal body weight (IBW) or adjusted body weight (AdjBW). The Japanese guidelines recommend the use of

TABLE 4 Initial dosing programs and target concentration ranges in patients with liver cirrhosis.

First author (Year)[4]	Country	Population[1]	Age/ Male(N)	Weight	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
Gao et al. (2018)	China	Acute-on-chronic liver failure patients with development probably or diagnosis invasive pulmonary aspergillosis	42 (26~70)/18	NR	20 (1 patients with cerebral failure, 9 patients with coagulation failure, and 2 patients with kidney failure)	The loading dose was 200 mg po q12 h. The maintenance dose was 100 mg po q.d	1.0~5.0	Resulted in rational trough plasma drug concentrations (1.0~5.5 mg/L), good clinical outcomes (90-day survival rate of 6/8) and no observed adverse events
Yamada et al. (2018)	Japan	Liver cirrhotic and non-liver cirrhotic patients	60(48~64)/3	NR	6 patients with Child-Pugh C	The oral maintenance dose of voriconazole should be reduce to approximately one-third that of the standard dose	1.0~5.0	Plasma voriconazole trough concentrations in all patients with Child-Pugh class C were almost within therapeutic range
Wang et al. (2021)	China	Patients with liver cirrhotic	50.5 ± 13.2 (22~82)/95	63.1 ± 9.6 (40.5~88)	120 (40 patients with Child-Pugh A/B and 80 patients with Child-Pugh C)[b]	The loading dose for Child-Pugh A/B patients was 200 mg q12 h with a maintenance dose of 75 mg q12 h or 150 mg q24 h, and the loading dose for Child-Pugh C patients was 200 mg q12 h with a maintenance dose of 50 mg q12 h or 100 mg q24 h	1.0~5.0	The probability of the program achieving PTA at steady state (day 7) was 66.8%–72.3% for Child-Pugh A/B patients and 70.3%–74.0% for Child-Pugh C patients
Zhao Y. et al. (2021)	Asian	Patients with Child-Pugh C	49.35 ± 11.65 (32~89)/39	61.27 ± 12.87 (36~99)	43 (RMs with 1, NMs with 20, IMs with 16, PMs with 6)[c]	The loading dose was 200 mg q24 h, and the maintenance dose was 100 mg q24 h	1.0~5.5	The target concentration range was achieved in 16 patients with initial dosing, 11 patients with 1 adjustment, 7 patients with 2 adjustments, and 9 patients with 3–9 adjustments
Tang et al. (2021)	China	Patients were diagnosed with liver cirrhotic	46.4 ± 12.8 (15~89)/43	60.0 ± 13.1 (36~99)	51 (4 patients with Child-Pugh A, 11 patients with Child-Pugh B, 36 patients with Child-Pugh C)	TBIL in the range of ULN to 51 μmol/L(TBIL-1), loading dose was 400 mg q12 h, followed by a maintenance dose of 100 mg q12 h iv/po TBIL in the range of 51–171 μmol/L(TBIL-2),A loading dose was 200 mg q12 h, followed by a maintenance dose of 50 mg q12 h or 100 mg qd iv/po TBIL ≥171 μmol/L(TBIL-3),A loading dose was 200 mg q12 h, followed by a maintenance dose of 50 mg qd iv/po	0.5~5.0	The PTA for patients with TBIL-1 was 91.7% and 85.2%, administered orally and intravenously respectively The PTA for patients with TBIL-2 and TBIL-3 was highest(all>90%)
Lin et al. (2022)	China	Severe liver dysfunction	25(9~31) /22	64.0 (47.5~87.0)	26 (4 patients with Child-Pugh A, 8 patients with Child-Pugh B, 14 patients with Child-Pugh C	The loading dose for Child-Pugh A/B patients was 5 mg/kg q12 h with a maintenance dose of 100 mg q12 h or 200 mg q24 h, and the loading dose for	2.0~6.0	The PTA for patients with Child-Pugh A/B and C was 87.9% and 94.0%, respectively

(Continued on following page)

10.3389/fphar.2024.1439586

TABLE 4 (*Continued*) Initial dosing programs and target concentration ranges in patients with liver cirrhosis.

First author (Year)[4]	Country	Population[1]	Age/ Male(N)	Weight	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
						Child-Pugh C patients was 5 mg/kg q12 h with a maintenance dose of 50 mg q12 h or 100 mg q24 h		
Zhang et al. (2023)	China	Patients with Child-Pugh C	53.2 ± 13.4 /52	(BMI)23.1 ± 4.0 kg/m^2	66 (NMs with 28, IMs with 25, PMs with 13)	The maintenance dose of voriconazole should be reduce to approximately one-third that of the standard dose	1.0~5.5	Only 16.7% of patients with a trough concentration >5.5 mg/L and 4.5% with a trough concentration <1 mg/L had only one drug-related adverse event

[a]All patients use voriconazole.
[b]UMs, with 1; EMs, with 24; IMs, with 21; PMs, with 5.
[c]RMs, with 12; IMs, with 11; PMs, with 3.
[d]The starting dose route for (Zhang et al., 2023; Yamada et al., 2018; Gao et al., 2018) is oral administration. The starting dose route for (Lin et al., 2022) is intravenous administration. The starting dose route for (Tang et al., 2021; Wang et al., 2021) is intravenous or oral administration. The starting dose route for (Zhao Y. C. et al., 2021) is intravenous administration, oral administration or intravenous to oral sequential therapy.
q12 h, every 12 h q.d once daily; Iv, intravenously; Po, orally; TBIL, total bilirubin; PTA, Probability of target attainment; CYP2C19, cytochrome P2C19; UMs, ultrarapid metabolizers; RMs, rapid metabolizers; NMs, normal metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers; SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicentre retrospective; RCT, randomized controlled trial; ULN, upper limit of normal; BMI, body mass index; NR, no reference.

IBW or adjusted body weight dosing. It has also been suggested that dosing programs based on TBW are not appropriate for patients with a BMI ≥35 kg/m^2, and the use of AdjBW for dosing calculation is recommended (Diller et al., 2021).

There are many factors that need to be considered in order to establish an individualized voriconazole dosing program, such as the type of infection, severity of infection, inflammation, BMI, and co-medication. The specifics of the 5 relevant studies are listed in Table 6, of which 3 were prospective studies, 2 were retrospective studies.

3.4 Target trough concentration range

In addition to the target concentration ranges recommended by the five guidelines, 5 (Zhou et al., 2020; Lin et al., 2018; Li et al., 2021; Lin et al., 2022; Wang et al., 2024) studies chose different lower concentration limits and 8 (Diller et al., 2021; Zembles et al., 2023; Pascual et al., 2012; Lin et al., 2018; Li et al., 2020; Zubiaur et al., 2021; Lin et al., 2022; John et al., 2019) studies chose different upper concentration limits.

5 studies (Zhou et al., 2020; Lin et al., 2018; Li et al., 2021; Lin et al., 2022; Wang et al., 2024) used 2.0 mg/L as the lower limit of trough concentration. It is based on the study which included 34 patients and the results showed that none of the cases with trough concentration >2 mg/L were ineffective for voriconazole, while two-sixths of the cases with TDM below this threshold were nonresponsive (Dolton and McLachlan, 2014).

The upper limit of trough concentration also varied among studies. 1 study (Zubiaur et al., 2021) used 3.0 mg/L as the upper limit of trough concentration based on the meta-analysis studies. The results of meta-analysis study showed a significantly lower probability of hepatotoxicity at a trough concentration of <3.0 mg/L compared to the control group (RR = 0.37, 95% CI = 0.16~0.83) (Jin et al., 2016). 1 study (Pascual et al., 2012) used 4.5 mg/L as the upper trough concentration limit, whose result shown that a >15% probability of neurotoxicity at trough concentrations >4.5 mg/L. Six studies (Diller et al., 2021; Zembles et al., 2023; Lin et al., 2018; Li et al., 2020; Lin et al., 2022; John et al., 2019) used 6.0 mg/L as the upper trough concentration limit based on the follow: Firstly, a meta-study consisting of 24 studies included literatures with >10 patients, TDM during voriconazole treatment, and studies that evaluated the relationship between trough concentration and clinical efficacy and/or safety. Literatures were searched from January 1998 through October 2013 and the following keywords were used: “voriconazole”, “triazole”, “vfend”, “drug monitoring”, “pharmacovigilance”, “adverse drug reaction/reporting system”. The meta-analysis showed that patients had an increased probability of adverse effects when trough concentrations ranged was 4.0~6.0 mg/L (OR = 4.17,95 CI% = 2.08~8.36) and that a supratherapeutic threshold of 6.0 mg/L was the most predictive of toxicity (OR = 4.60, 95% CI = 1.49–14.16) (Luong et al., 2016). The second is a study whose results show that elevated liver enzymes were frequently observed at voriconazole concentrations >6 mg/L, and this adverse event occurred in 8 of 11 cases at 6 mg/L or higher concentrations (Dolton and McLachlan, 2014). The target concentration ranges for each study are shown in Tables 4–8.

TABLE 5 Initial dosing program and target concentration range based on CYP2C19 genotype.

First author (Year)[b]	Country	Population[a]	Age/ Male(N)	Weight (kg)	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
Lin et al. (2018)	China	patients with renal transplant recipients and different CYP2C19 genotypes	36(18~58)/ 84	56.9 ± 10.5 (38.9~87.5)	105(NMs with 44, IMs with 49, PMs with 12)	With NMs, the dosing program was 300 mg q12 h iv With IMs, the dosing program was 200 mg q12 h iv or 350 mg q12 h po With PMs, the dosing program was 150 mg q12 h iv or 250 mg q12 h po	2.0~6.0	Patients with NMs, the PTA was 80.3% Patients with IMs, the PTA was 81.5% and 3.5% supratherapeutic concentrations Patients with PMs, the PTA was 90.9% and 6.3% supratherapeutic concentrations
Hicks et al. (2020)	America	patients with neutropenic AML and different CYP2C19 genotypes	64(19~86)/ 139	80.4 (38.0~165.8)	263(UMs with 5, RMs with 24, NMs with 105, IMs with 72, PMs with 7)[a]	With UMs, voriconazole is recommended to be avoided With RMs, the maintenance dose was 300 mg q12 h po With NMs, IMs, PMs, the standard dose program	The subtherapeutic trough concentration is < 1 mg/L	Subtherapeutic concentration were avoided in 83.8% of RMs receiving interventional dosage compared to 46.2% receiving standard dosage
Li et al. (2020)	Germany	Patients with different CYP2C19 genotypes	18~53/NR	NR	305(RMs with 62, NMs with 101, IMs with 77, PMs with 65)	With RMs and NMs, the maintenance dose was 400 mg q12 h po With IMs, the standard dose program With PMs, no recommendations	1.5~6.0	The dose program increased PTA two-fold while maintain a probability of reaching toxic concentration below 20%
Zubiaur et al. (2021)	Spanish	Patients with different CYP2C19 genotypes	23 (22~25)/57	69 (68~80)	106(UMs with 4, RMs with 33, NMs with 38, IMs with 29, PMs with 2)	With UMs, the dosing program was 500 mg q6h for 48 h,followed by 500 mg q8h With RMs, the dosing program was 400 mg q8h for 24 h,followed by 500 mg q12 h With NMs, the dosing program was 400 mg q6h for 24 h,followed by 200 mg q12 h With IMs, standard dosage or maintenance dose reduction to 100 mg q12 h (50% of the standard dose) With PMs, the dosing program was 200 mg q12 h for 24 h,followed by 100 mg q24 h for a maximum of 2 weeks, followed by 50 mg q24 h for a maximum of 2 months	0.5~3.0	After dosage adjustment, the patient reached well tolerated and therapeutic voriconazole plasma levels

(Continued on following page)

TABLE 5 (*Continued*) Initial dosing program and target concentration range based on CYP2C19 genotype.

First author (Year)[b]	Country	Population[a]	Age/ Male(N)	Weight (kg)	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
Li et al. (2021)	China	Patients with different CYP2C19 genotypes	37.5 ± 14.7/57	63.2 ± 12.3 (44.0~111.0)	78 (NMs with 27, IMs with 32, PMs with 16)	With NMs, the dosing program was 325 mg q12 h or 200 mg t.i.d With IMs, the dosing program was 275 mg q12 h or 175 mg t.i.d With PMs, the dosing program was 225 mg q12 h or 150 mg t.i.d	2.0~5.5	Patients with NMs, the PTA was 81.05% and 82.27% when the dosing program was 325 mg q12 h or 200 mg t.i.d respectively Patients with IMs, the PTA was 82.74% and 84.95% when the dosing program was 275 mg q12 h or 175 mg t.i.d respectively Patients with PMs, the PTA was 82.81% and 86.04% when the dosing program was 225 mg q12 h or 150 mg t.i.d respectively

[a]Voriconazole was applied to 219 of 263 patients, with 202 receiving prophylactic voriconazole and 176 receiving a dose-adjustment program.
[b]The starting dose route for (Hicks et al., 2020; Li et al., 2020; Li et al., 2021) is oral administration. The starting dose route for (Lin et al., 2018) is intravenous or oral administration. The starting dose pathway for (Zubiaur et al., 2021) is not mentioned.
AML, acute myeloid leukemia. q12 h, every 12 h q.d once daily. Iv, intravenously. Po, orally; TBIL, total bilirubin;; PTA, Probability of target attainment; CYP2C19, cytochrome P2C19; UMs, ultrarapid metabolizers; RMs, rapid metabolizers; NMs, normal metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers; ALB, albumin; SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicentre retrospective; RCT, randomized controlled trial; NR, no reference.

3.5 Dosage adjustment

A total of 4 dose-adjustment literatures were included in the study, 3 (Perreault et al., 2019; Zhou et al., 2020; Park et al., 2012) for adults and 1(15) for pediatrics. There is no consistently recommended program for dose adjustment of voriconazole. Of the 4 guidelines (Ashbee et al., 2014; Laverdiere et al., 2014; Chen et al., 2018; Chau et al., 2021) that propose a dosing program, details are given in Table 8.

In adult patients, 2 studies (Zhou et al., 2020; Park et al., 2012) recommended that if trough concentrations were much higher than supratherapeutic concentrations or if drug-related adverse events occurred, 1 dose should be reserved, subsequent doses should be reduced by 33% or 50%, and other antifungal drugs should be considered if toxicity was not reversed. In addition, the study by Sarah perreault et al. suggests that when trough concentration was 5.6~7.9 mg/L, hold dose, and recheck daily through concentration, then restart at 100 mg less when trough concentration was ≤2.5 mg/L. When trough concentration ≥8 mg/L, hold dose, and recheck daily through concentration, then restart at 50% dose reduction when trough is ≤ 2.5 mg/L (PTA = 80%) (Perreault et al., 2019). 3 studies (Perreault et al., 2019; Zhou et al., 2020; Park et al., 2012) all recommended that the dose of voriconazole be reduced by 25% ~ 50% if the trough concentration of voriconazole exceeded the therapeutic concentration and no drug-related adverse effects were observed. And sarah perreault et al. suggested that for trough concentration <0.5~1.0 mg/L, voriconazole dose increase by 25%~50%, which made 80% of patients were able to achieve the target concentration range with an adverse reaction rate of only 7.6% (Perreault et al., 2019).The study by WanBeom Park et al. recommended a 100% increase in voriconazole dose at trough concentrations <1 mg/L, with a dose-adjusted probability of target attainment (PTA) of 75% (Park et al., 2012). In addition to the above program, another program was proposed in the study by Pejun Yvonne Zhou et al. When the trough concentration was <0.5 mg/L, re-load voriconazole at a dose of 1.5 times the new maintenance dose for 24 h, followed by a 75% dose increase for the maintenance dose, which increased the level by > 10 times(absolute increment is unknown as 0.5 mg/L was the upper limit of assay detection). When the trough concentration was 1.0~1.9 mg/L, the increase was 25~33% or an increase of 67%, which increased the level by 70~130% or increased the level by 10%. When the trough concentration was 5.5~7.5 mg/L, reduction of 13% or reduction of 33%, which reduction level by 50% or reduction level by 80%. When the trough concentration was >7.5 mg/L, held off one dose or until neurological symptoms were resolved, followed by 33% reduction in dose, which reduction level by >33% (absolute reduction is unknown as 7.5 mg/L was the upper limit of assay detection) (Zhou et al., 2020).

There are fewer studies on dose adjustment for children and only 1 study by Zembles et al. (2023) was included in this study, which was studied in 59 pediatric patients aged 3.7~14.7 years old. Of these, the study by Jamie john et al. did not further explore the post-therapeutic efficacy or PTA of dose adjustments, while the study by Tracy N. Zembles et al. showed that after subsequent dose modifications based on TDM, they were able to eventually reach the

TABLE 6 Initial dosing program and target concentration range based on other factors[a].

First author (Year)[d]	Country	Population[b]	Age/Male(N)	Weight (kg)	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
Pascual et al. (2012)	NR	Patients with Aspergillus and *Candida* infections	58(23~78)/39	68(42~125)	55 (27 patients with Aspergillus infection, and 8 patients with Candidiasis infection)	In acute infection, the dosing program was 300 mg iv and 400 mg po q12 h in responding infection or prophylaxis, the dosing program was 200 mg iv and 300 mg po q12 h	1.5~4.5	The dosing programs of 300 mg iv and 400 mg po q12 h resulted in trough concentrations ≥1.5 in 87% and 78% of patients, respectively The dosing programs of 200 mg iv and 300 mg po q12 h resulted in trough concentrations ≥1.5 in 70% and 68% of patients, respectively
Wang et al. (2014)	China	Patients who diagnosed with a proven or probable IFIs	59 ± 21 (18~99)/104	59.1 ± 7.8(35.0~80.0)	151	with Aspergillus infections, the dosing program was 200 mg b. i.d iv/po with *candida* infections, the dosing program was 300 mg q12 h po or 200 mg q12 h iv	1.0~4.0	For patients with Aspergillus infections, the CFR of the dosing program 200 mg q12 h iv and po was 95.8% and 94.2% respectively For patients with *Candida* infections, the CFR of the dosing program 300 mg q12 h iv and 200 mg q12 h po was 95.6% and 86.7% respectively
Diller et al. (2021)	America	Obese patients with BMI ≥35 kg/m^2	TBW group was 61(44,70)/20 AdjBW group was 62(52,70)/47	TBW group was 87.1 (71.4, 96.7) AdjBW group was 96.2 (83.4, 109.1)	45 patients using TBW (Caucasian with 38, black with 5 and other with 2), 85 patients using AdjBW (Caucasian with 74, black with 8 and other with 3	AdjBW-based voriconazole dosing, combined with TDM, should be strongly considered in patients weighing ≥120% of their IBW.	1.0~6.0	Therapeutic trough attainment was significantly improved with AdjBW-based dosing compared to TBW-based dosing (64.7% *versus* 46.7%; $p = 0.047$)
Jiang et al. (2022)	China	Patients with talaromy cosis	57(54~69)/24 30(20~65)/31	61(52~72) 50(38~87)	35 and 34 in the two hospitals respectively	CRP ≤ 96 mg/L, the loading dose was 250 mg q12 h, the maintenance dose was 100 mg q12 h CRP > 96 mg/L, the loading dose was 200 mg q12 h, the maintenance dose was 75 mg q12 h	1.0~5.5	Patients with CRP ≤96 mg/L and CRP >96 mg/L had a 61.3% and 13.6% higher PTA with this optimal initial dosing program than the conventionally recommended program, respectively, and the potential for supratherapeutic concentrations decreased by 28.9%.[c]

(Continued on following page)

10.3389/fphar.2024.1439586

TABLE 6 (*Continued*) Initial dosing program and target concentration range based on other factors[a].

First author (Year)[d]	Country	Population[b]	Age/Male(N)	Weight (kg)	Number of patients	Initial dosing program	Target concentration range(mg/L)	Dosing program results
Wang et al. (2024)	China	Elderly patients with hypoproteinemia	Modeling group was 70(60~103)/70 Validation group was 79(65~93)/79	Modeling group was 63.00(36.1~97.9) Validation group was 62.35(40.5~100.0)	Modeling group had 128 patients Validation group had 22 patients	ALB≤35 g/L, the loading dose was 5 mg/kg q12 h, and the maintenance dose is 2 mg/kg q12 h iv ALB > 35 g/L,the loading dose was 5 mg/kg q12 h,and the maintenance dose is 3 mg/kg q12 h iv	2.0~5.0	The loading dose of 5 mg/kg q12 h was adequate for patients with ALB≤35 g/L and ALB>35 g/L to attain high probabilities of target trough concentration range (94.18% and 90.68%) For patients with ALB ≤ 35 g/L, the probabilities of voriconazole reaching the target concentration range after a maintenance dose change was 99.26% and for patients with ALB > 35 g/L was 96.07%

[a]Other factors are infection status, pathogens, body weight, C-reactive protein and albumin.
[b]All patients use voriconazole.
[c]The CRP, is an estimate of the proportion of the population achieving a target $\int AUC_{24}$/MIC, value ≥ 25, calculated by the PTAs, and the MIC, distribution of the microorganisms.
[d]The starting dose pathway for (Diller et al., 2021; Jiang et al., 2022) is not mentioned. The starting dose route for (Wang et al., 2024) is intravenous administration. The starting dose route for (Pascual et al., 2012; Wang et al., 2014) is intravenous or oral administration. q12 h, every 12 h q.d once daily; Iv, intravenously; Po, orally; PTA, Probability of target attainment; CYP2C19, cytochrome P2C19; UMs, ultrarapid metabolizers; RMs, rapid metabolizers; NMs, normal metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers; ALB, albumin; CFR, cumulative fraction of response; AdjBW, Adjusted body weight; TBW, total body weight; SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicentre retrospective; RCT, randomized controlled trial; CRP, C-reactive protein. NR, no reference.

target in over 80% of patients, though this requires multiple steady-state voriconazole serum trough concentrations measurements. The specifics of the study are represented in Table 7.

3.6 Timing of repeat therapy drug monitoring

The timing of monitoring after application of the initial dosing program of voriconazole has become clearer, but there is still no clear evidence on the timing of re-monitoring after dose adjustment. WanBeom Park et al. argue that if the voriconazole dosage were or administration route was altered or if the interacting drug was introduced or halted, follow-up TDM was repeated on day 4 (Park et al., 2012). The British guideline recommends routine second monitoring to ensure that concentrations are stable and in the effective range, as well as repeat monitoring after dose adjustments and sequential therapy (Ashbee et al., 2014). The timing of repeat monitoring after dose adjustment is mentioned in the Chinese guideline, which thinks the timing of repeated therapy drug monitoring is consistent with the initial sampling time under the circumstance of no voriconazole loading dose, which is expected to be 4~7 days after adjusting the voriconazole dosing program, or with initiating or withdrawing concomitant drugs that potentially influence voriconazole pharmacokinetic profiles (Chen et al., 2018). The Australian guidelines recommend that repeat testing should be on the fifth day after adjusting the dosing program, but no clear reason is given (Chau et al., 2021). Sarah Perreault et al. argued that trough concentrations should be rechecked on day 5 of the new dosing program (Perreault et al., 2019). Additionally, Tracy N. Zembles et al. suggested that steady state could be reached if voriconazole trough concentrations were repeated on ≥2.5 days after dose adjustment, but most studies chose to repeat monitoring on day 5 (Zembles et al., 2023).

With the exception of the Chinese guidelines, the remaining recommendations are expert opinions. The recommendations of the Chinese guidelines are based on the following 2 studies. Purkins L et al. evaluated the safety, tolerability, and pharmacokinetics of an intravenous to oral voriconazole program in 41 healthy males. The results showed that after switching from intravenous to oral dosing program, the majority of subjects reached a steady state on day 4, with the mean lowest trough concentration remaining above the clinically important Minimum Inhibitory Concentration (MIC) (Purkins et al., 2002). Visual inspection of trough concentration together with statistical analyses of peak concentration and Area under the curve (AUC) values suggest that steady-state levels were achieved by the 4–6 days of multiple dosing (Purkins et al., 2003).

3.7 Dose-prediction software

Several studies have used pharmacokinetic and pharmacodynamic modeling to accurately predict concentrations and dosages based on patient physiological data and drug concentration to guide rational clinical use. This approach is particularly useful for drugs with high pharmacokinetic variability, such as voriconazole. This study included four studies, 2 were software development studies (Hope et al., 2013; Neely et al.,

TABLE 7 Dose Adjustment program.

First author (Year)[a]	Population	Age/ Male(N)	Weight (kg)	No. patients	Target through concentration range	Dose adjustment	Dose-adjusted outcome
Park et al. (2012)	South Korean	Adult/42	NR	55	1.0~5.5 mg/L	<1.0 mg/L, increase dose by 100% >5.5 mg/L and there are no drug-related adverse events, decrease dose by 50% >10 mg/L or there are the drug-related adverse events happen, hold 1 dose, followed decrease dose by 50%	After subsequent dose modifications based on TDM, they were able to eventually reach the target in 75% of patients
Perreault et al. (2019)	Caucasian 78% Hispanic 12% Black 7% other 3%	Adult/72	NR[b]	128[c]	1.0~4.0 mg/L	0.0~0.6 mg/L, increase dose by 100 mg 0.7~0.9 mg/L, increase dose by 50 mg 1.0~4.0 mg/L, none 4.1~5.5 mg/L, decrease dose by 50 mg 5.6~7.9 mg/L, hold dose, recheck daily through concentration, then restart at 100 mg less when trough is ≤ 2.5 mg/L ≥8 mg/L, hold dose, recheck daily through concentration, then restart at 50% dose reduction when trough is ≤ 2.5 mg/L	After the second dose adjustment, they were able to eventually reach the target in 80% of patients Approximately 7.6% of patients developed an adverse effect with neurologic/psychological being the most common
Zhou et al. (2020)	Southeast Asians	Adult/113	75.0 (62.0~85.0)	70 [d] (55 Chinese, 6 Indians, 5 Malaysians, 4 other)	2.0~5.5 mg/L	<0.5 mg/L, re-load voriconazole at a dose of 1.5 times the new maintenance dose for 1 day, followed by 75% dose increase for maintenance dose (n = 1) 1.0~1.9 mg/L, increase of 25%–33% (n = 6) and increase in 67% (n = 1) 5.5~7.5 mg/L, reduction of 13% (n = 1) and reduction of 33% (n = 3) >7.5 mg/L, held off one dose or until neurological symptoms were resolved, followed by 33% reduction in dose (n = 6)	<0.5 mg/L, increased level by > 10 times(absolute increment is unknown as 0.5 mg/L was the upper limit of assay detection) 1.0~1.9 mg/L, increased level by 70~130% and increase level by 10% 5.5~7.5 mg/L, reduction level by 50% and reduction level by 80% >7.5 mg/L, reduction level by >33% (absolute reduction is unknown as 7.5 mg/L was the upper limit of assay detection)
Zembles et al. (2023)	American	Pediatric/30	31.4 (14.1~62.7)	59	1.0~6.0 mg/L	<1.0 mg/L, increase dose by 50% >6.0 mg/L, hold 1 dose, decrease subsequent dose by 25%	After subsequent dose modifications based on TDM, they were able to eventually reach the target in over 80% of patients, though this required multiple stead-state voriconazole serum trough concentrations measurements

[a]3 patients were underweight (BMI < 18.50 kg/m2), 42 patients were normal weight (BMI, of 18.50~24.99 kg/m2), 51 patients were overweight (BMI, of 25~29.99 kg/m2), 27 patients were obese (BMI≥30 kg/m2) and 5 patients were morbidly obese (BMI ≥ 40 kg/m2).

[b]A total of 250 monitoring sessions were performed in 128 patients, of which 237 were for preventive purposes (94.8%) and 13 for therapeutic purposes (5.2%).

[c]One patient received voriconazole as anti-fungal prophylaxis whereas 62/70(88.6%) and 7/70(10%) patients were treated for IFIs, and CPA, respectively.

[d]The starting dose route for (Perreault et al., 2019) is oral administration. The starting dose route for (Zhou et al., 2020) is intravenous or oral administration. The starting dose route for (Zembles et al., 2023) is intravenous or enteral administration. The starting dose route for (Park et al., 2012) is intravenous or oral or intravenous to oral sequential therapy.

SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicenter retrospective; RCT, randomized controlled trial; TDM, therapeutic drug monitoring; CAP, chronic pulmonary aspergillosis; BMI, body mass index; NR, no reference.

TABLE 8 Dose Adjustment program (Guideline).

First author (Year)	Country	Population	Target concentration range(mg/L)	Initial dosing program		Dose adjustment
				loading dose	Maintenance dose	
Ashbee et al. (2014)	Britain	All patients use voriconazole	1.0~5.5 mg/L	6 mg/kg q12 h	4 mg/kg q12 h	<1.0 mg/L, increase dose by 50%,with a maximum dose of 6 mg/kg q12 h, or the oral voriconazole maintenance dose should be increased from 200 mg q12 h to 300 mg q12 h
Laverdiere et al. (2014)	Canada	All patients use voriconazole	prophylaxis ≥ 0.5 mg/L Treatment 1.5~5.0 mg/L Toxicity < 5.5 mg/L	NR	NR	<0.5 mg/L, increase dose by 50% 0.5~1.5 mg/L, increase dose by 25% 1.5~5.5 mg/L, none ≥5.5 mg/L and drug-related toxicities, decrease dose by 25%
Chen et al. (2018)	China	All patients use voriconazole	0.5~5.0 mg/L	NR	NR	<0.5 mg/L, increase dose by 50% 5.0~10.0 mg/L without ≥ grade 2 adverse events, decrease dose by 20% >10.0 mg/L or has grade 2 adverse events, hold 1 dose, decrease subsequent dose by 50%
Chau et al. (2021)	Australia	Patient with haematological malignancy and haemopoietic stem cell transplant recipients	Prophylaxis and treatment 1.0–5.5 mg/L CNS infection, bulky disease, multifocal infection > 2 mg/L	NR	NR	0~0.5 mg/L, increase dose by 50% 0.5~1.0 mg/L, increase dose by 25% >5.5 mg/L and asymptomatic, decrease dose by 25% ≥5.5 mg/L and drug-related toxicities, hold 1 dose and decrease subsequent doses by 50%
Takesue et al. (2022)	Japan	Voriconazole in Asian and non-Asian populations	Asian 1.0~5.5 mg/L Non-Asian 1.0~4.0 mg/L	6 mg/kg q12 h	Asian 3 mg/kg q12 h Non-Asian 4 mg/kg q12 h	NR

q12 h, every 12 h. CNS, central nervous system; NR, no reference.

2015) and two (Chaudhri et al., 2020; Hope et al., 2019) were software evaluations. Meanwhile, the two software development studies applied the Pop PK model, 1 of which was evaluated through prospective studies and the other through Monte Carlo simulations. In Table 9 are some of the software evaluations and related content.

The names of the software developed in the two studies are Bestdose and Catrides. The Bestdose was created with data from 64 adults (20 healthy volunteers and 43 patients) and evaluated with pharmacokinetic data from 10 hematopoietic stem cell transplant (HSCT) patients. This program can be used to further optimize voriconazole for the treatment of critically immunocompromised patients, but still has many drawbacks for routine application (Hope et al., 2013). This prospective study has several limitations. Catrides, a nonparametric overall model containing 141 patients (85 children and 56 adults) and validated with 33 pediatric patients aged 8 months to 17 years old, showed that the advantages of the procedure are that patients do not have to be at steady state, sample sampling times do not have to be precisely timed, AUCs can be estimated even for a single concentration, and the procedure can be generalized to any drug with a nonparametric pharmacokinetic model, but prospective studies are still needed (Neely et al., 2015).

In a prospective clinical study evaluating Bestdose, results showed that 85.7% of patients had a trough concentration of 1.0–3.0 mg/L at 120 h after the start of treatment, which is above the 33% of the *a priori* expected proportion (Zembles et al., 2023). Kanika Chaudnri et al. included 90 patients to evaluate DoseMeRx and showed that dose prediction software enhances efficacy, is used to guide clinical decision-making, and can be generalized to other populations, although the model was developed in a Chinese population. However, the software did not monitor clinical outcomes and did not incorporate CYP2C19 genotypes (Chaudhri et al., 2020).

4 Discussion

4.1 Initial dosing program for special populations

There are accepted results for initial dosing programs, but dosing programs for special populations remain to be studied. The Japanese guidelines make different recommendations for maintenance doses for different diseases. The study was conducted by modeling Pop PK on data from 40 patients. The results suggest that transplant recipients receiving voriconazole for the prophylaxis of invasive candidiasis or aspergillosis may achieve target concentrations associated with the desired therapeutic

TABLE 9 Dose-prediction software.

First author (Year)	study design	Software	Population	Number of patients	Advantages and disadvantages	Covariates
Software Development						
Hope et al. (2013)	SCP	Bestdose	HSCT recipients	10	Because parametric models are a single-model approach, they have no means to evaluate and optimize the expected precision with which a dosage regimen will achieve a desired target.	NR
Neely et al. (2015)	SCP	Cartride	Pediatrics under 18 years old	33	The control algorithm can accurately manage voriconazole therapy in children independently of steady-state conditions, and it is generalizable to any drug with a nonparametric pharmacokinetic model	Age, Weight
Software Evaluation						
Hope et al. (2019)	SCP	Bestdose	Patients with hematological malignancy or those undergoing HSCT	19	It is possible to achieve precise control for a compound with significant pharmacokinetic variability and non-linear PK. There are too few data in this study to enable the construction of new software that could utilise both genetype and voriconazole concentration	NR
Chaudhri et al. (2020)	SCR	DoseMeRx	Adult Australian patients	90[a]	Although the model assessed was developed in a Chinese population, the findings demonstrate that it is generalizable and can be extrapolated to other ethnicities	Total body weight, Height

[a]A total of 110 surveillance sessions were performed in 90 patients, of which 41% were for prophylaxis and 59% for invasive fungal infections, with 86% of invasive fungal infections being Aspergillus infections.

SCR, single-centre retrospective; SCP, single-centre prospective; MCR, multicentre retrospective; RCT, randomized controlled trial; HSCT, hematopoietic stem cell transplantation; NR, no reference.

outcome if the maintenance dose is 200 mg q12 h. However, Aspergillus with high minimal inhibitory concentrations may require higher maintenance doses (Perez-Pitarch et al., 2019).

For those with liver cirrhosis, trough concentrations of voriconazole can be affected by hepatic function due to the fact that voriconazole is primarily metabolized by the liver, and severe cholestasis significantly reduces voriconazole clearance, leading to slower metabolism and higher blood concentrations, which can increase the risk of drug-related adverse reactions, thus requiring clinical modification of the initial voriconazole dosing program (Pascual et al., 2012; Grensemann et al., 2021). The dosing program for Child-Pugh A/B is currently clearer, and the dosing program for Child-Pugh C needs further study. Of the 7 studies, 5 (Yamada et al., 2018; Tang et al., 2021; Gao et al., 2018; Wang et al., 2021; Lin et al., 2022) were unifactorial and 2 (Zhang et al., 2023; Zhao Y. et al., 2021) were multifactorial. In the 2 multifactorial studies, 1 study first investigated the influencing factors associated with variability in voriconazole trough concentration, performed multivariate bivariate correlation analyses, and developed multivariate linear regression models. The multiple regression linear model explained 34.8% of the variability in voriconazole trough concentration (R2 = 0.348), which implies that there is still a relatively high level of unexplained variability that requires further improvement. The results of another study showed that the mean trough concentration of patients with NMs, IMs, and PMs were 4.34 ± 2.12 mg/L, 4.40 ± 2.29 mg/L, and 4.30 ± 2.14 mg/L, respectively, and there was no significant difference between the three groups ($p = 0.990$), which ultimately suggests that only Child-Pugh classification affects trough concentration. Both of the 2 multifactorial studies explored the effect of CYP2C19 genotype in Child-Pugh C patients and both concluded that CYP2C19 genotype did not have a significant effect on trough concentration of voriconazole ($p > 0.05$).

And voriconazole is primarily metabolized in the liver by the CYP2C19 enzyme, with contributions by CYP2C9 and CYP3A4, and CYP2C19 polymorphisms could explain a substantial part of the remarkable inter-individual variability in voriconazole pharmacokinetics (Dean et al., 2012). Patients with CYP2C19 genotypes of IMs and PMs may be at higher risk of supratherapeutic levels and toxicity and the CYP2C19 genotyping as a potential strategy to optimize voriconazole dosing (Zhang et al., 2021). There have also been studies showing that poor metabolizers (most commonly in Asian populations) may experience higher voriconazole concentrations as well as a shift to other metabolic pathways for voriconazole such as 3A4 and 2C9 (McCreary et al., 2023).

It has been suggested that the level of inflammation (expressed as C-reactive protein concentration) can have an impact on voriconazole trough concentrations. Morgan et al. showed that inflammation stimulates the release of cytokines, leading to the regulation of hepatic transcription factor activity. These changes ultimately lead to the downregulation of most cytochrome P450 enzymes, affecting the production of metabolized proteins and thus reducing the clearance of certain drugs. In addition, *in vitro* studies have shown that pro-inflammatory cytokines, particularly interleukin-1 (IL-1), interleukin-6, and tumor necrosis factor alpha (TNF-α), downregulate the biosynthesis of a number of CYP450 enzymes involved in the metabolism of voriconazole,

such as CYP2C9, CYP2C19, and CYP3A4 (Morgan, 2001; Aitken et al., 2006; Morgan et al., 2008). Van Wanrooy MJ et al. studied 128 patients and performed linear regression analyses of patient data unadjusted for covariates (sex, age, dose, route of administration, liver enzymes, and drug-drug interactions) and patient data adjusted for covariates. The results of the multiple linear regression analysis showed that for every 1 mg/L increase in C-reactive protein (CRP) concentration, voriconazole trough concentration increased by 0.015 mg/L (Encalada Ventura et al., 2015). Encalada Ventura MA et al. also correlated metabolic rate (MR) and CRP levels with voriconazole in 19 patients and showed a significant positive correlation between CRP and voriconazole concentration (rho = 0.62; 95% CI, 0.48 to 0.73; $p < 0.001$) and a negative correlation with MR (rho = −0.64; 95% CI, −0.77~−0.50; $p < 0.001$), and voriconazole trough concentration increased with 0.021 mg/L for unit increase in the CRP level, and MR decreased with a −0.010 for every unit increase in the CRP level ($p < 0.001$ for both results) (Lee et al., 2021). In addition, although no dose adjustment is considered necessary for elderly patients in the voriconazole manual, it has been shown that elderly patients (age ≥ 65 years) have median voriconazole trough concentrations that are 80%–90% higher than those of younger patients after intravenous or oral voriconazole administration (Wang et al., 2014). This may be due to the fact that liver injury occurs in elderly patients and Cytochrome P450 levels decline after age 70 and result in an approximately 30% decrease in drug clearance (Stahl et al., 2018; Abdul-Aziz et al., 2020).

4.2 Target trough concentration range

Voriconazole demonstrates nonlinear saturation pharmacokinetics, resulting in unpredictable change in drug exposure (Abdul-Aziz et al., 2020; Gómez-López, 2020). AUC/MIC is the most predictive pharmacologic parameter, which >25 is closely related to clinical efficacy and patient survival against invasive fungal disease. The relationship between AUC and trough concentration of voriconazole has been demonstrated, and trough concentration/MIC can be used clinically in place of AUC/MIC (Troke et al., 2011; Carmo et al., 2023). Therefore, a defined range of target trough concentrations is of great importance for the clinical application of voriconazole therapy. The evidence for the target concentration ranges for each specific study is described above. In addition, there is evidence that the proportion of drug-resistant fungi has increased in recent years. It is hypothesized that the widespread use of antifungal drugs, the prolonged use of suboptimal concentrations, and the use of fungicides in agriculture have led to the development of genetic mutations that make fungi resistant to the drugs. The fungi most commonly associated with antifungal resistance are *Candida*, particularly non-albicans *Candida* and Aspergillus (Kolwijck et al., 2016; Huygens et al., 2023). And it has been shown that the MIC of drugs such as voriconazole has increased due to increased resistance to azoles, which can also have an impact on the target concentration range of voriconazole (Snelders et al., 2015; Pérez-Cantero et al., 2020). Therefore, this suggests that the proposed new target concentration range for voriconazole is meaningful.

There are also studies suggesting different target concentration ranges depending on the type of disease or population. For patients with Aspergillus infections, voriconazole trough concentration should be ≥ 2.0 mg/L. One study compared 107 first samples and 151 subsequent samples from 107 patients. Approximately one-third of the samples had voriconazole trough concentrations that deviated from the target concentration range and were mostly subtherapeutic. After predictive modeling, it was found that voriconazole used for the treatment of invasive aspergillosis had a higher probability of trough concentration >1.0 mg/L in subsequent samples than in first samples ($p < 0.05$) (Guinea et al., 2016). Another study tested four clinical wild-type and non-wild-type Aspergillus fumigatus isolates in an *in vivo* pharmacokinetic/pharmacodynamic model with voriconazole Clinical and Laboratory Standards Institute (CLSI) MICs ranging from 0.125 to 2.00 mg/L. By correlating trough levels with MICs, the study estimated that the highest MIC of an A. fumigatus isolate that may be treated successfully attaining the PK/PD target of EC_{50} and avoiding toxic serum trough levels of >5.5 mg/L albeit in a small proportion (<10%) of patients was 2, 4 and 1.5 mg/L for the CLSI, EUCAST and MTS methodologies, respectively. Moreover, considering that >90% of A. fumigatus isolates have CLSI MICs of ≤1 mg/L, the trough concentration of 2 mg/L will be required for PK/PD target attainment (Siopi et al., 2014). In addition, a target trough concentration ≥0.5 mg/L may be applicable for prophylaxis. Data on file at the United States Food and Drug Administration show that success rate in patients with fungal infections, whose mean voriconazole plasma levels were <0.5 g/mL, was 46% compared to 56% with mean plasma levels >0.5 g/mL (Trifilio et al., 2007).

4.3 Dosage adjustment

Four dose-adjustment-related studies (Perreault et al., 2019; Zhou et al., 2020; Zembles et al., 2023; Park et al., 2012) were included in this paper. Voriconazole dose adjustments guided by therapeutic drug monitoring are available in the British, Canadian, Chinese and Australian guidelines (Ashbee et al., 2014; Laverdiere et al., 2014; Chen et al., 2018; Chau et al., 2021). However, none of the four guidelines mentioned whether it was suitable for adults or pediatrics, and the British guideline did not mention the strength of evidence for the dose-adjustment program. The Canadian guideline stated that the dose-adjustment program was weak recommendation and low level of evidence and the Chinese guideline stated that the dose-adjustment program was conditional recommendation, very low quality of evidence. A dose-adjustment program was also suggested in the Australian guideline, but as the program was modified from the 2019 study by John et al. (2019), it was not included in the study to avoid duplication. Of the 4 studies other than guidelines, 3 studies explored voriconazole dose adjustment programs in adults, 1 study explored voriconazole dose adjustment programs in children.

Dose adjustment programs for adults were mentioned in 3 studies. WanBeom Park et al. conducted a randomized, evaluator-blinded, controlled, single-center study. The study was computerized and 108 patients were randomly assigned to either the TDM group (55 patients) or the non-TDM group (53 patients). The

TDM group began blood collection on day 4 after voriconazole initiation and, based on the TDM results, adjusted the voriconazole dose according to the given dose adjustment program. dose to bring the trough concentration in line with the target concentration range. The non-TDM group maintained the standard dose of voriconazole. Ultimately, 27 patients in the TDM group had trough concentrations outside the target concentration range, six patients were not given dose adjustments due to discontinuation or death, and 21 patients received dose adjustments, of which 15 reached the target concentration range. The study still has limitations. First, the patients were only from a general hospital in Seoul, Korea, which was a single-center study, and the patients were all of Korean ethnicity. CYP2C19 test results showed that 43% of the patients were NM, 43% were IM, and 14% were PM, with a high percentage of poor metabolizers, which led to high levels of voriconazole concentrations in the study. Also, caution is needed when extrapolating this dose-adjustment program to other ethnic groups or pediatric populations whose pharmacokinetics different from those of adult patients. Second, the use of actual weight-based dosing in the study rather than fixed or ideal weight-based dosing may also have contributed to the high voriconazole levels. Third, the sample size was too small and larger sample sizes are still needed to determine the feasibility of the program (Park et al., 2012). Sarah perreault et al. conducted a prospective study with the primary objective of evaluating a voriconazole dose adjustment program. The study included 128 patients taking oral voriconazole for prophylaxis or treatment, of which 78% were Caucasian, 12% were Hispanic, 7% were black, 1% were Asian, and 2% were other populations. Of these 128 patients, 40% were overweight (BMI ≥ 25–29.99 kg/m^2), 21% were obese (BMI ≥ 30 kg/m^2), and 3.9% were morbidly obese (BMI ≥ 40 kg/m^2). Dose adjustment was performed in these 128 patients, and 80% were able to achieve the target concentration range at the second dose adjustment. A subgroup analysis of patient-specific characteristics was also performed to obtain a higher percentage of patients >30 years old and BMI > 25 kg/m^2 who initially reached the target concentration range, while age ≤30 years old and BMI ≤ 25 kg/m^2 were mostly at subtherapeutic levels. The study still has limitations. First, the study was a single-center prospective study with a homogeneous patient population, most of whom were Caucasian and only one Asian, so extrapolation of the dose-adjustment program to other ethnic populations and pediatric populations needs to be done with caution. Second, only 32.8% of patients had a normal BMI, 2.3% had a BMI < 18.5 kg/m^2, and 64.9% had a BMI ≥ 25 kg/m^2, which is a disproportionately large number of patients with abnormal body weights who were administered a fixed dose. Finally, the study did not test the genotype of the patients and voriconazole was used for prophylaxis rather than treatment in 94.8% of patients (Perreault et al., 2019). A single-center retrospective study was also conducted by Pejun Yvonne Zhou et al. Seventy patients were included in the study, 55 of whom were Chinese, 5 Malays, 6 Indians, and 4 from other Asian ethnic groups. And 25 of the patients had probable or confirmed Aspergillus infection and 9 had probable or confirmed *Candida* infection. The study recommended dose adjustments based on the patients' voriconazole trough concentration and obtained the effect on subsequent trough concentrations. In this study, only 45.7% of the patients achieved the target concentration range without dose adjustment. For patients with trough concentrations <0.5 mg/L, reloading voriconazole at a dose of 1.5 times the new maintenance dose for 1 day, followed by 75% dose increase for the maintenance dose (n = 1), which increased the level by > 10 times (absolute increment is unknown as 0.5 mg/L was the upper limit of assay detection). For patients with trough concentrations at 1.0~1.9 mg/L, increasing the dose by 25~33% (n = 6) and increase the dose by 67%(n = 1), which increased level by 70~130% and increase level by 10%. For patients with trough concentrations at 5.5~7.5 mg/L, reduction the dose by 13% (n = 1) and reduction the dose by 33% (n = 3), which reduction level by 50% and reduction level by 80%. For patients with trough concentrations >7.5 mg/L, held off one dose or until neurological symptoms were resolved, followed by 33% reduction in dose (n = 6),which reduction level by >33% absolute reduction is unknown as 7.5 mg/L was the upper limit of assay detection. There are several limitations to the study. First, the patients were all from Southeast Asian populations, 78.6% were Chinese, and only the adult population was included, so extrapolation of this dose adjustment program to other ethnic populations and pediatric populations still requires further study. Second, the study did not perform CYP2C19 genotype testing, so the effect of genetic polymorphisms on voriconazole trough concentration could not be determined. Finally, the sample size was too small, which resulted in the inability to elucidate the inhibitory or inducing effects of the various drugs and corresponding doses on CYP enzymes, and therefore further studies are still needed to recommend a voriconazole dose adjustment program (Zhou et al., 2020).

The incidence of invasive infections in children, although rare, is increasing with the rise of high-risk patients, including preterm infants, pediatric patients treated for hematologic malignancies, or allogeneic hematopoietic stem cell transplant recipients (Arrieta et al., 2023). In January 2019, the FDA expanded the indication for voriconazole to include children >2 years of age. Voriconazole pharmacokinetics is different and highly variable in pediatric patients compared to adults, and dosing is difficult, while oral bioavailability is lower (45%). Also, a dose-dependent pharmacokinetic profile of voriconazole was observed in the pediatric population, with a linear pharmacokinetic profile at voriconazole doses of 3~4 mg/kg q12 h and a non-linear pharmacokinetic profile at 7~8 mg/kg q12 h. Although the recommended dosage for children is given in the instructions, it has been shown that only 50% of pediatric patients achieve the target concentration at the first steady-state measurement and that children require a larger weight-based dose of voriconazole than adults to achieve the target concentration range, so pediatricians must often extrapolate voriconazole dosages for children from adult data (Zembles et al., 2023). In conclusion, it is challenging to optimize daily dosing to achieve the therapeutic range in pediatric patients (Arrieta et al., 2023; Resztak et al., 2021). A single-center retrospective study was conducted by Tracy N. Zembles et al. The study included 59 pediatric patients with a median age of 10.4 (3.7–14.7) years old. 42 patients had at least 1 measurement of steady-state trough concentration, 21 of whom were ≥12 years old and 21 of whom were <12 years old. Of these 42 patients, 13 patients (31%) had trough concentrations in the target concentration range at the first measurement, and after dose adjustment, 34 (81%) had trough concentrations in the target concentration range. The study included 7 years of longitudinal

data collection, but shortcomings remain. First, the sample size was small. Patients were expected to be divided into <2 years old, 2–12 years old, and ≥12 years old subgroups, but because of the small number of patients <2 years old, they were divided into only two groups, <12 years old and ≥12 years old. Second, only 21 patients received a loading dose, which may have led to premature timing of voriconazole TDM in some patients who did not achieve steady-state blood levels. Finally, the study applied both intravenous and enteral administration, which may have resulted in lower voriconazole concentrations (Zembles et al., 2023). In conclusion, all current voriconazole dose-adjustment programs guided by TDM have significant limitations and still require further study and refinement.

4.4 Timing of repeat therapy drug monitoring

TDM should be repeated if the dose or route of administration of voriconazole is changed or if interacting drugs are introduced or discontinued, but the exact timing remains to be determined.

Purkins L et al. conducted 2 studies, one of which was a randomized, placebo-controlled, parallel-group, double-blind study of intravenous escalation and intravenous-to-oral switch study. The study divided 42 patients into 2 cohorts; 28 subjects were enrolled in Cohort 1 (14 on voriconazole, 14 on placebo) and 14 subjects were enrolled in Cohort 2 (7 on voriconazole, 7 on placebo). Patients in cohort 1 were treated with voriconazole 6 mg/kg q12 h iv for 24 h, followed by 3 mg/kg q12h, and then changed to an oral program of 200 mg q12 h po on days 8~14. After 7 days of elution, switch to a higher maintenance dose (5 mg/kg q12 h iv, then change to an oral program 400 mg q12 h) Cohort 2 used a program of 4 mg/kg q12 h iv, followed by a switch to an oral program of 300 mg q12 h po. The results showed that after switching from intravenous to an oral dosing program, the majority of subjects reached a steady state on day 4, with the mean lowest trough concentration remaining above the clinically important MIC (Purkins et al., 2002). Another study is a single-blind, multiple-dose, placebo-controlled, parallel-group, dose-finding study. The study divided 64 patients into groups of 8 subjects each receiving voriconazole doses of 2 mg/kg q12 h, 4 mg/kg q12 h, 2 mg/kg t.i.d or 3 mg/kg q12 h. Eleven subjects received 1.5 mg/kg t.i.d, and 21 patients received placebo. The study demonstrated by statistical analysis of peak concentrations and area under the plasma concentration-time curve (AUCτ) from just before dosing to the end of the dosing interval, as well as visual inspection of trough concentrations, that steady state levels were reached on the third or fifth day of multiple dosing (Purkins et al., 2003). However, the former study included only 41 patients and the latter study included only 56 patients. Neither of these two papers were up-to-date. In the future, researchers should pay more attention to the timing of repeat TDM with voriconazole and study it further.

4.5 Dose-prediction software

MIPD is a mathematical modeling and simulation technology that integrates information about the patient, drug, and disease to provide a basis for precise patient dosing. The MIPD often uses nonlinear mixed-effects (NLME) models to predict and optimize treatment outcomes based on patient characteristics and therapeutic drug monitoring data. MIPD is indicated for drugs with narrow therapeutic ranges and complex pharmacokinetics (PK), such as voriconazole (Kluwe et al., 2023). Commonly used models include, but are not limited to, population pharmacokinetic (Pop-PK) models, pharmacokinetic/pharmacodynamic (PK/PD) models, population pharmacokinetic/pharmacodynamic models, physiologically based pharmacokinetic (PBRK) models and artificial intelligence (AI) models, and different modeling and analysis techniques have different characteristics. Voriconazole dose prediction procedures are mostly based on Pop-PK models. Such models should at a minimum contain the most relevant physiological and biological attributes determining the drug's disposition and enough attributes to explain a substantial portion of observed variability. A pop-PK model can be validated internally, externally, or prospectively to diagnose misspecifications (Darwich et al., 2021; Wicha et al., 2021).

Bestdose was created with data from 64 adults (20 healthy volunteers and 43 patients) and evaluated with pharmacokinetic data from 10 hematopoietic stem cell transplant (HSCT) patients. Validation of the performance of the voriconazole controller showed close agreement between the controller-calculated voriconazole dose and the actual dose administered in most cases, but in two patients the controller predicted significantly more medication than was actually administered. This program can be used to further optimize voriconazole for the treatment of critically immunocompromised patients, but still has many drawbacks for routine application (Hope et al., 2013). The procedure needs to be evaluated for accuracy in prospective clinical trials, and the applicability of oral voriconazole to the procedure needs to be tested, as well as other existential issues. In a prospective clinical study of Bestdose, 19 patients (18 Caucasian, 1 other) were included for evaluation of the procedure, but only 14 could be analyzed. 12 of the 14 patients (85.7%; 95% CI, 57.2%–98.2%) had a trough concentration of 1.0~3.0 mg/L at 120 h after the start of treatment, which is above the 33% of the *a priori* expected proportion (Hope et al., 2019). This prospective study has several limitations. The sample size of the study was relatively small, containing only patients in the early stages of HSCT rather than those with critical disease leading to potentially more variable and extreme pharmacokinetics, and the duration of the study was relatively short, leaving many issues unexposed. Cartrides, a nonparametric overall model containing 141 patients (85 children and 56 adults) and validated with 33 pediatric patients aged 8 months to 17 years old, showed that the advantages of the procedure are that patients do not have to be at steady state, sample sampling times do not have to be precisely timed, AUCs can be estimated even for a single concentration, and the procedure can be generalized to any drug with a nonparametric pharmacokinetic model, but prospective studies are still needed (Neely et al., 2015). Kanika Chaudnri et al. included 90 patients to evaluate DoseMeRx and showed that dose prediction software enhances efficacy, is used to guide clinical decision-making, and can be generalized to other populations, although the model was developed in a Chinese population. However, the software did not monitor clinical outcomes and did not incorporate CYP2C19 genotypes (Chaudhri et al., 2020).

The study summarized the initial treatment program, target concentration range, and dose adjustment program for voriconazole and identified the following shortcomings in the study. 1) the included studies did not have the same target concentration range, making it difficult to compare studies with the same factors; 2) some of the studies used modeling methods that were not implemented in the clinic, resulting in uncertainty about the clinical efficacy of the programs; and 3) the inclusion of fewer literatures related to dosage adjustments, which made it difficult to draw accurate conclusions.

5 Conclusion

There has been a great deal of research and partial consensus on individualized dosing of voriconazole, but there are still some critical issues that have not been resolved. Recently updated guidelines for TDM of voriconazole or antifungals focus on key issues that need to be addressed. The 2021 edition of the Australian guideline focuses on 9 issues regarding TDM of antifungals. The 2022 edition of the Japanese guideline focuses on 5 issues regarding TDM of voriconazole. There is still no clear and uniform program for dose adjustment of voriconazole guided by TDM. Based on the results of the study, it is recommended that all patients on voriconazole should have their initial dosing program selected on the basis of their hepatic function or other influencing factors (e.g., pathogens, infections, C-reactive protein, albumin, or obesity), and that therapeutic concentrations should be achieved through appropriate dosage adjustments guided by therapeutic drug monitoring. Routine genetic testing for voriconazole application in patients is not considered necessary at this time. In terms of dose adjustment, in adult patients, if the voriconazole trough concentration is subtherapeutic, the voriconazole dose should be increased by 25%~50%. If the voriconazole trough concentration is supratherapeutic,the voriconazole dose should be decreased by 25% ~50%. If a drug-related adverse event occurs, hold 1 dose, decrease subsequent dose by 50%.In pediatric patients, if the voriconazole trough concentration is subtherapeutic, increase the voriconazole dose by 1~2 mg/kg or increase the voriconazole dose by 50%. If the voriconazole trough concentration is supratherapeutic, reduce the voriconazole dose by 1 mg/kg or hold 1 dose, and decrease the subsequent dose by 25%. Most of the previous clinical studies have a low level of evidence-based medicine evidence, and more prospective, multicenter clinical studies are needed to promote individualized dosing of voriconazole.

Author contributions

LJ: Formal Analysis, Investigation, Writing–original draft, Writing–review & editing. ZL: Conceptualization, Funding acquisition, Methodology, Project administration, Writing–review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by Quanzhou City Science & Technology Program of China, High-level Talent Innovation Project of Quanzhou (2021C036R).

Acknowledgments

This article was completed under the guidance of my tutor ZL. I would like to express my heartfelt thanks to him for his guidance and help!

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abdul-Aziz, M. H., Alffenaar, J. C., Bassetti, M., Bracht, H., Dimopoulos, G., Marriott, D., et al. (2020). Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. *Intensive care Med.* 46 (6), 1127–1153. doi:10.1007/s00134-020-06050-1

Aitken, A. E., Richardson, T. A., and Morgan, E. T. (2006). Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* 46, 123–149. doi:10.1146/annurev.pharmtox.46.120604.141059

Arrieta, A. C., Lee, A., and Tran, M. T. (2023). Invasive Mold infections in children: Navigating Troubled Waters with a Broken Compass. *Infect. Dis. Ther.* 12 (6), 1465–1485. doi:10.1007/s40121-023-00819-9

Ashbee, H. R., Barnes, R. A., Johnson, E. M., Richardson, M. D., Gorton, R., and Hope, W. W. (2014). Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J. Antimicrob. Chemother.* 69 (5), 1162–1176. doi:10.1093/jac/dkt508

Carmo, A., Rocha, M., Pereirinha, P., Tomé, R., and Costa, E. (2023). Antifungals: from pharmacokinetics to clinical Practice. *Antibiot. Basel, Switz.* 12 (5), 884. doi:10.3390/antibiotics12050884

Chau, M. M., Daveson, K., Alffenaar, J. C., Gwee, A., Ho, S. A., Marriott, D. J. E., et al. (2021). Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy and haemopoietic stem cell transplant recipients, 2021. *Intern. Med. J.* 51 (Suppl. 7), 37–66. doi:10.1111/imj.15587

Chaudhri, K., Stocker, S. L., Williams, K. M., McLeay, R. C., Marriott, D. J. E., Di Tanna, G. L., et al. (2020). Voriconazole: an audit of hospital-based dosing and monitoring and evaluation of the predictive performance of a dose-prediction software package. *J. Antimicrob. Chemother.* 75 (7), 1981–1984. doi:10.1093/jac/dkaa098

Chen, K., Zhang, X., Ke, X., Du, G., Yang, K., and Zhai, S. (2018). Individualized medication of voriconazole: a Practice guideline of the Division of therapeutic drug

monitoring, Chinese pharmacological Society. *Ther. drug Monit.* 40 (6), 663–674. doi:10.1097/ftd.0000000000000561

Darwich, A. S., Polasek, T. M., Aronson, J. K., Ogungbenro, K., Wright, D. F. B., Achour, B., et al. (2021). Model-informed precision dosing: Background, Requirements, validation, implementation, and forward Trajectory of individualizing drug therapy. *Annu. Rev. Pharmacol. Toxicol.* 61, 225–245. doi:10.1146/annurev-pharmtox-033020-113257

Dean, L. (2012). "Voriconazole therapy and CYP2C19 genotype," in *Medical genetics Summaries*. Editors V. M. Pratt, S. A. Scott, M. Pirmohamed, B. Esquivel, B. L. Kattman, and A. J. Malheiro (Bethesda (MD): National Center for Biotechnology Information). (US).

Diller, E., Krekel, T., Spec, A., and Klaus, J. (2021). Evaluation of total body weight versus adjusted body weight voriconazole dosing in obese patients. *Antimicrob. agents Chemother.* 65 (7), e0246020. doi:10.1128/aac.02460-20

Dolton, M. J., and McLachlan, A. J. (2014). Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. *Int. J. Antimicrob. agents* 44 (3), 183–193. doi:10.1016/j.ijantimicag.2014.05.019

Encalada Ventura, M. A., Span, L. F., van den Heuvel, E. R., Groothuis, G. M. M., and Alffenaar, J. W. C. (2015). Influence of inflammation on voriconazole metabolism. *Antimicrob. agents Chemother.* 59 (5), 2942–2943. doi:10.1128/aac.04789-14

Gao, J., Zhang, Q., Wu, Y., Li, Y., Qi, T., Zhu, C., et al. (2018). Improving survival of acute-on-chronic liver failure patients complicated with invasive pulmonary aspergillosis. *Sci. Rep.* 8 (1), 876. doi:10.1038/s41598-018-19320-2

Ga Wells, B. S., O'Connell, D., Peterson, J., Welch, V., Losos, M., and Tugwell, P. (2013). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed August 10, 2024).

Gómez-López, A. (2020). Antifungal therapeutic drug monitoring: focus on drugs without a clear recommendation. *Clin. Microbiol. Infect. official Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* 26 (11), 1481–1487. doi:10.1016/j.cmi.2020.05.037

Grensemann, J., Pfaffendorf, C., Wicha, S. G., König, C., Roedl, K., Jarczak, D., et al. (2021). Voriconazole pharmacokinetics are not altered in critically ill patients with acute-on-chronic liver failure and Continuous renal Replacement therapy: an observational study. *Microorganisms* 9 (10), 2087. doi:10.3390/microorganisms9102087

Guinea, J., Escribano, P., Marcos-Zambrano, L. J., Peláez, T., Kestler, M., Muñoz, P., et al. (2016). Therapeutic drug monitoring of voriconazole helps to decrease the percentage of patients with off-target trough serum levels. *Med. Mycol.* 54 (4), 353–360. doi:10.1093/mmy/myv099

Hicks, J. K., Quilitz, R. E., Komrokji, R. S., Kubal, T. E., Lancet, J. E., Pasikhova, Y., et al. (2020). Prospective CYP2C19-guided voriconazole prophylaxis in patients with Neutropenic acute myeloid leukemia reduces the incidence of subtherapeutic antifungal plasma concentrations. *Clin. Pharmacol. Ther.* 107 (3), 563–570. doi:10.1002/cpt.1641

Hope, W., Johnstone, G., Cicconi, S., Felton, T., Goodwin, J., Whalley, S., et al. (2019). Software for dosage individualization of voriconazole: a prospective clinical study. *Antimicrob. agents Chemother.* 63 (4), e02353. doi:10.1128/aac.02353-18

Hope, W. W., Vanguilder, M., Donnelly, J. P., Blijlevens, N. M. A., Brüggemann, R. J. M., Jelliffe, R. W., et al. (2013). Software for dosage individualization of voriconazole for immunocompromised patients. *Antimicrob. agents Chemother.* 57 (4), 1888–1894. doi:10.1128/aac.02025-12

Huygens, S., Dunbar, A., Buil, J. B., Klaassen, C. H. W., Verweij, P. E., van Dijk, K., et al. (2023). Clinical impact of Polymerase Chain reaction-based Aspergillus and azole resistance detection in invasive aspergillosis: a prospective multicenter study. *Clin. Infect. Dis. official Publ. Infect. Dis. Soc. Am.* 77 (1), 38–45. doi:10.1093/cid/ciad141

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., et al. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control. Clin. trials* 17 (1), 1–12. doi:10.1016/0197-2456(95)00134-4

Jiang, Z., Wei, Y., Huang, W., Li, B., Zhou, S., Liao, L., et al. (2022). Population pharmacokinetics of voriconazole and initial dosage optimization in patients with talaromycosis. *Front. Pharmacol.* 13, 982981. doi:10.3389/fphar.2022.982981

Jin, H., Wang, T., Falcione, B. A., Olsen, K. M., Chen, K., Tang, H., et al. (2016). Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* 71 (7), 1772–1785. doi:10.1093/jac/dkw045

John, J., Loo, A., Mazur, S., and Walsh, T. J. (2019). Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. *Expert Opin. drug metabolism & Toxicol.* 15 (11), 881–895. doi:10.1080/17425255.2019.1671971

Kluwe, F., Michelet, R., Huisinga, W., Zeitlinger, M., Mikus, G., and Kloft, C. (2023). Towards model-informed precision dosing of voriconazole: challenging published voriconazole nonlinear mixed-effects models with Real-World clinical data. *Clin. Pharmacokinet.* 62 (10), 1461–1477. doi:10.1007/s40262-023-01274-y

Kolwijck, E., van der Hoeven, H., de Sévaux, R. G., ten Oever, J., Rijstenberg, L. L., van der Lee, H. A. L., et al. (2016). Voriconazole-susceptible and voriconazole-resistant Aspergillus fumigatus Coinfection. *Am. J. Respir. Crit. care Med.* 193 (8), 927–929. doi:10.1164/rccm.201510-2104LE

Laverdiere, M., Bow, E. J., Rotstein, C., Autmizguine, J., Broady, R., Garber, G., et al. (2014). Therapeutic drug monitoring for triazoles: a needs assessment review and recommendations from a Canadian perspective. *Can. J. Infect. Dis. & Med. Microbiol. = J. Can. des maladies Infect. de Microbiol. medicale* 25 (6), 327–343. doi:10.1155/2014/340586

Lee, Y., Puumala, E., Robbins, N., and Cowen, L. E. (2021). Antifungal drug resistance: Molecular mechanisms in Candida albicans and beyond. *Chem. Rev.* 121 (6), 3390–3411. doi:10.1021/acs.chemrev.0c00199

Lempers, V. J., Meuwese, E., Mavinkurve-Groothuis, A. M., Henriet, S., van der Sluis, I. M., Hanff, L. M., et al. (2019). Impact of dose adaptations following voriconazole therapeutic drug monitoring in pediatric patients. *Med. Mycol.* 57 (8), 937–943. doi:10.1093/mmy/myz006

Li, S., Wu, S., Gong, W., Cao, P., Chen, X., Liu, W., et al. (2021). Application of population pharmacokinetic analysis to characterize CYP2C19 Mediated metabolic mechanism of voriconazole and support dose optimization. *Front. Pharmacol.* 12, 730826. doi:10.3389/fphar.2021.730826

Li, X., Frechen, S., Moj, D., Lehr, T., Taubert, M., Hsin, C. H., et al. (2020). A physiologically based pharmacokinetic model of voriconazole integrating time-dependent inhibition of CYP3A4, genetic polymorphisms of CYP2C19 and predictions of drug-drug interactions. *Clin. Pharmacokinet.* 59 (6), 781–808. doi:10.1007/s40262-019-00856-z

Lin, X. B., Li, Z. W., Yan, M., Zhang, B. K., Liang, W., Wang, F., et al. (2018). Population pharmacokinetics of voriconazole and CYP2C19 polymorphisms for optimizing dosing regimens in renal transplant recipients. *Br. J. Clin. Pharmacol.* 84 (7), 1587–1597. doi:10.1111/bcp.13595

Lin, X. B., Lui, K. Y., Guo, P. H., Liu, X. M., Liang, T., Hu, X. G., et al. (2022). Population pharmacokinetic model-guided optimization of intravenous voriconazole dosing regimens in critically ill patients with liver dysfunction. *Pharmacotherapy* 42 (1), 23–33. doi:10.1002/phar.2634

Luong, M. L., Al-Dabbagh, M., Groll, A. H., Racil, Z., Nannya, Y., Mitsani, D., et al. (2016). Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J. Antimicrob. Chemother.* 71 (7), 1786–1799. doi:10.1093/jac/dkw099

McCreary, E. K., Davis, M. R., Narayanan, N., Andes, D. R., Cattaneo, D., Christian, R., et al. (2023). Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of infectious diseases Pharmacists: endorsed by the Mycoses study group Education and research Consortium. *Pharmacotherapy* 43 (10), 1043–1050. doi:10.1002/phar.2850

Morgan, E. T. (2001). Regulation of cytochrome p450 by inflammatory mediators: why and how? *Drug metabolism Dispos. Biol. fate Chem.* 29 (3), 207–212.

Morgan, E. T., Goralski, K. B., Piquette-Miller, M., Renton, K. W., Robertson, G. R., Chaluvadi, M. R., et al. (2008). Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. *Drug metabolism Dispos. Biol. fate Chem.* 36 (2), 205–216. doi:10.1124/dmd.107.018747

Neely, M., Margol, A., Fu, X., van Guilder, M., Bayard, D., Schumitzky, A., et al. (2015). Achieving target voriconazole concentrations more accurately in children and adolescents. *Antimicrob. agents Chemother.* 59 (6), 3090–3097. doi:10.1128/aac.00032-15

Niu Wanjie, J. Z., Yu, E., Wu, S., Jia, S., and Qin, W. (2018). Quality assessment of research papers on population pharmacokinetics in China. *Chin. J. Hosp. Pharm.* 38 (13), 1345–1349. doi:10.13286/j.cnki.chinhosppharmacyj.2018.13.01

Park, W. B., Kim, N. H., Kim, K. H., Lee, S. H., Nam, W. S., Yoon, S. H., et al. (2012). The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin. Infect. Dis. official Publ. Infect. Dis. Soc. Am.* 55 (8), 1080–1087. doi:10.1093/cid/cis599

Pascual, A., Csajka, C., Buclin, T., Bolay, S., Bille, J., Calandra, T., et al. (2012). Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin. Infect. Dis. official Publ. Infect. Dis. Soc. Am.* 55 (3), 381–390. doi:10.1093/cid/cis437

Pérez-Cantero, A., López-Fernández, L., Guarro, J., and Capilla, J. (2020). Azole resistance mechanisms in Aspergillus: update and recent advances. *Int. J. Antimicrob. agents* 55 (1), 105807. doi:10.1016/j.ijantimicag.2019.09.011

Perez-Pitarch, A., Guglieri-Lopez, B., Ferriols-Lisart, R., Pérez, A., Ezquer-Garín, C., Hernández-Boluda, J. C., et al. (2019). Pharmacokinetic/pharmacodynamic analysis of voriconazole against Candida spp. and Aspergillus spp. in allogeneic stem cell transplant recipients. *Ther. drug Monit.* 41 (6), 740–747. doi:10.1097/ftd.0000000000000657

Perreault, S., McManus, D., Anderson, A., Lin, T., Ruggero, M., and Topal, J. E. (2019). Evaluating a voriconazole dose modification guideline to optimize dosing in patients with hematologic malignancies. *J. Oncol. Pharm. Pract. official Publ. Int. Soc. Oncol. Pharm. Pract.* 25 (6), 1305–1311. doi:10.1177/1078155218786028

Purkins, L., Wood, N., Ghahramani, P., Greenhalgh, K., Allen, M. J., and Kleinermans, D. (2002). Pharmacokinetics and safety of voriconazole following intravenous-to oral-dose escalation regimens. *Antimicrob. agents Chemother.* 46 (8), 2546–2553. doi:10.1128/aac.46.8.2546-2553.2002

Purkins, L., Wood, N., Greenhalgh, K., Allen, M. J., and Oliver, S. D. (2003). Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. *Br. J. Clin. Pharmacol.* 56 (Suppl. 1), 10–16. doi:10.1046/j.1365-2125.2003.01993.x

Resztak, M., Sobiak, J., and Czyrski, A. (2021). Recent advances in therapeutic drug monitoring of voriconazole, Mycophenolic Acid, and Vancomycin: a literature review of pediatric studies. *Pharmaceutics* 13 (12), 1991. doi:10.3390/pharmaceutics13121991

Siopi, M., Mavridou, E., Mouton, J. W., Verweij, P. E., Zerva, L., and Meletiadis, J. (2014). Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and Aspergillus fumigatus in an *in vitro* pharmacokinetic/pharmacodynamic model. *J. Antimicrob. Chemother.* 69 (6), 1611–1619. doi:10.1093/jac/dku023

Slim, K., Nini, E., Forestier, D., Kwiatkowski, F., Panis, Y., and Chipponi, J. (2003). Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J. Surg.* 73 (9), 712–716. doi:10.1046/j.1445-2197.2003.02748.x

Snelders, E., Camps, S. M., Karawajczyk, A., Rijs, A. J. M. M., Zoll, J., Verweij, P. E., et al. (2015). Genotype-phenotype complexity of the TR46/Y121F/T289A cyp51A azole resistance mechanism in Aspergillus fumigatus. *Fungal Genet. Biol. FG & B* 82, 129–135. doi:10.1016/j.fgb.2015.06.001

Stahl, E. C., Haschak, M. J., Popovic, B., and Brown, B. N. (2018). Macrophages in the aging liver and age-related liver disease. *Front. Immunol.* 9, 2795. doi:10.3389/fimmu.2018.02795

Takesue, Y., Hanai, Y., Oda, K., Hamada, Y., Ueda, T., Mayumi, T., et al. (2022). Clinical Practice guideline for the therapeutic drug monitoring of voriconazole in non-Asian and Asian adult patients: consensus review by the Japanese Society of Chemotherapy and the Japanese Society of therapeutic drug monitoring. *Clin. Ther.* 44 (12), 1604–1623. doi:10.1016/j.clinthera.2022.10.005

Tang, D., Yan, M., Song, B. L., Zhao, Y. C., Xiao, Y. W., Wang, F., et al. (2021). Population pharmacokinetics, safety and dosing optimization of voriconazole in patients with liver dysfunction: a prospective observational study. *Br. J. Clin. Pharmacol.* 87 (4), 1890–1902. doi:10.1111/bcp.14578

Trifilio, S., Singhal, S., Williams, S., Frankfurt, O., Gordon, L., Evens, A., et al. (2007). Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone marrow Transplant.* 40 (5), 451–456. doi:10.1038/sj.bmt.1705754

Troke, P. F., Hockey, H. P., and Hope, W. W. (2011). Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob. agents Chemother.* 55 (10), 4782–4788. doi:10.1128/aac.01083-10

Wang, J., Shen, Y., Wu, Z., and Ge, W. (2024). Population pharmacokinetics of voriconazole and dose optimization in elderly Chinese patients. *J. Clin. Pharmacol.* 64 (2), 253–263. doi:10.1002/jcph.2357

Wang, T., Chen, S., Sun, J., Cai, J., Cheng, X., Dong, H., et al. (2014). Identification of factors influencing the pharmacokinetics of voriconazole and the optimization of dosage regimens based on Monte Carlo simulation in patients with invasive fungal infections. *J. Antimicrob. Chemother.* 69 (2), 463–470. doi:10.1093/jac/dkt369

Wang, T., Yan, M., Tang, D., Dong, Y., Zhu, L., Du, Q., et al. (2021). Using Child-Pugh Class to optimize voriconazole dosage regimens and improve safety in patients with liver cirrhosis: Insights from a population pharmacokinetic model-based analysis. *Pharmacotherapy* 41 (2), 172–183. doi:10.1002/phar.2474

Wicha, S. G., Märtson, A. G., Nielsen, E. I., Koch, B. C. P., Friberg, L. E., Alffenaar, J. W., et al. (2021). From therapeutic drug monitoring to model-informed precision dosing for Antibiotics. *Clin. Pharmacol. Ther.* 109 (4), 928–941. doi:10.1002/cpt.2202

Yamada, T., Imai, S., Koshizuka, Y., Tazawa, Y., Kagami, K., Tomiyama, N., et al. (2018). Necessity for a significant maintenance dosage reduction of voriconazole in patients with severe liver cirrhosis (Child-Pugh Class C). *Biol. & Pharm. Bull.* 41 (7), 1112–1118. doi:10.1248/bpb.b18-00164

Yi, W. M., Schoeppler, K. E., Jaeger, J., Mueller, S. W., MacLaren, R., Fish, D. N., et al. (2017). Voriconazole and posaconazole therapeutic drug monitoring: a retrospective study. *Ann. Clin. Microbiol. Antimicrob.* 16 (1), 60. doi:10.1186/s12941-017-0235-8

Zembles, T. N., Dasgupta, M., Kenkel, T. J., Lehrer, B., Simpson, P., Havens, P. L., et al. (2023). Higher weight-based doses are required to achieve and Maintain therapeutic voriconazole serum trough concentrations in children. *J. Pediatr. Pharmacol. Ther. JPPT official J. PPAG* 28 (3), 247–254. doi:10.5863/1551-6776-28.3.247

Zhang, Y., Hou, K., Liu, F., Luo, X., He, S., Hu, L., et al. (2021). The influence of CYP2C19 polymorphisms on voriconazole trough concentrations: systematic review and meta-analysis. *Mycoses* 64 (8), 860–873. doi:10.1111/myc.13293

Zhang, Y., Wu, R., Liu, F., Wang, Y., Zhang, J., Ji, C., et al. (2023). Factors influencing blood concentration of voriconazole and therapeutic drug monitoring in patients with Child–Pugh Class C cirrhosis. *J. Clin. Pharm. Ther.*, 2023, 1, 10. doi:10.1155/2023/4240869

Zhao, Y., Hou, J., Xiao, Y., Wang, F., Zhang, B., Zhang, M., et al. (2021). Predictors of voriconazole trough concentrations in patients with Child-Pugh Class C cirrhosis: a prospective study. *Antibiot. Basel, Switz.* 10 (9), 1130. doi:10.3390/antibiotics10091130

Zhao, Y. C., Zou, Y., Hou, J. J., Xiao, C. L., Zhang, B. K., Li, J. K., et al. (2021). Factors affecting voriconazole trough concentration and optimal maintenance voriconazole dose in Chinese children. *Antibiot. Basel, Switz.* 10 (12), 1542. doi:10.3390/antibiotics10121542

Zhou, P. Y., Lim, T. P., Tang, S. L. S., Liew, Y., Chua, S. G. N., Lim, L. L. C., et al. (2020). The utility of voriconazole therapeutic drug monitoring in a multi-racial cohort in Southeast Asia. *J. Glob. Antimicrob. Resist.* 21, 427–433. doi:10.1016/j.jgar.2019.12.004

Zubiaur, P., Kneller, L. A., Ochoa, D., Mejía, G., Saiz-Rodríguez, M., Borobia, A. M., et al. (2021). Evaluation of voriconazole CYP2C19 phenotype-guided dose adjustments by physiologically based pharmacokinetic modeling. *Clin. Pharmacokinet.* 60 (2), 261–270. doi:10.1007/s40262-020-00941-8

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 11 December 2024
DOI 10.3389/fphar.2024.1502047

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Giovanni Luca Romano,
Kore University of Enna, Italy
Pedro Eduardo Nascimento Silva Vasconcelos,
Universidade Federal de São Paulo, Brazil

*CORRESPONDENCE
Xusheng Cao,
13520023405@163.com

RECEIVED 26 September 2024
ACCEPTED 26 November 2024
PUBLISHED 11 December 2024

CITATION
Liu C, Wang X and Cao X (2024) Ophthalmic corticosteroids-related adverse events: the FDA adverse event reporting system (FAERS) database pharmacovigilance study.
Front. Pharmacol. 15:1502047.
doi: 10.3389/fphar.2024.1502047

Ophthalmic corticosteroids-related adverse events: the FDA adverse event reporting system (FAERS) database pharmacovigilance study

Chengzhi Liu, Xinyu Wang and Xusheng Cao*

Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Background: Corticosteroids are extensively used in ophthalmology, particularly for treating various inflammatory conditions. Despite their effectiveness, prolonged or high-dose corticosteroid use is associated with significant adverse drug reactions (ADRs), such as increased intraocular pressure, cataract formation, and secondary infections. However, there is currently no systematic study comparing the side effects of ophthalmic corticosteroids. This study aims to investigate the safety profiles of ophthalmic corticosteroids through pharmacovigilance analysis using the FDA Adverse Event Reporting System (FAERS) database.

Methods: We conducted a retrospective analysis of ADR reports related to commonly used ophthalmic corticosteroids from the FAERS database, covering the period from Q1 2004 to Q4 2023. Clinical features such as gender, age, administration route, and dosage form were also analyzed. Signal detection methods, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi-Item Gamma Poisson Shrinker (MGPS), were used to identify potential safety signals.

Results: A total of 9,854 ADRs related to ophthalmic corticosteroids were retrieved, with the most frequently reported drugs being Ozurdex (1,784 cases), Lotemax (3,239 cases), and Durezol (2,789 cases). Women accounted for a higher proportion of ADRs across most corticosteroids. ADR induction time analysis results showed that ADRs tend to occur in the early stages of drug use. The most common ophthalmic ADRs identified included eye inflammation, cataract, visual impairment, uveitis, eye pain, blurred vision, and retinal detachment. Additionally, Maxidex has been linked to endocrine disorders, while Ozurdex, Iluvien, and Triesence exhibited significant signals for product issues, likely related to their intraocular injection procedures. Notably, cataract was the most common PT among these drugs.

Conclusion: Our study reveals significant safety concerns related to using ophthalmic corticosteroids, particularly regarding adverse reactions that can impact visual function. These findings highlight the need for careful monitoring and individualized treatment plans to minimize the risk of ADRs in

patients receiving corticosteroid therapy. Future studies combining FAERS data with large-scale clinical research are needed to explore these safety concerns further.

KEYWORDS

FAERS, corticosteroids, adverse event, pharmacovigilance, signal mining, ocular diseases

1 Introduction

Corticosteroids are extensively used in ophthalmology, particularly for treating various inflammatory conditions such as uveitis, optic neuritis, thyroid-associated ophthalmopathy, and other ophthalmic inflammatory diseases (Raizman, 1996; McGhee et al., 2002). They possess powerful anti-inflammatory and immunosuppressive properties, enabling them to rapidly control inflammation, relieve symptoms, and help preserve vision (Cutolo et al., 2019). Corticosteroids are available in various dosage forms and administration methods in ophthalmology, with a specific choice depending on the type and severity of the condition (Kiernan and Mieler, 2012; Puglia et al., 2021; Romano et al., 2023). Common forms include topical eye drops, eye ointments, intraocular injections, and systemic medications such as oral or intravenous injections (Figure 1). Topical eye drops and ointments are commonly used for anterior eye diseases like keratitis and anterior uveitis, delivering medication directly to the affected area. Intraocular injections are preferred for treating posterior eye conditions such as posterior uveitis and diabetic retinopathy, providing efficient local drug concentrations. Additionally, low-solubility Corticosteroid polymer sustained-release systems are employed for long-term intraocular treatments, such as in cases of diabetic macular edema, to ensure prolonged therapeutic effects (Busch et al., 2018). Systemic Corticosteroids are reserved for severe or widespread inflammatory diseases, including optic neuritis (Fung et al., 2020; Gaballa et al., 2021).

Although Corticosteroids are crucial in treating ophthalmic diseases, long-term or high-dose use can lead to side effects such as increased intraocular pressure, cataract formation, corneal ulcers, and secondary infections (Huscher et al., 2009; Roberti et al., 2020). Therefore, ophthalmologists must carefully balance the benefits and risks, tailoring individualized treatment plans based on the specific disease, its severity, and patient conditions (Bucolo et al., 2018). The choice of Corticosteroid dosage form and application can also vary depending on the disease's severity and location and the individual patient's circumstances (Caplan et al., 2017; Boscia et al., 2024). However, no current studies provide sufficient data to compare the safety profiles of different glucocorticoid drugs, highlighting the need for further research in this area.

The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) is a public, accessible, and free database containing millions of voluntarily submitted adverse drug reactions (ADRs) reports from healthcare professionals, consumers, and manufacturers (Hoffman et al., 2014). It is an important tool for post-marketing drug safety surveillance and signal detection and is widely used in pharmacovigilance research, including ocular ADRs (Fang et al., 2019; Ma et al., 2022; Zhao et al., 2023). Signal detection from FAERS data has become a recognized and effective method to identify potential safety risks associated with medications in real-world settings. By utilizing FAERS data, researchers can identify disproportionate reporting of ADRs, helping to establish hypotheses about causal relationships between drugs and adverse events, particularly for rare or severe outcomes (Fukazawa et al., 2018; Subeesh et al., 2018).

Despite the widespread use of glucocorticoids in ophthalmology, there is limited real-world data on their associated ADRs. Therefore, this study aims to utilize the FAERS database to conduct a pharmacovigilance analysis of glucocorticoids used in ophthalmology, identifying potential ADR signals and evaluating their severity and clinical impact. The findings from this research will contribute to a better understanding of the safety profile of glucocorticoids in ophthalmic settings, offering valuable insights for clinicians in minimizing the risk of adverse outcomes while optimizing therapeutic benefits.

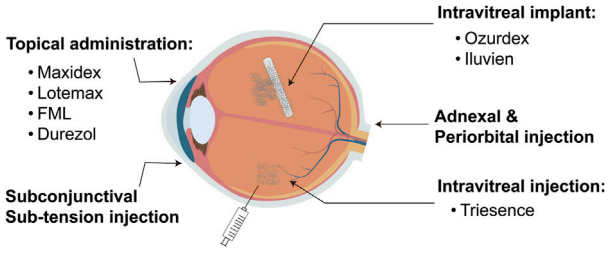


FIGURE 1
Routes of administration for ophthalmic corticosteroids.

2 Methods

2.1 Data source

This study primarily conducts a pharmacovigilance analysis of corticosteroids used in ophthalmology by mining voluntarily reported adverse reactions and medication error data from the FAERS database. The classification and standardization of ADRs in FAERS are based on the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 (Brown et al., 1999). Each report is encoded using preferred terms (PTs), which are categorized into one or more high-level terms (HLT), high-level group terms (HLGT), and system organ class (SOC) levels in MedDRA. The FAERS database is updated quarterly and consists of seven data files: Patient Demographic and Management Information (DEMO), Drug Information (DRUG), Adverse Event Codes (REAC), Patient Outcomes (OUTC), Report Sources (RPSR), Treatment Start and End Dates (THER) for the reported drugs, Drug Administration Indications (INDI), and Deleted Cases. This

structured framework allows for standardized reporting and analysis of adverse events related to corticosteroid use in ophthalmology.

2.2 Data screening and processing

This study extracted reports from the FAERS database covering the period from the first quarter of 2004 to the fourth quarter of 2023. Given the inclusion of reports for other diseases in direct drug retrieval, we conducted a more refined search using various brand names of corticosteroids commonly used in ophthalmology to minimize false positive results. These brand names included Ozurdex, Maxidex, Dexapar, Dexachlor, Pred Mild, Orchapred, Kapimox-P, Predsol, Trivaris, Triesence, Retisert, Iluvien, Lotemax, Flucon, FML, Visipred, Diflustero, and Durezol (Gaballa et al., 2021). We limited our analysis to reports in which the drug was classified as the primary suspect, using results with the role code 'PS'. Two researchers were responsible for the data procession by removing duplicates, classifying relevant adverse events through standardized MedDRA queries and PTs, and extracting clinical feature information such as gender, age, reporting region, reporter, route of administration, and dosage form from the reports (Veronin et al., 2020).

2.3 ADRs induction time analysis

The induction time of adverse reactions is defined as the interval between the date of the adverse event and the start date of drug use. Adverse reaction induction time was evaluated using quartile tests. In addition, we conducted a Weibull distribution test to assess changes in ADR incidence over time. The scale parameter (α) determines the distribution's spread, with larger values indicating a wider distribution. The shape parameter (β) affects the curve's shape; a larger β produces a left-skewed curve, while a smaller β yields a right-skewed curve. Specifically, $\beta < 1$ with a 95% confidence interval (CI) less than 1 suggests a decreasing ADR incidence (early failure curve), β close to 1 with the 95% CI including 1 indicates a constant ADR incidence (random failure curve), and $\beta > 1$ with the 95% CI not including 1 implies an increasing ADR incidence (wear-out failure curve) (Leroy et al., 2014).

2.4 Signal detection and statistical analysis

Disproportionality analysis is a key technique in pharmacovigilance studies for identifying potential safety signals (Montastruc et al., 2011). This study employed various signal detection methods, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Polynomial Gamma Poisson Shrinker (MGPS). Among them, ROR is the main method. These methods use a 2 × 2 contingency table to calculate signal strength, as illustrated in Table 1. The study enhances safety signal detection and verification from multiple perspectives by applying these algorithms. This comprehensive approach improves the accuracy of safety signal recognition, minimizes false positives through cross-validation, and enhances the detection of rare adverse events by adjusting thresholds and variances (Michel et al., 2017). Table 2 summarizes the formulas and thresholds for all signal detection methods used. Stronger signals reflect a more significant correlation between drugs and adverse events, aiding in the identification of potential safety issues. All analyses were performed using R 4.3.2 software, GraphPad 10.1.2, and Microsoft Excel for data extraction, analysis, and visualization, ensuring efficient data management and comprehensive analysis. By consulting FDALabel (https://nctrcrs.fda.gov/fdalabel/ui/search), detailed medication instructions can be obtained.

3 Results

3.1 Basic information of adverse event report

This study obtained safety signals for corticosteroids used in ophthalmology from Q1 2004 to Q4 2023 through data mining. A total of 9,854 ADR reports were retrieved from the FAERS database, including 1,784 reports for Ozurdex, 3,239 for Lotemax, 2,789 for Durezol, 822 for Maxitrol, 455 for Iluvien, 582 for FML, and 193 for Triesence. Other drugs were either not retrieved from the database, had fewer than 50 cases, and were excluded from subsequent analysis.

The demographic characteristics of ADR reports related to corticosteroids are summarized in Tables 3, 4, presenting the clinical and report characteristics, respectively. A pie chart was used to visualize the regional sources of these reports (Figure 2), showing that most of the reports were from the United States and European countries. From a gender perspective, except for Ozurdex, women reported 2.3%–49.9% more corticosteroid-related ADRs than men. Most of the reports, excluding those for Triesence, were submitted by healthcare professionals.

3.2 Analysis of adverse reaction time

We also analyzed the induction time of adverse reactions for these drugs, as shown in Figure 3. The figure shows that the median onset time for adverse reactions is shortest for Triesence and longest for Iluvien. A Weibull distribution test conducted on these drugs revealed that the ADR incidence follows an early failure distribution pattern, indicating a significant decrease in ADR occurrence over time (Table 5).

3.3 Disproportionality analysis results

We analyzed the signals at the SOC level for these drugs using the (ROR method, with the results presented in Figure 4. Notable findings include a strong signal for eye disorders across all corticosteroids, with Ozurdex showing the highest ROR of 34.03, indicating a substantial association with ocular ADRs. Additionally, significant signals were detected for renal and urinary disorders with Durezol (ROR = 1.77) and endocrine disorders with Maxidex (ROR = 2.16). Product issues also showed significant signals, particularly for Ozurdex (ROR = 8.08) and Iluvien (ROR = 7.44), suggesting certain risks associated with their intraocular injection

TABLE 1 The 2 × 2 contingency table presents the variables used to calculate the reporting odds ratio and proportional reporting ratio.

	Targeted AEs	Other AEs	Total
Reports with ocular corticosteroids	a	b	a + b
Reports with all other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

a: Number of reports containing both the target drug and the target adverse drug reaction. b: Number of reports containing other adverse drug reactions related to the target drug. c: Number of reports containing the target adverse drug reaction associated with other drugs. d: Number of reports containing other drugs and other adverse drug reactions.

TABLE 2 Principle of dis-proportionality measure and standard of signal detection in this study.

Method	Formula	Threshold
ROR	$\mathrm{ROR} = \frac{(\frac{a}{c})}{(\frac{b}{d})} = \frac{ad}{bc}$ $\mathrm{SE}\ (\ln \mathrm{ROR}) = \sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}$ $95\%cl = e^{ln(PRR)} \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	a≥3 and 95% Cl (lower limit) > 1
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$ $\mathrm{SE}\ (ln(PRR)) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$ $95\%cl = e^{ln(PRR)} \pm 1.96\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$	a≥3 and 95% Cl (lower limit) > 1
BCPNN	$\mathrm{IC} = log_2\frac{P(x,y)}{P(x)_P(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$ $\mathrm{E}\ (\mathrm{IC}) = log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha_1)(a+c+\beta_1)}$ $\mathrm{V(IC)} = \frac{1}{(ln2)^2}\left\{[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}] + [\frac{(a+b+c+d)-(a+b)+\alpha-\alpha_1}{(a+b+\alpha_1)(1+a+b+c+d+\alpha)}]\right.$ $\left.+[\frac{(a+b+c+d)-(a+c)+\beta-\beta_1}{(a+c+\beta_1)(1+a+b+c+d+\beta)}]\right\}$ $\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha_1)(a+c+\beta_1)}$ $\mathrm{IC\text{-}2SD} = \mathrm{E}\ (\mathrm{IC})\text{-}2\ \sqrt{V(IC)}$	IC025 > 0
EBGM	$\mathrm{EBGM} = \frac{a(a+b+c+d)(a+b+c+d+\beta)}{(a+c)(a+b)}$ $95\%cl = e^{ln(EBGM)} \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	EBGM05 > 2

procedures. Furthermore, Iluvien exhibited a high signal in the surgical and medical procedures.

At the PTs level, through screening via four signal detection methods, the number of ophthalmic-related PTs identified were: Ozurdex (92), Lotemax (87), Durezol (88), Maxitrol (56), Iluvien (33), FML (32), and Triesence (26). We used Venn diagrams to visualize the overlap of these PTs across different drugs (Figure 5), revealing a total of seven PTs that appeared in these drugs: eye inflammation, cataract, visual impairment, uveitis, eye pain, vision blurred, visual acuity reduced, and retinal detachment. These shared adverse events highlight common risks associated with these ophthalmic drugs.

4 Discussion

Corticosteroids are steroid hormones known for their anti-inflammatory, anti-allergic, anti-shock, and immunosuppressive properties (Barnes, 2006; Kapugi and Cunningham, 2019). Their mechanism of action primarily involves a genomic pathway mediated by glucocorticoid receptors, which bind to specific DNA sites, initiating gene transcription and the synthesis of various proteins (Claman, 1975). These drugs are widely used in ophthalmology, with different molecular structures and dosage forms developed to cater to the specific needs of ocular treatments (McGhee et al., 2002; Gaballa et al., 2021). However, glucocorticoids are also associated with numerous adverse reactions, including increased risk of infections, elevated intraocular pressure, cataract formation, delayed wound healing, and systemic effects such as weight gain, osteoporosis, and hyperglycemia, especially with prolonged use. Clinical practice must carefully manage These potential side effects to balance therapeutic benefits with risks (Carnahan and Goldstein, 2000; Vetro et al., 2022). Pharmacovigilance analysis is an effective tool for monitoring drug safety and identifying potential risks, ensuring that adverse effects are detected and addressed promptly (Ventrice et al., 2013; Gozzo et al., 2021; Vetro et al., 2022). To our knowledge, this study is the first to identify and describe adverse reactions significantly associated with commonly used glucocorticoids in ophthalmology, offering valuable insights into their safety profiles and highlighting the importance of monitoring potential risks in treatment.

TABLE 3 Clinical characteristics of patients with ophthalmic corticosteroids-related ADRs.

Corticosteroid	Total	Ozurdex	Lotemax	Durezol	Maxidex	Iluvien	FML	Triesence
		Dexamethasone	Loteprednol etabonate	Difluprednate	Dexamethasone	Fluocinolone acetonide	Fluorometholone	Triamcinolone acetonide
Formula		$C_{22}H_{29}FO_5$	$C_{24}H_{31}ClO_7$	$C_{27}H_{34}F_2O_7$	$C_{22}H_{29}FO_5$	$C_{24}H_{30}F_2O_6$	$C_{22}H_{29}FO_4$	$C_{24}H_{31}FO_6$
The marketing authorization date for eye diseases in the U.S.		6/17/2009	09/28/2012	09/30/2008	17/09/2003	26/09/2014	28/07/1982	11/29/2007
Number of individuals	9,854	1784	3,229	2,789	822	455	582	193
Sex								
Female	5,370	645 (36.2%)	2,359 (73.1%)	1,360 (48.8%)	434 (52.8%)	107 (23.5%)	381 (65.5%)	84 (43.5%)
Male	2,875	699 (39.2%)	748 (23.2%)	736 (26.4%)	336 (40.9%)	115 (25.3%)	165 (28.4%)	76 (39.4%)
Unknown	1,609	440 (24.7%)	122 (3.8%)	693 (24.8%)	52 (6.3%)	233 (51.2%)	36 (6.2%)	33 (17.1%)
Weight								
<50 kg	143	5 (0.3%)	65 (2.0%)	20 (0.7%)	32 (3.9%)	0	20 (3.4%)	1 (0.5%)
>100 kg	370	12 (0.7%)	169 (5.2%)	125 (4.5%)	34 (4.1%)	1 (0.2%)	17 (2.9%)	12 (6.2%)
50~100 kg	1,647	109 (6.1%)	812 (25.1%)	364 (13.1%)	219 (26.6%)	2 (0.4%)	131 (22.5%)	10 (5.2%)
Missing	7,694	1,658 (92.9%)	2,183 (67.6%)	2,280 (81.7%)	537 (65.3%)	452 (99.3%)	414 (71.1%)	170 (88.1%)
Age								
≤17	119	14 (0.8%)	28 (0.9%)	23 (0.8%)	38 (4.6%)	2 (0.4%)	11 (1.9%)	3 (1.6%)
≥86	224	30 (1.7%)	100 (3.1%)	49 (1.8%)	22 (2.7%)	1 (0.2%)	21 (3.6%)	1 (0.5%)
18~64	2,130	331 (18.6%)	866 (26.8%)	376 (13.5%)	319 (38.8%)	72 (15.8%)	122 (21.0%)	44 (22.8%)
65~85	2,314	339 (19.0%)	966 (29.9%)	491 (17.6%)	239 (29.1%)	71 (15.6%)	149 (25.6%)	59 (30.6%)
Missing	5,067	1,070 (60.0%)	1,269 (39.3%)	1850 (66.3%)	204 (24.8%)	309 (67.9%)	279 (47.9%)	86 (44.6%)
Outcome of event								
Congenital anomaly	5	0	1 (0.0%)	2 (0.1%)	2 (0.2%)	0	0	0
Death	287	49 (2.5%)	100 (2.8%)	76 (2.5%)	41 (4.2%)	6 (1.2%)	13 (2.0%)	2 (1.0%)
Disability	280	86 (4.4%)	61 (1.7%)	46 (1.5%)	52 (5.3%)	20 (4.0%)	13 (2.0%)	2 (1.0%)
Hospitalization	1,224	194 (9.9%)	405 (11.5%)	288 (9.6%)	197 (20.2%)	33 (6.6%)	92 (14.2%)	15 (7.5%)
Life-threatening	94	5 (0.3%)	22 (0.6%)	18 (0.6%)	34 (3.5%)	0	13 (2.0%)	2 (1.0%)
Others	3,936	1,046 (53.3%)	895 (25.4%)	858 (28.5%)	535 (54.9%)	282 (56.4%)	179 (27.7%)	141 (70.1%)
Required intervention	21	2 (0.1%)	9 (0.3%)	4 (0.1%)	2 (0.2%)	1 (0.2%)	0	3 (1.5%)
Missing	4,978	581 (29.6%)	2036 (57.7%)	1719 (57.1%)	112 (11.5%)	158 (31.6%)	336 (52.0%)	36 (17.9%)

10.3389/fphar.2024.1502047

TABLE 4 Report characteristics of patients with ophthalmic corticosteroids-related ADRs.

	Total	Ozurdex	Lotemax	Durezol	Maxidex	Iluvien	FML	Triesence
Reporter								
Healthcare professional	5,818	1,251 (70.1%)	1943 (60.2)	1,644 (58.9%)	250 (30.4%)	373 (82.0%)	328 (56.4)	29 (15.0%)
Non-Healthcare professional	3,605	525 (29.4%)	1,084 (33.5%)	1,004 (36%)	527 (64.2%)	74 (16.3%)	230 (39.5%)	161 (83.5%)
Missing	431	8 (0.4%)	202 (6.3%)	141 (5.1%)	45 (5.5%)	8 (1.8%)	24 (4.1%)	3 (1.6%)
Reporting year								
2023	475	162	124	93	39	21	30	6
2022	967	302	274	166	72	97	43	13
2021	951	196	295	233	72	73	77	5
2020	1,086	169	314	320	136	36	94	17
2019	1,212	233	333	346	61	165	51	23
2018	946	139	302	387	40	30	31	17
2017	1,060	131	332	474	53	23	34	13
2016	1,085	107	348	476	52	9	78	15
2015	579	76	262	144	47	1	34	15
2014	360	76	144	53	31	0	25	31
2013	240	74	75	51	31	0	6	3
2012	279	69	116	29	47	0	10	8
2011	130	36	55	9	21	0	9	0
2010	188	14	104	3	35	0	26	6
2009	122	0	64	5	21	0	11	21
2008	62	0	32	0	20	0	10	0
2007	39	0	17	0	19	0	3	0
2006	35	0	21	0	8	0	6	0
2005	22	0	12	0	8	0	2	0
2004	16	0	5	0	9	0	2	0

In this study, we conducted basic demographic statistics on patients primarily suspected of experiencing adverse reactions related to ophthalmic glucocorticoids, as shown in Table 3. The results showed that the number of women was significantly higher than that of men, which may be due to the higher incidence of most autoimmune diseases in women. Women are generally more frequently affected by these conditions than men (Ngo et al., 2014). Consequently, when using glucocorticoids for treatment, women may require longer treatment durations or higher doses, potentially increasing their risk of side effects. The Weibull distribution test results indicate that seven ophthalmic glucocorticoids follow an early failure distribution pattern, suggesting that ADRs tend to occur in the early stages of drug use, highlighting the need for careful monitoring for adverse reactions soon after initiating treatment.

Maxidex has been linked to endocrine disorders (ROR = 2.16). The associated PT adrenal insufficiency has a count of 13 and a notably high ROR of 19.44, indicating a strong association with the condition studied. Additionally, Cushing's syndrome has a count of 5 and a high ROR of 18.64, further suggesting a significant association. Similar reports have also been found in many studies, particularly concerning children (Bangsgaard et al., 2018; De Vleeschhauwer et al., 2024). Reports of adrenal suppression with local ocular steroids have also been documented in adults (Sandhu et al., 2012). Given the lack of precise data on the systemic and local concentrations of pediatric eye drops, the use of topical ocular steroids in children requires special attention to avoid potential risks such as adrenal suppression. Durezol was found to be associated with an increased risk of renal and urinary disorders (ROR = 1.77). Through searching related PTs, Chronic kidney disease (CKD) has the highest count (85) and a relatively high ROR of 7.33, indicating a strong association with the condition being studied. End-stage renal disease (ESRD) has a high ROR of 8.62, suggesting that it is also significantly associated, despite having a lower count (24). Renal failure and acute kidney

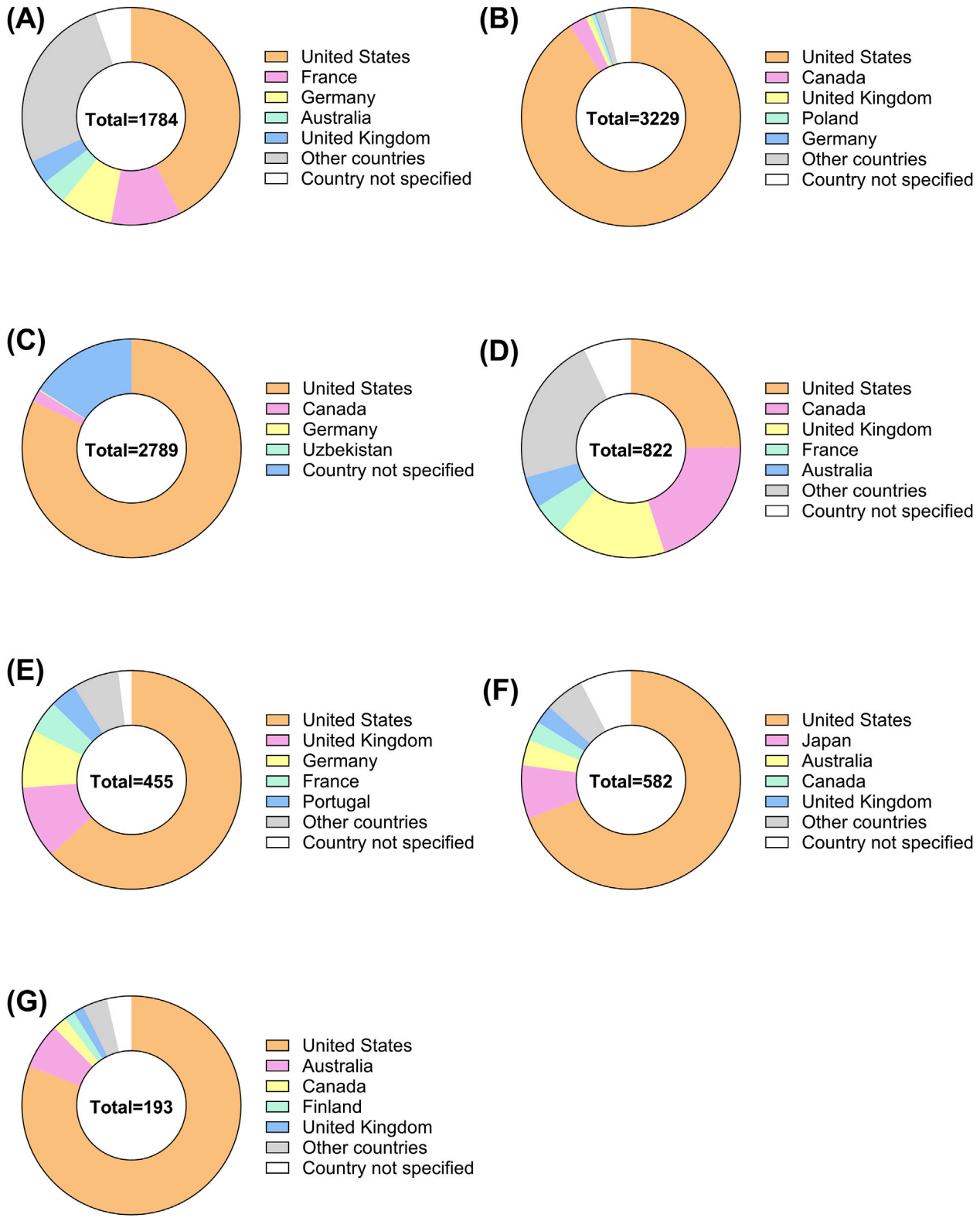


FIGURE 2
Global distribution of ADRs for ophthalmic corticosteroids by country. The pie charts illustrate the distribution of ADR reports from different countries for ophthalmic corticosteroids, categorized by specific drugs **(A)** Ozurdex, **(B)** Lotemax, **(C)** Durezol, **(D)** Maxitrol, **(E)** Iluvien, **(F)** FML, **(G)** Triesence.

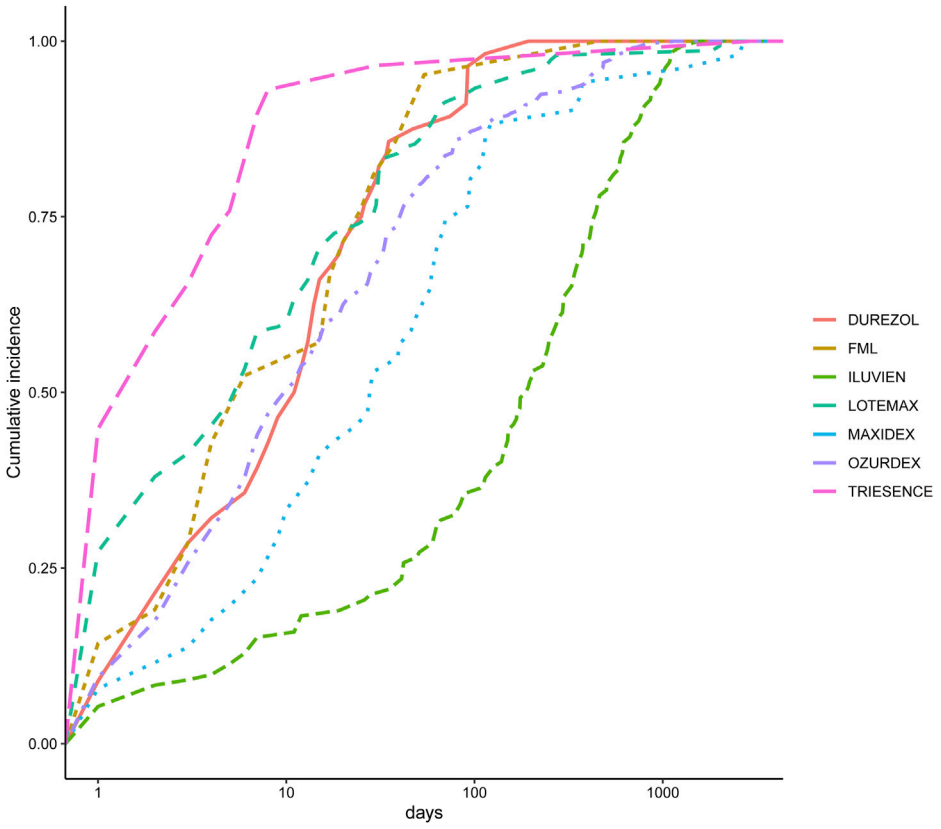


FIGURE 3
Induction time of adverse reactions for seven different ophthalmic corticosteroids.

TABLE 5 Weibull distribution test results.

Drug	Median(d) (25%–75%)	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	Type
Ozurdex	10 (3–40.5)	32.5402454 (24.9826452–40.0978455)	0.5522789 (0.5044848–0.6000731)	Early failure
Lotemax	6 (1–29)	17.8824034 (11.584674–24.1801325)	0.4836633 (0.431619–0.5357077)	Early failure
Durezol	11.5 (3–25.25)	19.5742346 (12.4302627–26.718207)	0.7610364 (0.6133568–0.908716)	Early failure
Maxidex	28 (9–81)	72.0359004 (30.8829917–113.1888091)	0.5106478 (0.4124943–0.6088014)	Early failure
Iluvien	190 (42–442)	254.6536707 (192.1846462–317.1226953)	0.7283638 (0.6250662–0.8316614)	Early failure
FML	6 (3–25)	20.1654305 (4.8068383–35.5240226)	0.5972066 (0.4202388–0.7741744)	Early failure
Triesence	2 (1–5)	7.5668018 (0.05949738–15.074106)	0.3919074 (0.30562079–0.478194)	Early failure

injury have relatively lower RORs (2.84 and 2.09, respectively). Currently, there is no research documenting the relationship between Durezol and renal/urinary diseases. However, corticosteroids are known to directly cause vasoconstriction of arterioles and increase salt and water retention in the kidneys, which may contribute to their impact on renal health (Gibbison et al., 2020). Ozurdex, Iluvien, and Triesence have a high signal regarding product issues, which may be attributed to the invasive procedures involved in administering these medications. Furthermore, Ozurdex and Iluvien, being intravitreal implants with relatively recent marketing authorization, also carry the risk of device dislocation and device malfunction.

A total of seven PTs appeared in these drugs: eye inflammation, cataract, visual impairment, uveitis, eye pain, vision blurred, visual acuity reduced, and retinal detachment. Apart from the clinical manifestations of indications, cataract is the common ADR of these drugs. The increased risk of cataracts is widely acknowledged as a significant side effect of long-term corticosteroid use, although its pathogenesis remains incompletely understood (Smeeth et al., 2003; Wang et al., 2009). Several mechanisms have been proposed to explain this association, including alterations in protein structure and function mediated by glucocorticoid receptors, abnormal cell differentiation influenced by growth factors, modifications in the structure and function of lens proteins, and the role of oxidative

FIGURE 4
Signal detection analysis of ADRs associated with ophthalmic corticosteroids across various SOCs. The heatmap represents the ROR values for ADRs associated with seven different ophthalmic corticosteroids.

stress (Jobling and Augusteyn, 2002; James, 2007). These factors may contribute to lens opacification, ultimately leading to the development of cataracts in individuals undergoing prolonged corticosteroid therapy.

The FAERS database offers significant advantages for studying ADRs. It provides extensive real-world data, enabling the identification of rare or previously unrecognized ADRs, making it an essential tool for post-market drug safety surveillance. By using signal detection methods such as ROR, FAERS data can help screen for potential ADRs and is widely employed in pharmacovigilance efforts. However, the database has its limitations. As a spontaneous reporting system, FAERS data may be influenced by underreporting, misreporting, and duplicate reports, potentially compromising data completeness. Furthermore, FAERS does not support the calculation of ADR incidence rates and lacks detailed patient characteristics and clinical information, which hinders the ability to establish causal relationships. Reporting bias is another concern, as most reports come from Western countries, limiting the generalizability of the findings to other regions. While signal detection can reveal statistical associations, it does not confirm causality between drugs and ADRs. Therefore, FAERS data should be combined with large-scale, well-designed epidemiological studies to investigate further ocular adverse events associated with glucocorticoids in future studies (Gozzo et al., 2023).

5 Conclusion

In summary, this study utilized data mining methods to explore the systemic and, particularly, ocular safety concerns associated with currently marketed corticosteroid drugs used in ophthalmology. The findings provide valuable data to support the rational use of corticosteroids in eye treatments and serve as a reference for future safety research. Physicians should remain vigilant for potential adverse

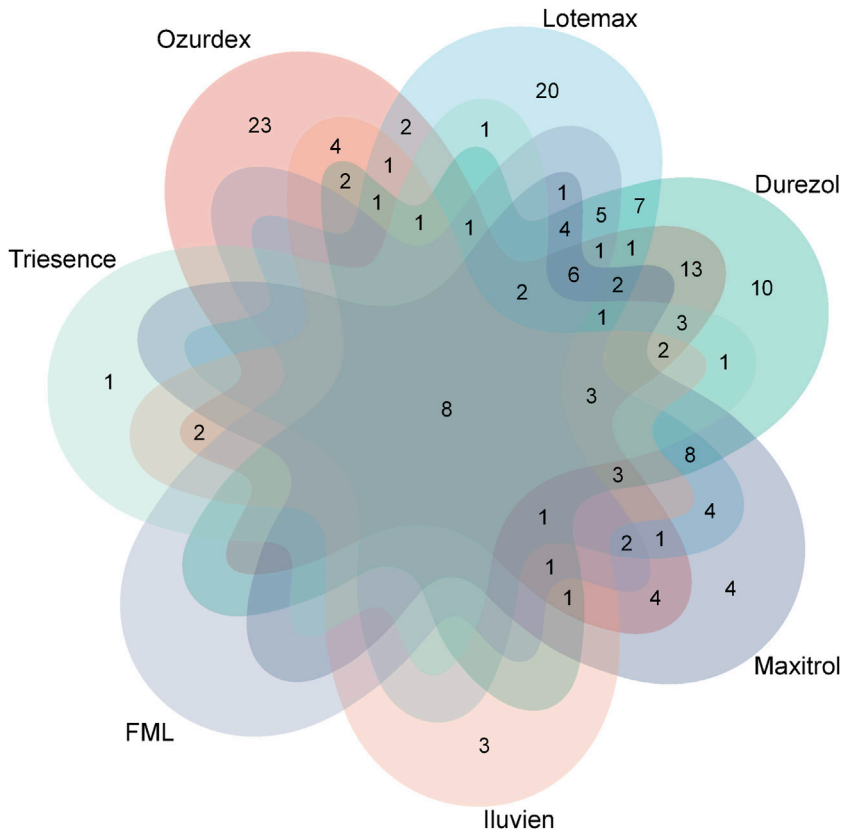


FIGURE 5
Veen diagram displaying the common ADRs among seven different ophthalmic corticosteroids.

reactions, especially in the early stages of glucocorticoid therapy. Early diagnosis and timely intervention can help prevent or mitigate serious consequences stemming from these adverse reactions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

CL: Conceptualization, Data curation, Formal Analysis, Software, Visualization, Writing–original draft. XW: Data curation, Investigation, Writing–original draft. XC: Conceptualization, Funding acquisition, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Beijing Natural Science Foundation (Z200014).

Acknowledgments

The authors express gratitude to all participants for their help.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that Gen AI was used in the creation of this manuscript. ChatGPT is only used for language polishing and grammar checking in articles, helping to enhance clarity, coherence, and overall readability.

Publisher's note

References

Bangsgaard, R., Main, K. M., Boberg-Ans, G., La Cour, M., Forman, J. L., Haargaard, B., et al. (2018). Adrenal suppression in infants treated with topical ocular glucocortic oids. *Ophthalmology* 125, 1638–1643. doi:10.1016/j.ophtha.2018.04.035

Barnes, P. J. (2006). How corticosteroids control inflammation: quintiles prize lecture 2005. *Br. J. Pharmacol.* 148, 245–254. doi:10.1038/sj.bjp.0706736

Boscia, F., Veritti, D., Iaculli, C., Lattanzio, R., Freda, S., Piergentili, B., et al. (2024). Management of treatment-naïve diabetic macular edema patients: review of real-world clinical data. *Eur. J. Ophthalmol.* 34, 1675–1694. doi:10.1177/11206721241237069

Brown, E. G., Wood, L., and Wood, S. (1999). The medical dictionary for regulatory activities (MedDRA). *Drug Saf.* 20, 109–117. doi:10.2165/00002018-199920020-00002

Bucolo, C., Gozzo, L., Longo, L., Mansueto, S., Vitale, D. C., and Drago, F. (2018). Long-term efficacy and safety profile of multiple injections of intravitreal dexamethasone implant to manage diabetic macular edema: a systematic review of real-world studies. *J. Pharmacol. Sci.* 138, 219–232. doi:10.1016/j.jphs.2018.11.001

Busch, C., Zur, D., Fraser-Bell, S., Laíns, I., Santos, A. R., Lupidi, M., et al. (2018). Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol.* 55, 789–796. doi:10.1007/s00592-018-1151-x

Caplan, A., Fett, N., Rosenbach, M., Werth, V. P., and Micheletti, R. G. (2017). Prevention and management of glucocorticoid-induced side effects: a comprehensive review: ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients. *J. Am. Acad. Dermatology* 76, 201–207. doi:10.1016/j.jaad.2016.02.1241

Carnahan, M. C., and Goldstein, D. A. (2000). Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr. Opin. Ophthalmol.* 11, 478–483. doi:10.1097/00055735-200012000-00016

Claman, H. N. (1975). How corticosteroids work. *J. Allergy Clin. Immunol.* 55, 145–151. doi:10.1016/0091-6749(75)90010-x

Cutolo, C. A., Barabino, S., Bonzano, C., and Traverso, C. E. (2019). The use of topical corticosteroids for treatment of dry eye syndrome. *Ocular Immunol. Inflamm.* 27, 266–275. doi:10.1080/09273948.2017.1341988

De Vleeschhauwer, F., Casteels, K., Hoffman, I., Proesmans, M., and Rochtus, A. (2024). Systemic adverse events associated with locally administered corticosteroids. *Child. (Basel)* 11, 951. doi:10.3390/children11080951

Fang, T., Maberley, D. A., and Etminan, M. (2019). Ocular adverse events with immune checkpoint inhibitors. *J. Curr. Ophthalmol.* 31, 319–322. doi:10.1016/j.joco.2019.05.002

Fukazawa, C., Hinomura, Y., Kaneko, M., and Narukawa, M. (2018). Significance of data mining in routine signal detection: analysis based on the safety signals identified by the FDA. *Pharmacoepidemiol. Drug Saf.* 27, 1402–1408. doi:10.1002/pds.4672

Fung, A. T., Tran, T., Lim, L. L., Samarawickrama, C., Arnold, J., Gillies, M., et al. (2020). Local delivery of corticosteroids in clinical ophthalmology: a review. *Clin. Exp. Ophthalmol.* 48, 366–401. doi:10.1111/ceo.13702

Gaballa, S. A., Kompella, U. B., Elgarhy, O., Alqahtani, A. M., Pierscionek, B., Alany, R. G., et al. (2021). Corticosteroids in ophthalmology: drug delivery innovations, pharmacology, clinical applications, and future perspectives. *Drug Deliv. Transl. Res.* 11, 866–893. doi:10.1007/s13346-020-00843-z

Gibbison, B., Villalobos Lizardi, J. C., Avilés Martínez, K. I., Fudulu, D. P., Medina Andrade, M. A., Pérez-Gaxiola, G., et al. (2020). Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass. *Cochrane Database Syst. Rev.* 10, Cd013101. doi:10.1002/14651858.CD013101.pub2

Gozzo, L., Nardo, A., Brancati, S., Judica, A., Duminuco, A., Maugeri, C., et al. (2023). Severe gastrointestinal toxicity following the use of gilteritinib: a case series and analysis of postmarketing surveillance data. *Healthc. (Basel)* 11, 1479. doi:10.3390/healthcare11101479

Gozzo, L., Vetro, C., Brancati, S., Longo, L., Vitale, D. C., Romano, G. L., et al. (2021). Off-label use of venetoclax in patients with acute myeloid leukemia: single center experience and data from pharmacovigilance database. *Front. Pharmacol.* 12, 748766. doi:10.3389/fphar.2021.748766

Hoffman, K. B., Demakas, A. R., Dimbil, M., Tatonetti, N. P., and Erdman, C. B. (2014). Stimulated reporting: the impact of US food and drug administration-issued alerts on the adverse event reporting system (FAERS). *Drug Saf.* 37, 971–980. doi:10.1007/s40264-014-0225-0

Huscher, D., Thiele, K., Gromnica-Ihle, E., Hein, G., Demary, W., Dreher, R., et al. (2009). Dose-related patterns of glucocorticoid-induced side effects. *Ann. rheumatic Dis.* 68, 1119–1124. doi:10.1136/ard.2008.092163

James, E. R. (2007). The etiology of steroid cataract. *J. Ocul. Pharmacol. Ther.* 23, 403–420. doi:10.1089/jop.2006.0067

Jobling, A. I., and Augusteyn, R. C. (2002). What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. *Clin. Exp. Optom.* 85, 61–75. doi:10.1111/j.1444-0938.2002.tb03011.x

Kapugi, M., and Cunningham, K. (2019). Corticosteroids. *Orthop. Nurs.* 38, 336–339. doi:10.1097/NOR.0000000000000595

Kiernan, D. F., and Mieler, W. F. (2012). Intraocular corticosteroids for posterior segment disease: 2012 update. *Expert Opin. Pharmacother.* 13, 1679–1694. doi:10.1517/14656566.2012.690736

Leroy, F., Dauxois, J.-Y., Théophile, H., Haramburu, F., and Tubert-Bitter, P. (2014). Estimating time-to-onset of adverse drug reactions from spontaneous reporting databases. *BMC Med. Res. Methodol.* 14, 17–11. doi:10.1186/1471-2288-14-17

Ma, P., Pan, X., Liu, R., Qu, Y., Xie, L., Xie, J., et al. (2022). Ocular adverse events associated with anti-VEGF therapy: a pharmacovigilance study of the FDA adverse event reporting system (FAERS). *Front. Pharmacol.* 13, 1017889. doi:10.3389/fphar.2022.1017889

Mcghee, C. N., Dean, S., and Danesh-Meyer, H. (2002). Locally administered ocular corticosteroids: benefits and risks. *Drug Saf.* 25, 33–55. doi:10.2165/00002018-200225010-00004

Michel, C., Scosyrev, E., Petrin, M., and Schmouder, R. (2017). Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? *Clin. drug Investig.* 37, 415–422. doi:10.1007/s40261-017-0503-6

Montastruc, J.-L., Sommet, A., Bagheri, H., and Lapeyre-Mestre, M. (2011). Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br. J. Clin. Pharmacol.* 72, 905–908. doi:10.1111/j.1365-2125.2011.04037.x

Ngo, S. T., Steyn, F. J., and Mccombe, P. A. (2014). Gender differences in autoimmune disease. *Front. Neuroendocrinol.* 35, 347–369. doi:10.1016/j.yfrne.2014.04.004

Puglia, C., Santonocito, D., Romeo, G., Intagliata, S., Romano, G. L., Strettoi, E., et al. (2021). Lipid nanoparticles traverse non-corneal path to reach the posterior eye segment: *in vivo* evidence. *Molecules* 26, 4673. doi:10.3390/molecules26154673

Raizman, M. (1996). Corticosteroid therapy of eye disease: fifty years later. *Archives Ophthalmol.* 114, 1000–1001. doi:10.1001/archopht.1996.01100140208016

Roberti, G., Oddone, F., Agnifili, L., Katsanos, A., Michelessi, M., Mastropasqua, L., et al. (2020). Steroid-induced glaucoma: epidemiology, pathophysiology, and clinical management. *Surv. Ophthalmol.* 65, 458–472. doi:10.1016/j.survophthal.2020.01.002

Romano, G. L., Gozzo, L., Maurel, O. M., Di Martino, S., Riolo, V., Micale, V., et al. (2023). Fluoxetine protects retinal ischemic damage in mice. *Pharmaceutics* 15, 1370. doi:10.3390/pharmaceutics15051370

Sandhu, S. S., Smith, J. M., Doherty, M., James, A., and Figueiredo, F. C. (2012). Do topical ophthalmic corticosteroids suppress the hypothalmic-pituitary-adrenal axis in post-penetrating keratoplasty patients? *Eye* 26, 699–702. doi:10.1038/eye.2012.12

Smeeth, L., Boulis, M., Hubbard, R., and Fletcher, A. E. (2003). A population based case-control study of cataract and inhaled corticosteroids. *Br. J. Ophthalmol.* 87, 1247–1251. doi:10.1136/bjo.87.10.1247

Subeesh, V., Maheswari, E., Saraswathy, G. R., Swaroop, A. M., and Minnikanti, S. S. (2018). A comparative study of data mining algorithms used for signal detection in FDA AERS database. *J. Young Pharm.* 10, 444–449. doi:10.5530/jyp.2018.10.97

Ventrice, P., Leporini, C., Aloe, J. F., Greco, E., Leuzzi, G., Marrazzo, G., et al. (2013). Anti-vascular endothelial growth factor drugs safety and efficacy in ophthalmic diseases. *J. Pharmacol. Pharmacother.* 4, S38–S42. doi:10.4103/0976-500X.120947

Veronin, M. A., Schumaker, R. P., Dixit, R. R., Dhake, P., and Ogwo, M. (2020). A systematic approach to 'cleaning' of drug name records data in the FAERS database: a case report. *Int. J. Big Data Manag.* 1, 105–118. doi:10.1504/ijbdm.2020.10034546

Vetro, C., Duminuco, A., Gozzo, L., Maugeri, C., Parisi, M., Brancati, S., et al. (2022). Pegylated asparaginase-induced liver injury: a case-based review and data from pharmacovigilance. *J. Clin. Pharmacol.* 62, 1142–1150. doi:10.1002/jcph.2052

Wang, J. J., Rochtchina, E., Tan, A. G., Cumming, R. G., Leeder, S. R., and Mitchell, P. (2009). Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 116, 652–657. doi:10.1016/j.ophtha.2008.12.001

Zhao, X., Wu, J., and Zhu, S. (2023). Ocular disorders associated with PCSK9 inhibitors: a pharmacovigilance disproportionality analysis. *Br. J. Clin. Pharmacol.* 89, 458–469. doi:10.1111/bcp.15494

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 11 December 2024
DOI 10.3389/fphar.2024.1438661

OPEN ACCESS

EDITED BY
Anick Bérard,
Montreal University, Canada

REVIEWED BY
Francisco Abad-Santos,
Universidad Autónoma de Madrid, Spain
Wenjun Wang,
Xi'an Jiaotong University, China

*CORRESPONDENCE
Siying Luo,
313029909@qq.com
Song Li,
lisong74584847@qq.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 26 May 2024
ACCEPTED 18 November 2024
PUBLISHED 11 December 2024

CITATION
Zhang Y, Deng W, Wang M, Luo S and Li S (2024) A real-world pharmacovigilance study of neuroleptic malignant syndrome based on FDA adverse event reporting system.
Front. Pharmacol. 15:1438661.
doi: 10.3389/fphar.2024.1438661

A real-world pharmacovigilance study of neuroleptic malignant syndrome based on FDA adverse event reporting system

Yu Zhang[1†], Wei Deng[2†], Minjian Wang[3], Siying Luo[3*] and Song Li[4*]

[1]Department of Hospital Infection Control, Chongqing Mental Health Center, Chongqing, China, [2]Nursing Department, Chongqing Mental Health Center, Chongqing, China, [3]Department of Children and Adolescents, Chongqing Mental Health Center, Chongqing, China, [4]Sleep Medicine Center, Chongqing Mental Health Center, Chongqing, China

Background: Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening adverse drug reaction. This study aims to identify the most prevalent drugs associated with the risk of NMS according to the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database.

Methods: Analyses were performed using data from the FAERS database from January 2004 to June 2024. Single-drug signals were evaluated using the reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and empirical Bayes geometric mean (EBGM). Meanwhile, comparisons were performed with drug labels. Additionally, subgroup analysis was conducted, focusing on adverse drug reaction signals among populations of different genders and age groups.

Results: A total of 10,433 adverse event reports related to NMS were identified, with the top 50 drugs ranked by ROR mainly involving antipsychotics (18, 36%), antiparkinson drugs (10, 20%), antidepressants (7, 14%), antiepileptics (3, 6%), anxiolytics (3, 6%), as well as hypnotics and sedatives (3, 6%). NMS is more prevalent in males (5,713, 54.76%). Among the top 20 drugs with the strongest signal strength, the pediatric group showed an additional presence of benzodiazepines and antiepileptic drugs compared to the adult group.

Conclusion: The current comprehensive pharmacovigilance study identified more drugs associated with NMS and provides references to clinicians for clinical practice. Also, further research is needed to investigate the causal relationship between these drugs and NMS.

KEYWORDS

neuroleptic malignant syndrome, FAERS, disproportionality analysis, pharmacovigilance, adverse event reports

1 Introduction

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening adverse drug reaction to dopamine antagonists, characterized by hyperthermia, rigidity, altered mental status, autonomic dysfunction (i.e., diaphoresis, tachycardia, tachypnea, and labile blood pressure), as well as elevated creatine kinase and white blood cell count. In antipsychotic

users, the incidence of NMS ranges from 0.06% to 1.4%, with mortality as high as 7.6% (Lao et al., 2020; Pileggi and Cook, 2016). The pathophysiology is not fully known, but there is a consensus that the use of dopamine receptor antagonists leads to the blockade of dopamine D2 signaling or related pathways in the substantia nigra-striatum, hypothalamus, and cortex, resulting in neurological dysfunction. It can be caused by all classes of antipsychotic drugs and other drugs that might also block dopamine receptors, such as antihistaminergic antiemetics. Beyond that, there are also reports of lithium salts, carbamazepine, and antidepressants causing NMS (Patil et al., 2016). The complications of NMS are common causes of death in critically ill patients, including rhabdomyolysis, renal failure, cardiac arrhythmias, circulatory collapse, and disseminated intravascular coagulation (DIC). With the increasing incidence of mental disorders and the widespread use of antipsychotics and non-antipsychotics, reports of NMS are gradually increasing. NMS is often misdiagnosed, lacks specific treatments, and has a high mortality rate, with the key to treatment lying in early drug cessation. Therefore, being familiar with the adverse reactions of high-risk medications in clinical practice is crucial for preventing the occurrence of NMS.

The majority of case reports concerning NMS typically involve both typical and atypical antipsychotics, occasionally including antidepressants, antiepileptic drugs, etc., It's important to note that information regarding the potential risk of NMS with specific medications largely stems from case reports, as conducting clinical randomized controlled trials is challenging due to the rarity of NMS. Additionally, there are limited retrospective observational studies on this topic. As one of the largest pharmacovigilance databases, the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database has played a major role in the evaluation of drug safety. Based on safety signals obtained by data mining using the post-marketing surveillance database, it is possible to detect unknown adverse events (AEs) that have not been discovered in clinical trials as well as evaluate safety in specific populations and reflect actual clinical uses. Currently, only a few pharmacovigilance studies on NMS are conducted based on Japanese populations, and data from other regions is lacking. Therefore, this study aims to analyze drugs associated with NMS occurrence based on the FAERS database and provide evidence for the selection of clinical drugs.

2 Materials and methods

2.1 Data collection

This retrospective pharmacovigilance study extracted data from the FAERS database, which contains demographic information, drug information, and reaction information. For this study, the AEs of NMS were searched from the first quarter of 2004 to the second quarter of 2024. The patient's information, including demographic and administrative data, drug and therapy data, and reporting sources, was collected. We searched the FAERS database by adopting the preferred term (PT) "Neuroleptic malignant syndrome (PT code: 10029282)" according to the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. There are four classifications to group each case according to the role of the medications administered in the adverse events: primary suspect drug (PS), secondary suspect drug (SS), concomitant (C), and interaction (I). We extracted data for every case that received the designation of PS.

In this study, duplicate reports that described the same adverse medication occurrence in the same patient were eliminated. Because the data used in the current study were de-identified and publicly available from the FAERS website, the study was exempt from ethical review.

2.2 Statistical analysis

The R software, specifically version 4.3.3, was used for data processing, statistical calculations, and visualization. A descriptive analysis was conducted to describe the clinical characteristics of NMS cases, including the patient's gender, age, reporting country, and indications. The top 50 drugs related to NMS were selected based on the number of reports. The 50 drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Based on the contrast between observed and expected numbers of reports, disproportionality analysis was used to generate hypotheses on possible associations between drugs and AEs. To improve the results' reliability, disproportionality analysis was carried out using the reported odds ratio (ROR), proportional reporting rate (PRR), information component (IC), and empirical Bayes geometric mean (EBGM) to detect the NMS risk signal for each drug and conducted calculations using a 2-by-2 contingency table (Supplementary Table S1). The Equation and Criteria of the above four methods are detailed in Supplementary Table S2. A larger value indicates a stronger signal value and a safety signal was considered when it met four algorithm criteria simultaneously. Following that, separate disproportionality analyses were performed based on gender and age.

3 Results

3.1 Characteristics of adverse event reports

From Q1 2004 to Q2 2024, there were 10,433 adverse event reports (AERs) in FAERS database reported for NMS. As shown in Figure 1, the number of reported NMS peaked in 2017 at 863 reports. Starting in 2018, the number began to decline, but the general trend from 2004 to 2024 shows an increase in volatility. The clinical characteristics of these 10,433 reports are listed in Table 1. The median age of the study population was 48 years (interquartile range 31–62). Excluding those of unknown age, the remaining cases were mainly in the 18–64 age group (57.42%). The number of reports from males (5,713, 54.76%) is higher than from females (3,780, 36.23%). The top five indications for drug use were: schizophrenia (1,985, 19.03%), bipolar disorder (836, 8.01%), depression (714, 6.84%), psychotic disorder (514, 5.56%), and Parkinson's disease (280, 4.93%). The country with the highest number of reports was the United States (1,727, 16.55%),

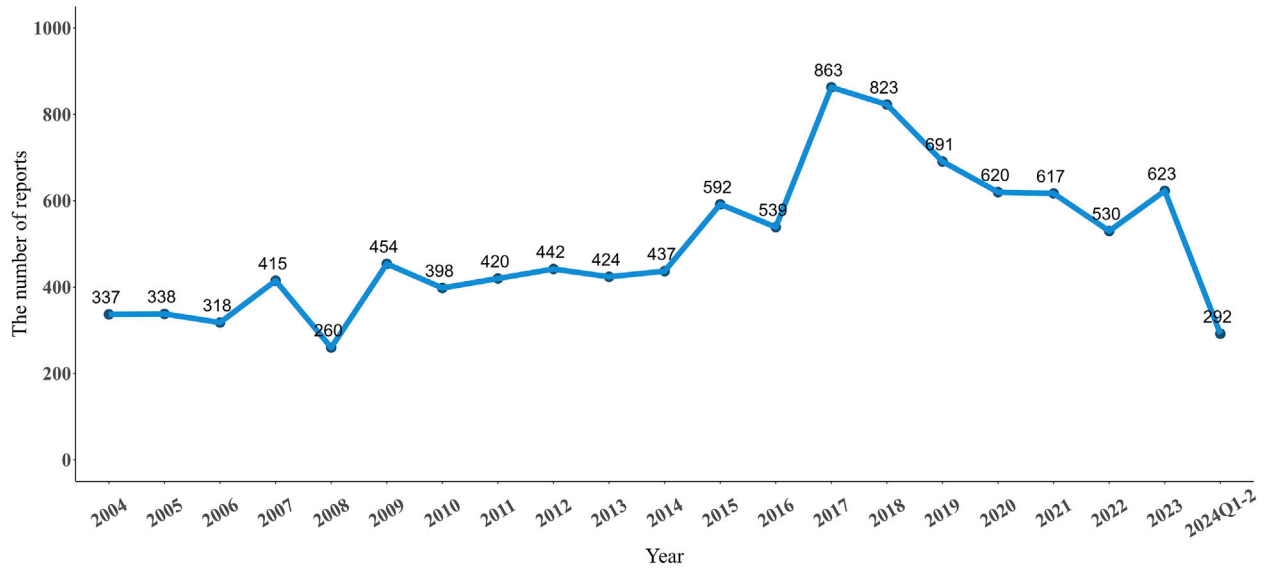


FIGURE 1
Annual neuroleptic malignant syndrome reports from Q1 2004 to Q2 2024.

followed by the United Kingdom (942, 9.03%), Japan (923, 8.85%), France (446, 4.27%), and Canada (319, 3.06%).

3.2 Disproportionality analysis

3.2.1 Overall

The current study summarized the top 50 drugs ranked by the frequencies of AERs (Figure 2). These drugs were classified according to the World Health Organization (WHO) ATC system. As for the frequencies of AERs, quetiapine (1,328 reports) is the most frequently reported drug, followed by olanzapine (1,305 reports), risperidone (925 reports), aripiprazole (888 reports), haloperidol (630 reports), clozapine (607 reports), paliperidone (283 reports), valproic acid (265 reports), ziprasidone (219 reports) and paroxetine (174 reports). The main categories with a high number of drugs among these 50 were antipsychotics (15, 30%), antidepressants (11, 22%), antiparkinson drugs (7, 14%), antiepileptics (6, 12%), and anxiolytics (3, 6%). Of these 50 drugs, 24 drugs didn't indicate NMS risk on the label, mainly including antidepressants (9, 37.5%) and antiepileptics (6, 25%), while the remaining 26 drugs did.

According to the signal strength, the top 50 drugs are listed in Table 2, all of which have statistically significant signal strengths. The results of ROR, PRR, IC, and EBGM are consistent. The top 5 drugs ranked by ROR were: favipiravir (ROR 1727.47, 95%CI 431.97-6908.26), biperiden (ROR 348.41, 95%CI 250.95-483.71), amisulpride (ROR 216.12, 95%CI 121.38-384.80), trihexyphenidyl (ROR 149.84, 95%CI 84.99-264.17), and fluphenazine (ROR 145.77, 95%CI 103.19-205.93). According to drug classification, the most common type of drugs is antipsychotics (18, 36%), followed by antiparkinson drugs (10, 20%), antidepressants (7, 14%), antiepileptics (3, 6%), anxiolytics (3, 6%), and hypnotics and sedatives (3, 6%). Of the top 50 drugs, 28 drugs indicate NMS risk on the label, mainly including antipsychotics (17, 60.7%) and antiparkinson drugs (7, 25%), while the other 22 drugs did not.

3.2.2 Subgroup analysis

Figure 3 shows the disproportionality results based on gender, we listed the top 20 drugs related to NMS in males and females based on ROR values. Of the 10,433 reports associated with NMS, 9,493 reported known gender and were divided into male (5,713, 54.76%) and female (3,780, 36.23%) groups. Additionally, among the top 20 drugs in different genders, antipsychotics, antidepressants, and antiparkinson drugs were predominant. Biperiden, amisulpride, maprotiline, fluphenazine, and trihexyphenidyl are the top 5 drugs with high ROR in males. While biperiden, trihexyphenidyl, loxapine, chlorpromazine, and haloperidol are the top 5 drugs with high ROR in females.

Figure 4 displays the disproportionality results based on age, we found that there are different types of risk drugs detected between the pediatric and adult groups. Besides antipsychotics, antiparkinson drugs, and antidepressants, the drugs with strong positive signals detected in patients under 18 years old included another antiepileptic (zonisamide) and benzodiazepine (triazolam). Notably, exclusive to the 18–65 years old group, favipiravir exhibited the highest signal strength (ROR 2275.64, 95% CI 509.22-10169.53).

4 Discussion

Based on all spontaneous adverse event reports in the FAERS database since 2004, the study comprehensively investigated drug safety signals associated with NMS occurrence. Through frequency and four disproportionality analysis methods, this study found that drugs primarily associated with NMS include antipsychotics, antidepressants, antiparkinson drugs, antiepileptic drugs, and anxiolytics. Apart from antipsychotics and some antiparkinson drugs, many of these drugs do not mention NMS risks in their labels. Furthermore, when using favipiravir in adult patients, it is

TABLE 1 Clinical characteristics of reported neuroleptic malignant syndrome.

Characteristics	Reports, n (%)
Overall	10,433
Age, years	
Median, IQR	48.00 (31.00,62.00)
≤17	593 (5.68)
18–64	5,991 (57.42)
≥65	1,834 (17.58)
Unknow	2,015 (19.31)
Gender	
Female	3,780 (36.23)
Male	5,713 (54.76)
Unknown	940 (9.01)
Indications	
Schizophrenia	1,985 (19.03)
Unknown	1,875 (17.97)
Bipolar disorder	836 (8.01)
Depression	714 (6.84)
Psychotic disorder	514 (5.56)
Parkinson's disease	280 (4.93)
Agitation	274 (2.63)
Dementia	105 (1.01)
Anxiety	90 (0.86)
Mania	87 (0.83)
Reported country	
United States	1,727 (16.55)
United Kingdom	942 (9.03)
Japan	923 (8.85)
France	446 (4.27)
Canada	319 (3.06)
Spain	269 (2.58)
India	209 (2.00)
Portugal	207 (1.98)
Germany	202 (1.94)
Italy	199 (1.91)
Time to onset, days	
Median, IQR	16.00 (3.00,137.00)

Abbreviations: IQR, interquartile range.

necessary to pay attention to NMS. In children, additional attention should be given to the adverse reactions of antiepileptic drugs and benzodiazepines.

NMS is a rare but potentially fatal adverse drug reaction. Previously published studies related to NMS are very limited and most of the information comes from case reports. Due to its pathogenesis mainly involving excessive blockade of dopamine uptake, an increasing number of non-antipsychotic drugs are being reported in association with NMS. Therefore, real-world pharmacovigilance studies are of significant importance in improving drug safety information. Currently, there are only two NMS drug safety monitoring studies, targeting the Japanese population. Through single-drug signal analysis, Kyotani et al. found that drugs related to NMS are primarily antipsychotics, as well as other non-antipsychotic medications, including antidepressants and antiparkinson drugs. In addition, they suggested that various pathways related were mainly neuroactive ligand-receptor interactions, dopaminergic synapses, or serotonergic synapses (Kyotani et al., 2023). Hirofuji et al. conducted disproportionality analysis and hierarchical cluster analysis for antipsychotic drugs, revealing stronger safety signals for haloperidol, chlorpromazine, risperidone, and aripiprazole. They also concluded that typical and atypical antipsychotic drugs exhibit different clinical manifestations related to NMS (Hirofuji et al., 2023). The FAERS reports are sourced from global data, encompassing a more diverse population dataset. To our knowledge, this is the first drug adverse reaction analysis targeting NMS based on the FAERS database, aiming to assist healthcare professionals in understanding post-market safety information of medications and managing NMS from the perspective of drug selection.

Among the top 50 drugs associated with NMS, antipsychotic medications, including both typical antipsychotics and atypical antipsychotics, dominate in terms of report count and safety signal strength rankings, which is consistent with previous studies (Hirofuji et al., 2023; Singhai et al., 2019). Although the pathophysiology of NMS is incompletely understood, the most widely held hypothesis is that NMS symptoms seem related to a rapid decrease in central dopaminergic activity because of the blockade of D2 receptors or the abrupt cessation of D2 receptor stimulation. The clinical manifestations can be explained as follows: The reduction in central dopaminergic neurotransmission in the striatum and hypothalamus leads to impaired thermoregulation. Blockade of striatal dopamine receptors contributes to muscle rigidity and tremor. Hypothalamic and spinal dopamine receptor antagonism results in altered mental status (Berloffa et al., 2021; Ware et al., 2018). This hypothesis can also explain the close association between metoclopramide, which acts as a dopamine D2 receptor antagonist, and NMS (Kocyigit et al., 2017; Wittmann et al., 2016). Due to the reduced dopaminergic blockade and the antagonistic effects on 5-HT receptors of non-typical antipsychotic medications, NMS induced by atypical antipsychotics is characterized by lower incidence, lower clinical severity, and less mortality (Belvederi Murri et al., 2015; Stevens, 2008). On the other hand, abrupt discontinuation or rapid switching of dopaminergic drugs that act as D2 receptor stimulation for Parkinson's disease may precipitate NMS (Waqas et al., 2023; Wei and Chen, 2014). In line with case reports, this study categorizes carbidopa, bromocriptine, entacapone, amantadine, pramipexole, and others as suspected drugs for NMS,which respective labels also warn of the risk of NMS with dosage reduction and discontinuation, leading us

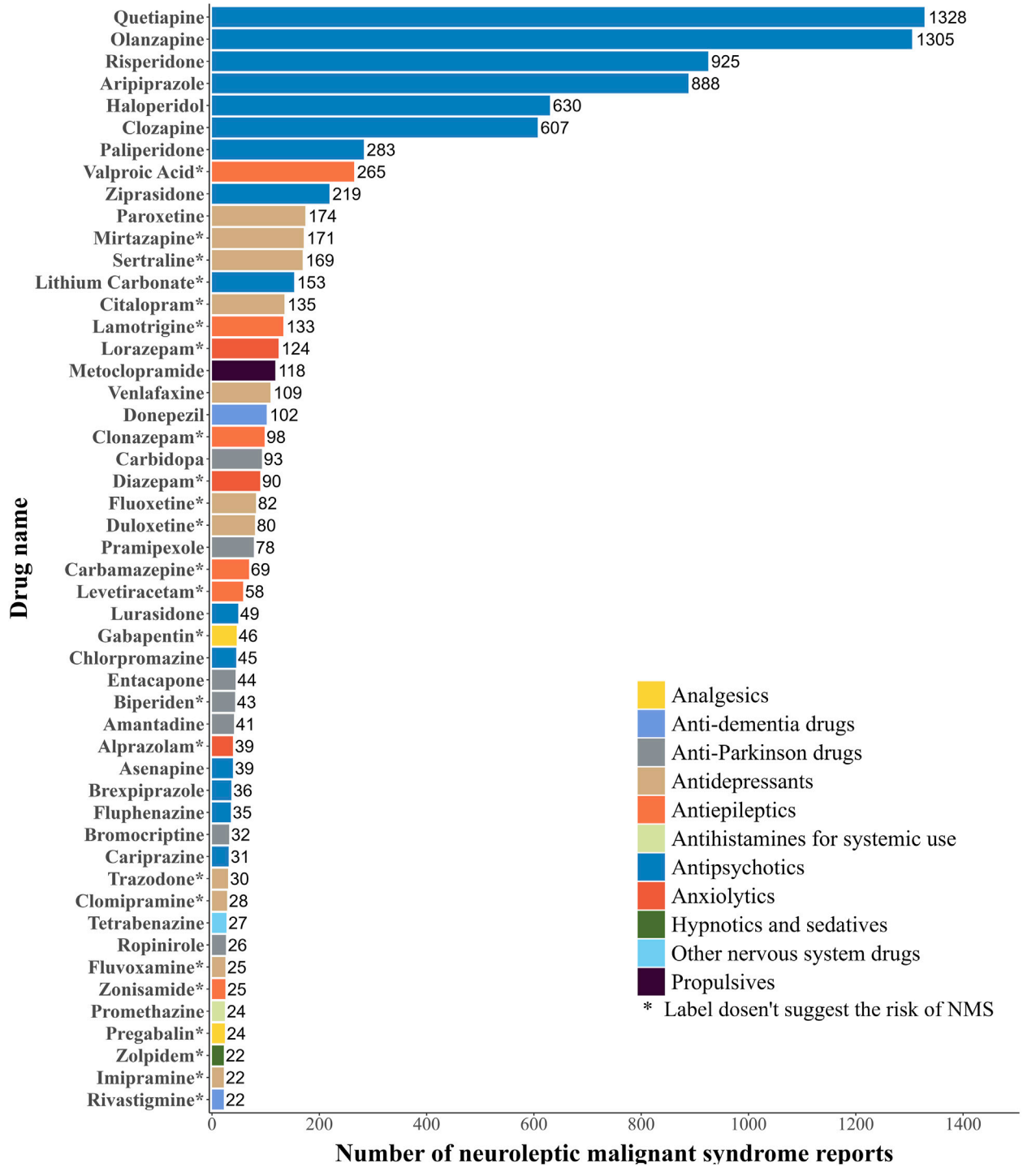


FIGURE 2
Top 50 drugs with the highest number of reported neuroleptic malignant syndrome.

to speculate that NMS occurrences in these reports occurred following dosage adjustment of these drugs.

Interestingly, an unexpected significant signal was identified with favipiravir. In this pharmacovigilance study, all 4 reported indications were COVID-19 infections. There is little knowledge about NMS related to COVID-19 infection. Reviewing the literature, only 6 case reports of NMS in COVID-19 patients have been published globally, with only 2 case reports involving patients using favipiravir (Borah et al., 2021; Durbach et al., 2022; Espiridion et al., 2021; Gökçen and Akkuş, 2024; Kajani et al., 2020; Soh et al., 2020). According to Soh et al., two COVID-19 patients diagnosed with NMS experienced a rapid reduction in elevated CK levels, a gradual resolution of fever, and stabilization of breathing following the discontinuation of favipiravir (Soh et al.,

TABLE 2 Signal strength for drugs associated with neuroleptic malignant syndrome.

WHO ATC category	Drug name	Case reports	ROR (95% CI)	PRR (95% CI)	IC(IC025)	EBGM(EBGM05)
Antipsychotics	Amisulpride	13	216.12 (121.38, 384.8)	192.22 (115.47, 319.97)	7.58 (6.79)	191.98 (118.47)
	Fluphenazine	35	145.77 (103.19, 205.93)	134.53 (98.32, 184.08)	7.07 (6.58)	134.09 (100.42)
	Loxapine	6	124.9 (54.53, 286.09)	116.55 (54.27, 250.32)	6.86 (5.75)	116.48 (58.22)
	Chlorpromazine	45	122.13 (90.21, 165.34)	114.16 (86.76, 150.2)	6.83 (6.4)	113.67 (88.22)
	Haloperidol	630	102.26 (94.15, 111.07)	96.92 (89.61, 104.82)	6.51 (6.39)	91.13 (85.04)
	Olanzapine	1,305	55.64 (52.46, 59)	54.13 (51.04, 57.41)	5.57 (5.49)	47.49 (45.21)
	Ziprasidone	219	40.94 (35.75, 46.87)	40.03 (34.9, 45.92)	5.29 (5.1)	39.21 (35.01)
	Lithium Carbonate	153	39.66 (33.74, 46.6)	38.8 (33.17, 45.39)	5.26 (5.03)	38.25 (33.41)
	Perphenazine	5	38.39 (15.82, 93.15)	37.58 (15.86, 89.02)	5.23 (4.06)	37.56 (17.89)
	Quetiapine	1,328	34.82 (32.85, 36.9)	34.23 (32.28, 36.3)	4.91 (4.82)	30 (28.58)
	Prochlorperazine	10	32.8 (17.54, 61.33)	32.21 (17.54, 59.14)	5.01 (4.15)	32.18 (19.06)
	Aripiprazole	888	25.01 (23.34, 26.8)	24.69 (23.28, 26.19)	4.5 (4.4)	22.68 (21.4)
	Risperidone	925	24.17 (22.58, 25.86)	23.87 (22.51, 25.32)	4.45 (4.35)	21.84 (20.64)
	Paliperidone	283	14.46 (12.84, 16.28)	14.35 (12.76, 16.14)	3.81 (3.64)	13.99 (12.67)
	Lumateperone	22	13.05 (8.58, 19.86)	12.96 (8.59, 19.56)	3.69 (3.1)	12.94 (9.11)
	Clozapine	607	11.53 (10.62, 12.51)	11.46 (10.6, 12.39)	3.44 (3.32)	10.85 (10.13)
	Cariprazine	31	11.49 (8.06, 16.36)	11.42 (8.03, 16.25)	3.51 (3.01)	11.39 (8.47)
	Asenapine	39	10.01 (7.31, 13.73)	9.96 (7.28, 13.63)	3.31 (2.86)	9.93 (7.63)
Antidepressants	Maprotiline	11	120.35 (65.29, 221.82)	112.58 (63.77, 198.75)	6.81 (5.97)	112.46 (67.42)
	Imipramine	22	45.21 (29.6, 69.07)	44.09 (29.21, 66.54)	5.46 (4.86)	43.99 (30.86)
	Clomipramine	28	40.84 (28.06, 59.44)	39.92 (27.51, 57.93)	5.32 (4.78)	39.82 (29.09)
	Fluvoxamine	25	34.18 (23, 50.8)	33.54 (22.66, 49.64)	5.06 (4.5)	33.46 (24.02)
	Mirtazapine	171	16.67 (14.32, 19.4)	16.52 (14.12, 19.32)	4.02 (3.81)	16.27 (14.33)
	Trazodone	30	9.85 (6.87, 14.1)	9.8 (6.89, 13.95)	3.29 (2.78)	9.77 (7.23)
	Paroxetine	174	7.88 (6.78, 9.16)	7.85 (6.71, 9.18)	2.95 (2.74)	7.74 (6.82)

(Continued on following page)

TABLE 2 (*Continued*) Signal strength for drugs associated with neuroleptic malignant syndrome.

WHO ATC category	Drug name	Case reports	ROR (95% CI)	PRR (95% CI)	IC(IC025)	EBGM(EBGM05)
Antiparkinson drugs	Biperiden	43	348.41 (250.95, 483.71)	290.28 (220.62, 381.93)	8.18 (7.71)	289.09 (219.68)
	Trihexyphenidyl	13	149.84 (84.99, 264.17)	137.97 (81.27, 234.21)	7.11 (6.32)	137.8 (85.75)
	Bromocriptine	32	53.19 (37.4, 75.65)	51.64 (37.01, 72.06)	5.69 (5.19)	51.48 (38.34)
	Entacapone	44	45.63 (33.81, 61.59)	44.49 (33.16, 59.7)	5.47 (5.04)	44.3 (34.47)
	Amantadine	41	24.98 (18.34, 34.02)	24.64 (18.01, 33.72)	4.62 (4.18)	24.55 (18.96)
	Benztropine	6	23.35 (10.43, 52.26)	23.05 (10.32, 51.48)	4.53 (3.45)	23.04 (11.74)
	Pergolide	4	22.08 (8.23, 59.2)	21.81 (8.19, 58.11)	4.45 (3.17)	21.8 (9.55)
	Pramipexole	78	15.81 (12.64, 19.77)	15.67 (12.63, 19.44)	3.96 (3.64)	15.56 (12.91)
	Cabergoline	20	11.57 (7.45, 17.97)	11.5 (7.47, 17.7)	3.52 (2.9)	11.48 (7.94)
	Stalevo 100 (levodopa/carbidopa/entacapon)	6	8.73 (3.91, 19.48)	8.69 (3.89, 19.41)	3.12 (2.05)	8.69 (4.44)
Antiepileptics	Valproic Acid	265	14.06 (12.44, 15.9)	13.96 (12.41, 15.7)	3.77 (3.59)	13.63 (12.3)
	Zonisamide	25	13.22 (8.91, 19.6)	13.13 (8.87, 19.43)	3.71 (3.15)	13.1 (9.42)
	Clonazepam	98	8.89 (7.29, 10.86)	8.85 (7.27, 10.77)	3.13 (2.85)	8.78 (7.43)
Anxiolytics	Lorazepam	124	14.75 (12.34, 17.61)	14.63 (12.26, 17.45)	3.85 (3.6)	14.47 (12.47)
	Buspirone	13	12.39 (7.18, 21.39)	12.31 (7.11, 21.31)	3.62 (2.86)	12.29 (7.79)
	Diazepam	90	9.2 (7.47, 11.33)	9.16 (7.38, 11.36)	3.18 (2.89)	9.09 (7.64)
Hyponotics and Sedatives	Dexmedetomidine	15	12.11 (7.29, 20.14)	12.04 (7.23, 20.04)	3.59 (2.88)	12.02 (7.86)
	Lemborexant	4	10.95 (4.1, 29.27)	10.89 (4.09, 29.02)	3.44 (2.17)	10.88 (4.78)
	Triazolam	7	7.83 (3.72, 16.45)	7.8 (3.7, 16.43)	2.96 (1.96)	7.79 (4.19)
Antivirals for systemic use	Favipiravir	4	1727.47 (431.97, 6908.26)	864.23 (435.21, 1716.15)	9.75 (8.18)	863.9 (270.88)
Anti-dementia drugs	Donepezil	102	20.37 (16.74, 24.78)	20.15 (16.56, 24.51)	4.32 (4.04)	19.96 (16.94)
Antihistamines for systemic use	Promethazine	24	11.76 (7.87, 17.57)	11.69 (7.9, 17.3)	3.54 (2.98)	11.66 (8.33)
Muscle relaxants	Dantrolene	5	31.3 (12.92, 75.81)	30.76 (12.99, 72.87)	4.94 (3.78)	30.74 (14.67)
Drugs for functional gastrointestinal disorders	Dicyclomine	4	12.25 (4.58, 32.76)	12.17 (4.57, 32.43)	3.6 (2.33)	12.17 (5.34)
Propulsives	Metoclopramide	118	9.5 (7.92, 11.4)	9.45 (7.92, 11.27)	3.23 (2.96)	9.36 (8.04)

Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; IC, information component; EBGM, empirical Bayes geometric mean; CI, confidence interval.

2020). Considering that these patients were also concurrently taking antipsychotic medications, we speculate that favipiravir may have influenced the metabolism of these medications to some extent. Its inhibitory effect on cytochrome P450 could disrupt the dopamine system, leading to neurotransmitter imbalance and potentially promoting the onset of NMS. However, there is currently

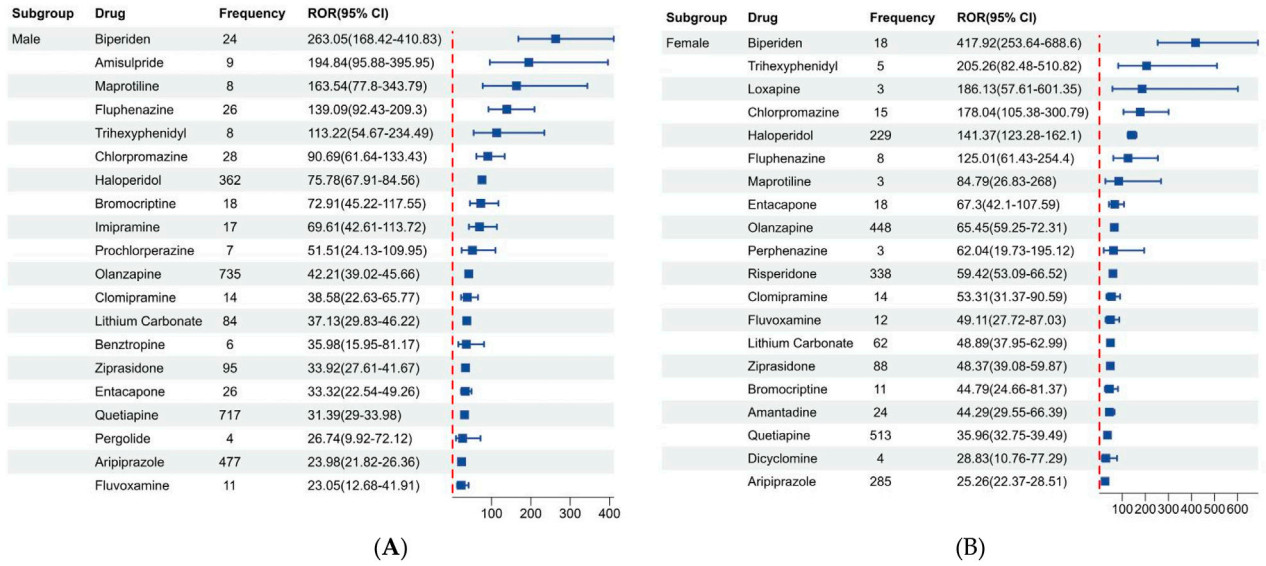


FIGURE 3
Signals detection among different gender groups. **(A)** Male group. **(B)** Female group.

insufficient evidence to fully explain the mechanism linking favipiravir to NMS. Based on the research findings, a causal relationship between favipiravir and NMS cannot be established. Firstly, coronaviruses are known for their neurotropic properties, which can lead to neurological and psychiatric symptoms ranging from peripheral to central nervous system involvement. In reported cases, some COVID-19 patients did not receive favipiravir, suggesting that the impact of COVID-19 on the central nervous system could increase susceptibility to the development of NMS. Furthermore, in the aforementioned cases, patients were also taking medications such as risperidone alongside favipiravir, and these medications were discontinued immediately following the onset of NMS. Therefore, the potential influence of antipsychotic drugs cannot be ruled out. In a word, when antipsychotic and anti-viral treatment is needed during any infection, especially in COVID-19, the risk of NMS should be taken into consideration.

Currently, there are some case reports about antidepressants triggering NMS (Garcia et al., 2001; Janati et al., 2012). In this study, antidepressants demonstrated a significant safety signal. The antidepressants included in the analysis comprise selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), as well as tricyclic antidepressants (TCAs). NMS may be associated with a dysregulation of the dopamine and serotonin systems. Antidepressants may potentially inhibit the release of dopamine by increasing serotonin levels, thereby affecting the development of NMS. Spivak et al. measured eight NMS patients and found that dopamine concentrations were significantly lower during acute NMS states, while serotonin concentrations and the serotonin/dopamine ratio tended to be higher (Spivak et al., 2000). If antidepressants were used in combination with antipsychotics, it may exacerbate the antipsychotic-induced dopamine depletion, further increasing the risk of NMS. Additionally, considerations need to be given to the pharmacokinetic factors in the occurrence of NMS. For example, paroxetine may increase the blood concentration of antipsychotic drugs by inhibiting the metabolism of drugs such as risperidone through CYP2D6 inhibition (Stevens, 2008).

This study also evaluated potential differences in NMS reporting based on sex and age. As described in the baseline profile, males comprised the majority of reported NMS submitted to the FDA, which aligns with prior literature indicating a higher incidence of NMS among males (Gurrera, 2017). One possible reason may be the difference in the incidence of mental and neurological disorders between genders. Diseases like schizophrenia and Parkinson's disease are more common in males, leading to males being more likely to be prescribed antipsychotics and antiparkinson drugs, thus increasing the risk of NMS (Bergen et al., 2014; Lubomski et al., 2014). In gender subgroup analysis, this study observed similar drug classes for signal strength in both males and females, which included antipsychotics, antiparkinson drugs, and antidepressants. However, in age subgroup analysis, the study found additional safety signals for antiepileptic drugs and benzodiazepines in the pediatric group compared to the adult group. Similarly, due to the different disease spectra of mental and neurological disorders, the types of medications used cannot be entirely consistent between pediatric and adult patients. In the indications recorded in this study, the proportion of pediatric epilepsy is higher than that in adults. Benzodiazepines are recommended for treating NMS, used for sedation and reducing peripheral muscle tone. There are literature reports of several cases developing NMS-like symptoms during withdrawal from benzodiazepines, hence considering a potential association between benzodiazepine withdrawal and NMS (Bobolakis, 2000; Kishimoto et al., 2013). The exact mechanism for how NMS is associated with antiepileptic is not yet completely understood. However, literature suggest that the co-administration of carbamazepine

10.3389/fphar.2024.1438661

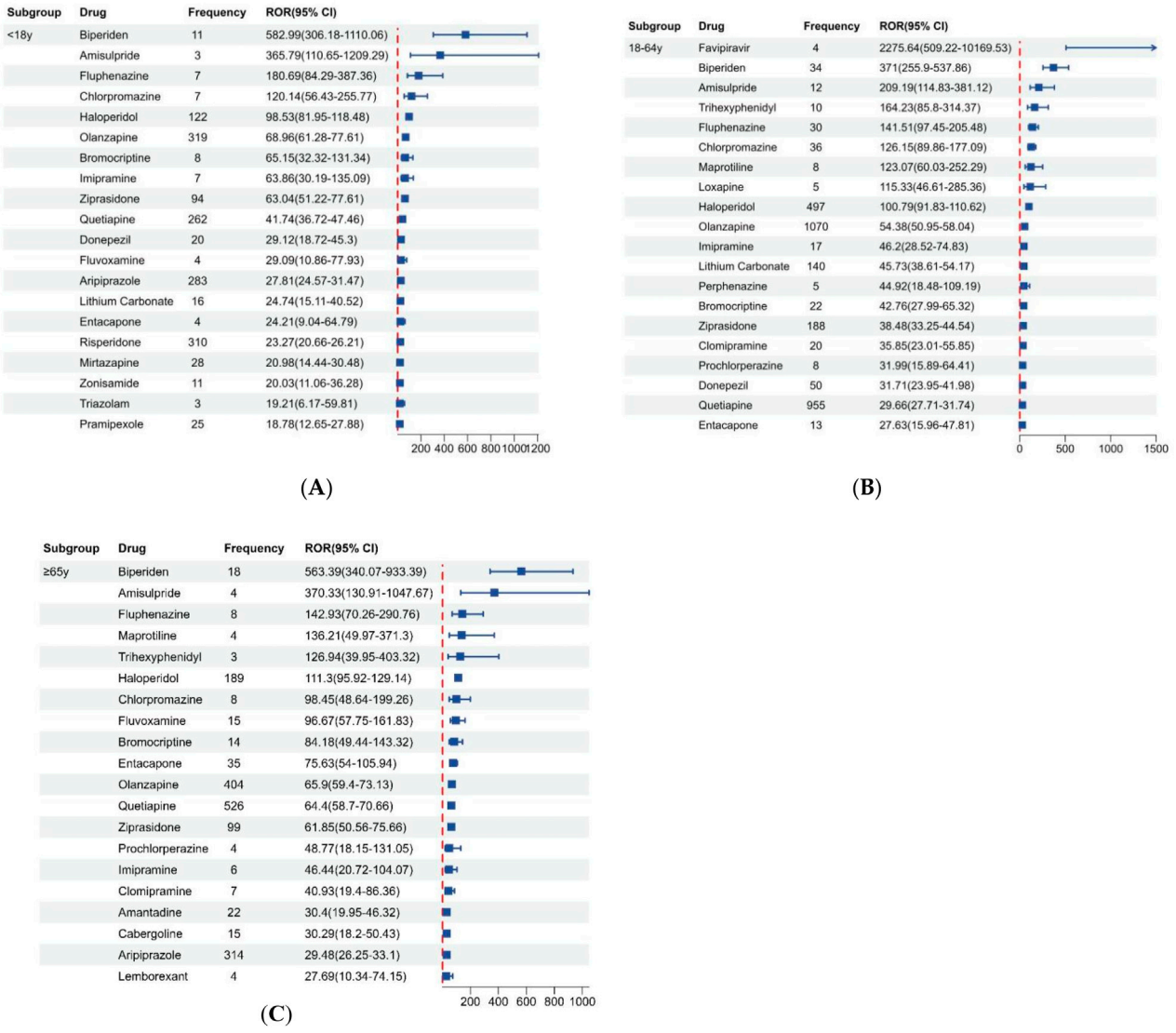


FIGURE 4
Signals detection based on patient age. **(A)** Age group under 18 years old. **(B)** Age group 18–64 years old. **(C)** Age group over 65 years old.

with tricyclic antidepressants and lamotrigine with antipsychotics may contribute to the occurrence of NMS, possibly due to the impact of antiepileptic drugs on the release of γ-aminobutyric acid (GABA) (Janati et al., 2012; Szota et al., 2020).

The current study has some strengths. First, FAERS is one of the largest public pharmacovigilance databases, with a sample size large enough to detect rare adverse events which would be difficult to detect in traditional epidemiological studies. Second, this study conducted subgroup analysis on different gender and age groups, providing essential insights for personalized medication management for different subgroup populations. Meanwhile, this study also has certain limitations. First, statistically detected signals cannot identify the causality between drugs and NMS. Second, due to limitations in the proactive, accurate, and timely reporting of adverse events by physicians and other healthcare providers, there may be possibilities of under-reporting and misreporting. Third, this study focuses on the safety signal analysis of a single drug. Due to the limitations of the database, further analysis of treatment regimens and drug dosage adjustments could not be conducted. However, in clinical practice, adjustments to medications and combination therapies may impact the occurrence of adverse events. Future research needs to further refine the analysis of these risk factors.

5 Conclusion

In conclusion, the present study comprehensively assessed NMS reports and associated drugs using the FAERS database. In addition to the known antipsychotic drugs, we detected significant safety signals related to NMS with non-antipsychotic medications such as antidepressants, antiparkinson drugs, and antiepileptic drugs. Also, future prospective clinical trials and epidemiologic investigations are needed to investigate the causal relationship between these drugs and NMS.

Data availability statement

The datasets presented in this study can be found in online repository: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Ethics statement

The studies involving humans were approved by the U.S. Food and Drug Administration. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing–original draft. WD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing–original draft. MW: Funding acquisition, Methodology, Software, Visualization, Writing–original draft. SiL: Methodology, Project administration, Supervision, Writing–review and editing. SoL: Methodology, Project administration, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by hospital-level medical research project of Chongqing Mental Health Center (2024-yjpy-07, 2024-yjfh-01).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1438661/full#supplementary-material

References

Belvederi Murri, M., Guaglianone, A., Bugliani, M., Calcagno, P., Respino, M., Serafini, G., et al. (2015). Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. *Drugs R. D.* 15 (1), 45–62. doi:10.1007/s40268-014-0078-0

Bergen, S. E., O'Dushlaine, C. T., Lee, P. H., Fanous, A. H., Ruderfer, D. M., Ripke, S., et al. (2014). Genetic modifiers and subtypes in schizophrenia: investigations of age at onset, severity, sex and family history. *Schizophr. Res.* 154 (1-3), 48–53. doi:10.1016/j.schres.2014.01.030

Berloffa, S., Dosi, C., Tascini, B., Fossati, B., Lupetti, I., and Masi, G. (2021). Neuroleptic malignant syndrome in children with autism spectrum disorder (asd): a case report and brief review of recent literature. *Child. (Basel)* 8 (12), 1201. doi:10.3390/children8121201

Bobolakis, I. (2000). Neuroleptic malignant syndrome after antipsychotic drug administration during benzodiazepine withdrawal. *J. Clin. Psychopharmacol.* 20 (2), 281–283. doi:10.1097/00004714-200004000-00033

Borah, P., Deb, P. K., Chandrasekaran, B., Goyal, M., Bansal, M., Hussain, S., et al. (2021). Neurological consequences of SARS-CoV-2 infection and concurrence of treatment-induced neuropsychiatric adverse events in COVID-19 patients: navigating the uncharted. *Front. Mol. Biosci.* 8, 627723. doi:10.3389/fmolb.2021.627723

Durbach, J. R., Rosen, G., De La Cuesta, C., and Gottlieb, S. (2022). Atypical neuroleptic malignant syndrome in a COVID-19 intensive care unit. *Cureus* 14 (8), e27923. doi:10.7759/cureus.27923

Espiridion, E. D., Mani, V., and Oladunjoye, A. O. (2021). Neuroleptic malignant syndrome after Re-introduction of atypical antipsychotics in a COVID-19 patient. *Cureus* 13 (2), e13428. doi:10.7759/cureus.13428

Garcia, G., Ghani, S., Poveda, R. A., and Dansky, B. L. (2001). Neuroleptic malignant syndrome with antidepressant/antipsychotic drug combination. *Ann. Pharmacother.* 35 (6), 784–785. doi:10.1345/aph.19368

Gökçen, O., and Akkuş, M. (2024). Neuroleptic malignant syndrome concurrent with COVID-19 infection: a case report. *Turk Psikiyatri Derg.* 35 (1), 75–77. doi:10.5080/u27125

Gurrera, R. J. (2017). A systematic review of sex and age factors in neuroleptic malignant syndrome diagnosis frequency. *Acta Psychiatr. Scand.* 135 (5), 398–408. doi:10.1111/acps.12694

Hirofuji, S., Miyasaka, K., Maezawa, M., Wakabayashi, W., Oura, K., Nakao, S., et al. (2023). Evaluation of neuroleptic malignant syndrome induced by antipsychotic drugs using spontaneous reporting system. *Heliyon* 9 (11), e21891. doi:10.1016/j.heliyon.2023.e21891

Janati, A. B., Alghasab, N., and Osman, A. (2012). Neuroleptic malignant syndrome caused by a combination of carbamazepine and amitriptyline. *Case Rep. Neurol. Med.* 2012, 183252. doi:10.1155/2012/183252

Kajani, R., Apramian, A., Vega, A., Ubhayakar, N., Xu, P., and Liu, A. (2020). Neuroleptic malignant syndrome in a COVID-19 patient. *Brain Behav. Immun.* 88, 28–29. doi:10.1016/j.bbi.2020.05.042

Kishimoto, S., Nakamura, K., Arai, T., Yukimasa, O., and Fukami, N. (2013). Postoperative neuroleptic malignant syndrome-like symptoms improved with intravenous diazepam: a case report. *J. Anesth.* 27 (5), 768–770. doi:10.1007/s00540-013-1602-z

Kocyigit, S. E., Soysal, P., and Isik, A. T. (2017). Neuroleptic malignant syndrome associated with only one dose of metoclopramide in an older adult. *Geriatr. Gerontol. Int.* 17 (8), 1232–1233. doi:10.1111/ggi.13044

Kyotani, Y., Zhao, J., Nakahira, K., and Yoshizumi, M. (2023). The role of antipsychotics and other drugs on the development and progression of neuroleptic malignant syndrome. *Sci. Rep.* 13 (1), 18459. doi:10.1038/s41598-023-45783-z

Lao, K. S. J., Zhao, J., Blais, J. E., Lam, L., Wong, I. C. K., Besag, F. M. C., et al. (2020). Antipsychotics and risk of neuroleptic malignant syndrome: a population-based cohort and case-crossover study. *CNS Drugs* 34 (11), 1165–1175. doi:10.1007/s40263-020-00767-9

Lubomski, M., Louise Rushworth, R., Lee, W., Bertram, K. L., and Williams, D. R. (2014). Sex differences in Parkinson's disease. *J. Clin. Neurosci.* 21 (9), 1503–1506. doi:10.1016/j.jocn.2013.12.016

Patil, V., Gupta, R., Verma, R., and Balhara, Y. P. (2016). Neuroleptic malignant syndrome associated with lithium toxicity. *Oman Med. J.* 31 (4), 309–311. doi:10.5001/omj.2016.59

Pileggi, D. J., and Cook, A. M. (2016). Neuroleptic malignant syndrome. *Ann. Pharmacother.* 50 (11), 973–981. doi:10.1177/1060028016657553

Singhai, K., Kuppili, P. P., and Nebhinani, N. (2019). Atypical neuroleptic malignant syndrome: a systematic review of case reports. *Gen. Hosp. Psychiatry* 60, 12–19. doi:10.1016/j.genhosppsych.2019.06.009

Soh, M., Hifumi, T., Isokawa, S., Shimizu, M., Otani, N., and Ishimatsu, S. (2020). Neuroleptic malignant syndrome in patients with COVID-19. *Am. J. Emerg. Med.* 38 (10), 2243.e1–2243.e3. doi:10.1016/j.ajem.2020.05.042

Spivak, B., Maline, D. I., Vered, Y., Kozyrev, V. N., Mester, R., Neduva, S. A., et al. (2000). Prospective evaluation of circulatory levels of catecholamines and serotonin in neuroleptic malignant syndrome. *Acta Psychiatr. Scand.* 102 (3), 226–230. doi:10.1034/j.1600-0447.2000.102003226.x

Stevens, D. L. (2008). Association between selective serotonin-reuptake inhibitors, second-generation antipsychotics, and neuroleptic malignant syndrome. *Ann. Pharmacother.* 42 (9), 1290–1297. doi:10.1345/aph.1L066

Szota, A. M., Radajewska, I., Grudzka, P., and Araszkiewicz, A. (2020). Lamotrigine, quetiapine and aripiprazole-induced neuroleptic malignant syndrome in a patient with renal failure caused by lithium: a case report. *BMC Psychiatry* 20 (1), 179. doi:10.1186/s12888-020-02597-x

Waqas, S., Talty, M., O'Keeffe, S., Flood, J., and Doherty, A. M. (2023). There is more to this fever than meets the eye: a case of neuroleptic malignant-like syndrome (NMLS) secondary to withdrawal of procyclidine and L-dopa on a background of long-standing flupenthixol depot use. *Ir. J. Psychol. Med.* 40 (2), 288–291. doi:10.1017/ipm.2020.14

Ware, M. R., Feller, D. B., and Hall, K. L. (2018). Neuroleptic malignant syndrome: diagnosis and management. *Prim. Care Companion CNS Disord.* 20 (1), 17r02185. doi:10.4088/PCC.17r02185

Wei, L., and Chen, Y. (2014). Neuroleptic malignant-like syndrome with a slight elevation of creatine-kinase levels and respiratory failure in a patient with Parkinson's disease. *Patient Prefer Adherence* 8, 271–273. doi:10.2147/ppa.S59150

Wittmann, O., Sadot, E., Bisker-Kassif, O., Scolnik, D., Tavor, O., and Glatstein, M. M. (2016). Neuroleptic malignant syndrome associated with metoclopramide use in a boy: case report and review of the literature. *Am. J. Ther.* 23 (5), e1246–e1249. doi:10.1097/mjt.0000000000000320

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 18 December 2024
DOI 10.3389/fphar.2024.1486422

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Mamunur Rashid,
University of Nebraska Medical Center, United States
Anoop Kumar,
Delhi Pharmaceutical Sciences and Research University, India

*CORRESPONDENCE
Yanjun Lu,
13792830916@163.com

RECEIVED 26 August 2024
ACCEPTED 05 December 2024
PUBLISHED 18 December 2024

CITATION
Lu Y, Xu Q and Zhu S (2024) Drug-induced coagulopathies: a real-world pharmacovigilance study using the FDA adverse event reporting system.
Front. Pharmacol. 15:1486422.
doi: 10.3389/fphar.2024.1486422

Drug-induced coagulopathies: a real-world pharmacovigilance study using the FDA adverse event reporting system

Yanjun Lu*, Qian Xu and Shita Zhu

Pharmacy Department, Xiamen Fifth Hospital, Xiamen, Fujian, China

Background: This study aims to investigate adverse drug reaction signals associated with coagulopathies through data mining using the Adverse Event Reporting System (FAERS) of the US Food and Drug Administration. Prompt identification of high-risk drugs provides a valuable basis for enhancing clinical drug safety.

Methods: The adverse event reports related to coagulopathies from Q1 2004 to Q2 2024 were extracted from the ASCII data packages in FAERS. The reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN) were used to identify adverse drug reaction signals associated with coagulopathies.

Results: During the reporting period, 40,545 reports were retrieved, with a slightly higher proportion of females than males. Among the top 30 drugs associated with the occurrence of coagulopathies, 24 drugs exhibited positive signals in risk analysis. Based on the individual drug reporting odds ratio (95% confidence interval) as a measure of risk signal strength, the top five drugs are as follows: gemcitabine [ROR (95% CI):16.87 (15.83–17.98)], busulfan [ROR (95% CI):15.51 (13.69–17.58)], anti-thymocyte globulin [ROR (95% CI):15.49 (13.49–17.78)], tacrolimus [ROR (95% CI):12.7 (11.57–13.95)], etonogestrel and ethinylestradiol vaginal ring [ROR (95% CI):11.88 (10.95–12.89)]. After categorizing the drugs, the strongest risk signal is sex hormones and modulators of the genital system [ROR (95% CI):11.88 (10.95–12.89)], followed by analgesics [ROR (95%CI): 6.73 (6.38–7.1)], immunosuppressants [ROR (95% CI):3.91 (3.76–4.05)], antineoplastic agents [ROR (95% CI):3.33 (3.22–3.45)], corticosteroids for systemic use [ROR (95% CI): 2.94 (2.73–3.18)], antiepileptics [ROR (95% CI): 1.93 (1.71–2.18)], drugs used in diabetes [ROR (95% CI):1.5 (1.34–1.67)], antibacterials for systemic use [ROR (95% CI):1.46 (1.28–1.68)].

Conclusion: Our findings indicate that multiple drugs are associated with an increased risk of coagulopathies. From the pharmacovigilance perspective, proactive analysis of these drugs aids in clinical monitoring and enhances risk identification of coagulopathies.

KEYWORDS

coagulopathies, FAERS database, adverse event, data mining, disproportionality analyses, pharmacovigilance

1 Introduction

Coagulopathies are diseases characterized by reduced blood clotting capacity, resulting in a pathological tendency toward bleeding and thrombosis (Iba et al., 2019a; Iba and Levy, 2020). Coagulopathies arise from various conditions, such as severe trauma, sepsis, cancer, hematological malignancies, and pregnancy-related complications (Levi, 2014; Lockhart et al., 2016; Iba et al., 2019b; Kleinveld et al., 2022). In addition, drug-induced coagulopathies are also common in clinical practice (Novak et al., 2012; Cui et al., 2019; Kumar et al., 2019). Coagulopathies can stem from platelet dysfunction, impaired thrombin generation, hypofibrinogenemia, and hyperfibrinolysis (Gando et al., 2016; Bartoszko and Karkouti, 2021). Coagulopathies are severe complications in patients, which can lead to multiple organ dysfunction and are linked to poorer patient prognosis (Helms et al., 2023; Li et al., 2023). Studies have shown that up to 56% of trauma patients and over 40% of critically-ill patients develop coagulopathies (Stensballe et al., 2017; Petros, 2019). Severe coagulopathies are associated with a more than fourfold increase in adverse bleeding events, blood transfusion volume, and mortality, along with prolonged hospital and ICU stays. This heightened risk highlights the importance of early identification and prevention of coagulopathies (Zhao et al., 2021; Li et al., 2023).

Clinical manifestations of coagulopathies are diverse, primarily including bleeding tendency (such as skin ecchymosis, joint hematoma, and visceral hemorrhage), thrombosis (e.g., deep vein thrombosis and pulmonary embolism). They are usually accompanied by abnormal laboratory results, such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen concentration, platelet count, function testing, and special coagulation factor testing (Moore et al., 2020; Giustozzi et al., 2021; Gómez-Mesa et al., 2021). Drugs can affect the coagulation system through multiple biomolecules and signal pathways. For example, some drugs inhibit the activity of catalases, while others cause bleeding by interfering with the interaction between platelets and blood vessel walls. These complex mechanisms of action complicate the diagnosis and treatment of drug-induced coagulopathies (Cassar et al., 2005; Xiao et al., 2013; Izzedine and Perazella, 2015; Bauer et al., 2022). Due to the complex pathogenesis and diagnostic challenges of coagulopathies, which often require multidisciplinary collaboration, research in this area is limited. Identifying drugs closely linked to coagulopathies is essential, as it enables medical institutions to develop precise monitoring and intervention strategies while providing critical safety information for clinicians and pharmacists to support safer drug use for patients.

Currently, information on adverse reactions related to coagulopathies is mainly recorded in drug labels. Although drug safety is evaluated in clinical trials, these clinical trials may not fully capture the real-world scenario due to sample limits, treatment duration, and co-morbid conditions (Javed and Kumar, 2024). Therefore, conducting real-world research offers a more comprehensive approach to understanding drug safety. Although identifying drugs related to coagulopathies is crucial, no comprehensive list of these drugs currently exists. While most existing research focuses on evaluating the coagulopathy risks of individual drugs, it is equally important to investigate coagulopathies associated with a broader range of medications (Chai and Babu, 2014; Cui et al., 2019; Peralta et al., 2019; Guo et al., 2022).

Compared to laboratory and clinical trial data, pharmacovigilance data reflects real-world drug use more accurately and is vital for post-market surveillance (Raschi et al., 2020b). The FAERS is the largest public drug alert database for spontaneous reports of adverse events, gathering data from medical personnel, consumers, manufacturers, *etc.* It plays an essential role in informing healthcare professionals and the public about the potential risks of drugs (Sakaeda et al., 2013; Raschi et al., 2019; Raschi et al., 2020a).

A signal is new or previously unknown information linking an adverse event to a drug (Javed and Kumar, 2024). Generating a signal requires more than one high-quality report (Subeesh et al., 2017; Sharma and Kumar, 2022). Data mining algorithms (DMAs) such as reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN) are common analytical methods for detecting signals in pharmacovigilance databases (Kubota et al., 2004; Rothman et al., 2004). These methods identify patterns of associations or unexpected occurrences of events in large databases using statistical analysis.

The purpose of this study is to comprehensively investigate the risks of drug-induced coagulopathies through the FAERS and identify drugs with potential coagulopathy risks that are not listed in the package insert. This research aims to provide an overview of drugs that may induce coagulopathies from a pharmacovigilance perspective, offering valuable insights for clinical practice.

2 Materials and methods

2.1 Data sources and processing procedures

The FAERS database is the central system for post-marketing adverse drug reaction monitoring in the United States and is also one of the main approaches for current pharmacovigilance research (Zhang et al., 2024). In our study, ASCII data packages submitted from the first quarter of 2004 to the second quarter of 2024 were retrieved from the database. Each package contains demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates for reported drugs (THER), indications for use (INDI) (Yang et al., 2022). Import all data analysis into R version 4.3.3 and Excel software for data cleaning and analysis. Delete duplicate data according to the FDA's suggestion. If the case has the same case ID, it will retain the latest report with FDA_DT; if the case ID is the same as the FDA_DT, it will retain a large master ID. After the repeated data is eliminated, some primary ID repeated items are still found, so the auxiliary duplicate data is performed (Yu et al., 2021).

The symptoms of AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is an internationally standardized and clinically validated terminology system (Kumar et al., 2019). In the FAERS database, encode each report using the

TABLE 1 Summary of algorithms used for signal detection.

Measure	Calculation formula	Criteria
ROR	ROR = ad/bc	a≥3; lower limit of 95% CI > 1
	95%CI = $e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)0.5}$	
PRR	PRR = a (c + d)/c (a + b)	a≥3; PRR≥2, $\chi^2 \geq 4$
	χ^2 = [(ad-bc)2](a+b + c + d)/[(a+b) (c + d) (a+c) (b + d)]	
BCPNN	IC = log2a (a+b + c + d)/[(a+c) (a+b)]	IC025 > 0
	95%CI = E (IC)±2 [V(IC)]^0.5	

PRR, proportional reporting ratio; ROR, reporting odds ratio; BCPNN, bayesian confidence propagation neural network; a, number of reports with coagulation dysfunction caused by the target drug; b, number of reports with other AEs, caused by the target drug; c, number of reports with coagulation dysfunction caused by other drugs; d,number of reports with other AEs, caused by other drugs; CI, confidence interval; IC, information component; IC025, the lower limit of the 95% CI, of the IC; E (IC), the IC, expectations; V (IC), the variance of IC.

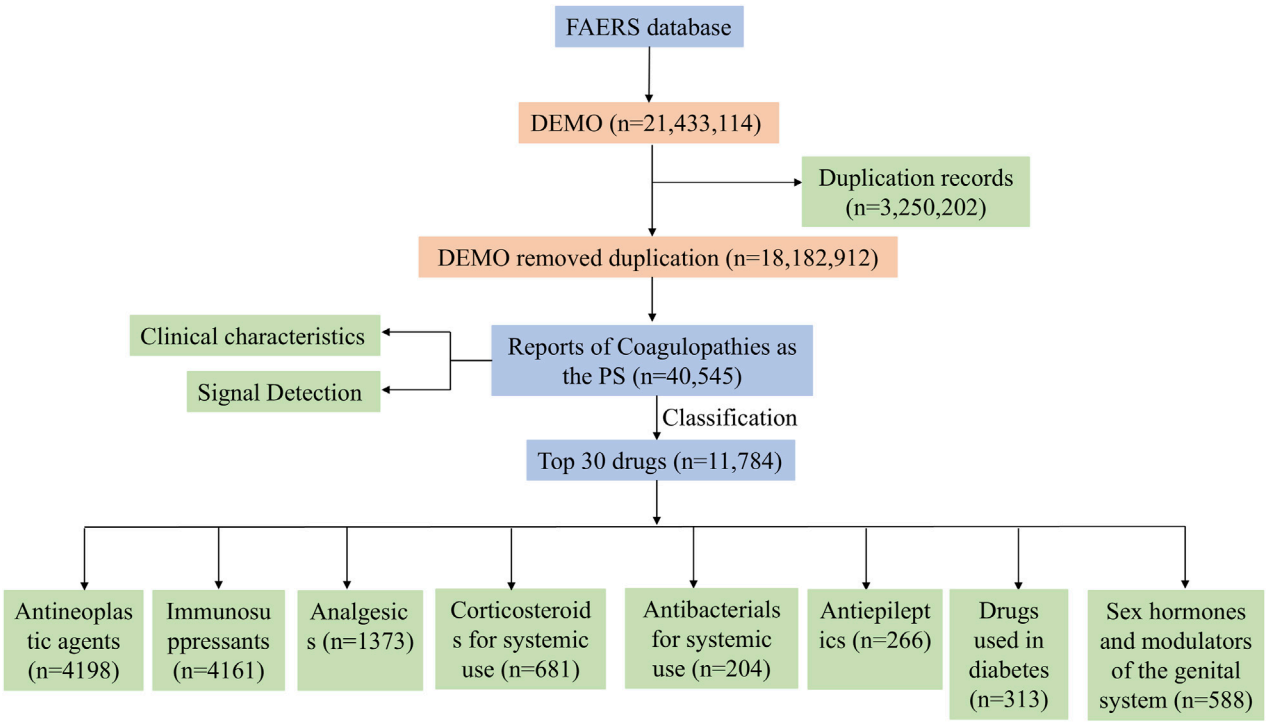


FIGURE 1
Flow chart for identifying suspected coagulopathies reports.

preferred term (PT) from MedDRA terminology, which is categorized into High-Level Term (HLT), High-Level Group Term (HLGT), and System Organ Class (SOC) in MedDRA (Zhang et al., 2023; Li et al., 2024). According to the latest MedDRA 27.0 version, our study searched for "coagulopathies (MedDRA 10064477)" at the HLT level and identified 26 related PTs, mainly including coagulopathy, disseminated intravascular coagulation, thrombotic microangiopathy, hypercoagulation, antiphospholipid, *etc.* In line with MedDRA 27.0 standards, only "primary suspect (PS)" drugs coded by PT were included to focus on the highest level of suspicion for drug-related coagulopathies. The Anatomical Therapeutic Chemical (ATC) classification system was used to code the preliminary drug list, the final drug list for analysis was obtained after excluding ambiguous drug names and integrating drugs with the same ingredient (Fan et al., 2024; Li et al., 2024).

2.2 Data analysis

In this study, we employed ROR, PRR, and BCPNN to identify signals for potential increased risk of drug-related coagulopathies (Poluzzi et al., 2009; Sakaeda et al., 2013; Sharma and Kumar, 2022; Zou et al., 2023; Javed and Kumar, 2024). The ROR and PRR

TABLE 2 Clinical characteristics of reported drug-induced coagulopathies.

Characteristics	Reports, n (%)
Age	
<18	3,675 (9.1)
>85	974 (2.4)
18–64.9	16,547 (40.8)
65–85	10,419 (25.7)
Unknown	8,930 (22.0)
Gender	
Male	17,893 (44.1%)
Female	18,734 (46.2%)
Unknown	3,918 (9.7%)
Reporting country	
United States	14,951 (36.9)
Japan	7,310 (18)
France	1876 (4.6)
Germany	1,225 (3.0)
Spain	1,151 (2.8)
Others or unknown	14,032 (34.6)
Outcome	
Death	13,183 (32.5)
Hospitalization or prolongation of hospitalization	12,511 (30.9)
Life-threatening	4,558 (11.2)
Disability	180 (0.4)
Congenital anomaly	28 (0.1)
Others or unknown	10,085 (24.9)

algorithms are frequentist (non-Bayesian) algorithms, which are simple to calculate and have high sensitivity. The advantage of ROR is that it corrects for bias due to the low number of reports of certain events compared to PRR, while the advantage of PRR is that it is less affected by the omission of adverse events (Evans et al., 2001; Rothman et al., 2004). BCPNN, a Bayesian algorithm, effectively integrates data from multiple sources and supports cross-validation (Kubota et al., 2004). It accounts for uncertainties in the disproportionate rate, especially with smaller adverse event samples, reduces false positives, and is used for pattern recognition in higher dimensions (Tang et al., 2022). This study combines multiple algorithms to leverage their respective strengths, expanding the detection range and cross-validating results to enhance sensitivity and specificity in signal detection (Noguchi et al., 2018; Zhou et al., 2023). Higher values of these parameters indicate stronger signal strength, representing the level of association between drugs and coagulopathies. The formulas and criteria for each algorithm are shown in Table 1 (Sharma et al., 2023; Liu et al., 2024). Positive signals are identified if any of the three methods' criteria are met, indicating a possible association between the drugs and the event (Alenzi et al., 2024).

3 Results

3.1 Descriptive analysis

3.1.1 The basic process for retrieving adverse event reports of target drugs

A total of 21, 433, 114 reports were retrieved from the FAERS database. After data cleaning and analysis, 40,545 reports on coagulopathies were collected. We found that 4,687 drugs are related to coagulopathies. After removing anticoagulant and antiplatelet drugs, we conducted a comprehensive analysis of the top 30 drugs, which is detailed in the flowchart (Figure 1).

3.1.2 Clinical information on adverse event reports

Detailed information on the adverse event reports of the patient was introduced in Table 2. As for patients, males reported 17,893 (44.1%) adverse event reports, while females submitted 18,734 (46.2%), with a slightly higher number of reports from females than males. Regarding age composition, patients aged 18–64.9 submitted 16,547 (40.8%) adverse event reports, accounting for the most significant proportion. These data come from submissions from many countries. The United States is the most extensive reporting country, and it submitted 14,951 (36.9%) reports, followed by Japan, which submitted 7,310 (18%) adverse event reports. In terms of the ending of the patient, the number of "deaths" in patients is the largest, with a total of 13,183 (32.5%) adverse event reports, followed by "hospitalization or prolongation of hospitalization" with 12,511 (30.9%) adverse event reports. In terms of reporting year, 2014 had the highest reported cases (Figure 2). After searching the PTs contained in "coagulopathies", a total of 26 related PTs were obtained. Among them, "coagulopathy" is the most reported PT (Table 3).

3.2 Drugs that increase the risk of coagulopathies

To evaluate the risk signals associated with various drugs that cause coagulopathies, analyze the top 30 drugs with representative reported quantities. These drugs can be divided into the following categories: antineoplastic agents, immunosuppressants, analgesics, corticosteroids for systemic use, sex hormones and modulators of the genital system, antiepileptics, drugs used in diabetes, antibacterials for systemic use. We analyzed the risk signal intensity of individual drugs, and the specific analysis results are shown in Figure 3 and Supplementary Table S1. At the same time, we also evaluated the strength of risk signals after classification, and a comprehensive summary of the detailed analysis is provided in Figure 4 and Supplementary Table S2. To provide a more comprehensive profile of these top 30 drugs, we compiled a list of drugs containing indications, dose, mode of administration, and adverse effects based on drug labels, which are summarized in Supplementary Table S3.

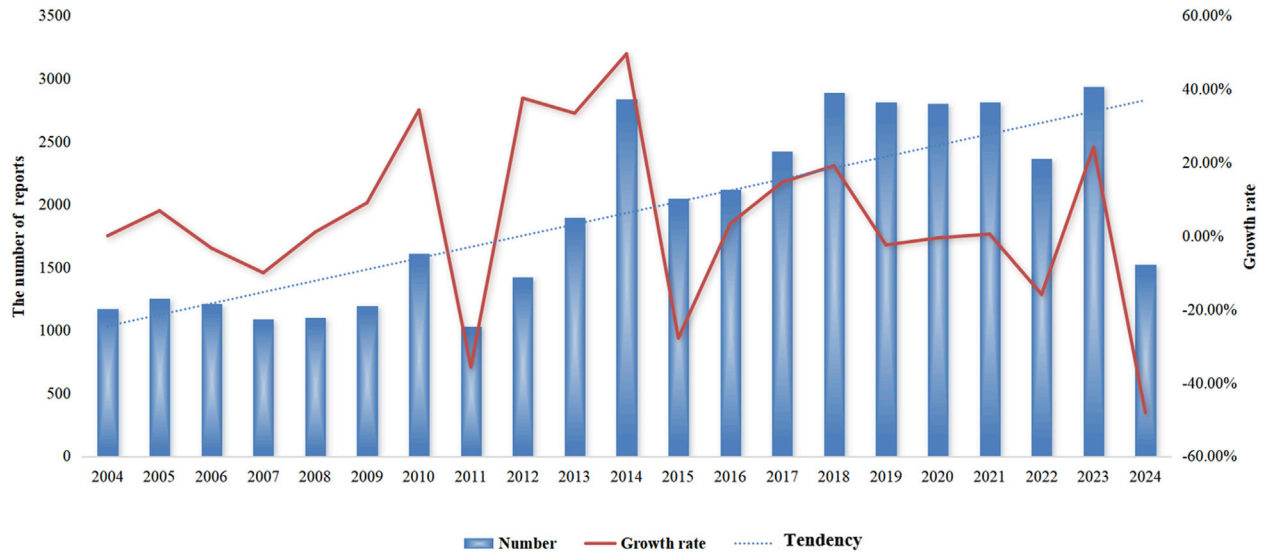


FIGURE 2
Annual trend in reporting of adverse drug events related to coagulopathies.

3.2.1 Single drug risk signal detection

From Supplementary Table S1, it can be seen that 24 drugs exhibit positive signals. The top 5 drugs with positive signals are gemcitabine [ROR (95% CI):16.87 (15.83–17.98)], busulfan [ROR (95% CI):15.51 (13.69–17.58)], anti-thymocyte globulin [ROR (95% CI):15.49 (13.49–17.78)], tacrolimus [ROR (95% CI):12.7 (11.57–13.95)], etonogestrel and ethinylestradiol vaginal ring [ROR (95% CI):11.88 (10.95–12.89)]. Other positive signal drugs are arranged in order of risk signal strength: eculizumab, ciclosporin, mycophenolate mofetil, paracetamol, prednisolone, cyclophosphamide, bevacizumab, carboplatin, dexamethasone, sunitinib, cytarabine, nivolumab, lamotrigine, pembrolizumab, ibuprofen, capecitabine, metformin, ciprofloxacin, methotrexate. The larger the value of the ROR, the stronger the risk signal, indicating a greater risk of causing coagulopathies. The higher the ROR value, the greater the possibility of adverse events related to the use of specific drugs.

3.2.2 Risk signals after classification of drugs

After the drug classification, the ranking is based on ROR: sex hormones and modulators of the genital system [ROR (95% CI): 11.88 (10.95–12.89)], analgesics [ROR (95%CI): 6.73 (6.38–7.1)], immunosuppressants [ROR (95% CI):3.91 (3.76–4.05)], antineoplastic agents [ROR (95% CI):3.33 (3.22–3.45)], corticosteroids for systemic use [ROR (95% CI): 2.94 (2.73–3.18)], antiepileptics [ROR (95% CI):1.93 (1.71–2.18)], drugs used in diabetes [ROR (95% CI):1.5 (1.34–1.67)], antibacterials for systemic use [ROR (95% CI):1.46 (1.28–1.68)]. The strongest risk signal is sex hormones and modulators of the genital system, followed by analgesics, immunosuppressants, antineoplastic agents, corticosteroids for systemic use, antiepileptics, drugs used in diabetes, antibacterials for systemic use.

4 Discussion

This study provides a comprehensive and systematic investigation of adverse events related to drug-induced coagulopathies using the FAERS database. We identified drugs significantly associated with coagulopathies based on case numbers and signal strength. We observed that some drugs do not list coagulopathy-related adverse reactions in their labeling, highlighting the need to further explore drugs closely associated with coagulopathies.

To minimize bias and reduce the occurrence of false positives and false negatives, we used ROR, PRR, and BCPNN methods for analysis. A total of 24 drugs exhibited positive signals in the risk analysis. In addition, standardized naming was used to ensure precise and reliable analysis of our findings. According to their pharmacological effects, the drugs with positive signals can be divided into the following categories: anti-tumor drugs, immunosuppressants, anti-inflammatory and analgesic drugs, hypoglycemic drugs, antiepileptic drugs, steroid hormone drugs, antibacterial drugs, and contraceptive drugs. Higher ROR values indicate a greater risk of coagulopathy-related adverse reactions. Our research provides a basis for clinicians to make informed prescribing decisions and serves as a reminder for healthcare professionals to be vigilant about potential coagulopathies of these drugs in clinical practice.

Anti-tumor drugs accounted for the largest proportion of coagulopathy cases in our study. The incidence of coagulopathies in cancer patients is approximately 6%–15%. With cancer increasingly managed as a chronic disease and the use of new drugs on the rise, their incidence rate is expected to rise (Lechner and Obermeier, 2012; Al-Nouri et al., 2015). Anti-tumor drug therapies appear to be more common contributors to coagulopathies than cancer itself, with associated conditions including thrombotic microangiopathy (TMA),

TABLE 3 Number of drugs associated with PT group.

Group	Code	No. (%) of drugs
Coagulopathy	10,009802	15057 (35.84)
Disseminated Intravascular Coagulation	10,013442	12954 (30.83)
Thrombotic Microangiopathy	10079988	8,050 (19.16)
Hypercoagulation	10020608	1771 (4.22)
Antiphospholipid Syndrome	10002817	1,395 (3.32)
Factor Viii Inhibition	10048619	1,007 (2.40)
Hypocoagulable State	10020973	861 (2.05)
Abnormal Clotting Factor	10049862	198 (0.47)
Factor V Inhibition	10056335	180 (0.43)
Factor Ix Inhibition	1,0051778	127 (0.30)
Heparin Resistance	10059598	93 (0.22)
Hyperfibrinogenaemia	10051124	61 (0.15)
Coagulation Disorder Neonatal	10009732	55 (0.13)
Hyperfibrinolysis	10074737	52 (0.12)
Activated Protein C Resistance	10067648	33 (0.08)
Von Willebrand'S Factor Inhibition	10070690	30 (0.07)
Factor Xiii Inhibition	10059608	27 (0.06)
Disseminated Intravascular Coagulation In Newborn	10013443	25 (0.06)
Factor Vii Inhibition	10075240	16 (0.04)
Acquired Dysfibrinogenaemia	10051122	7 (0.02)
Lupus Anticoagulant Hypoprothrombinaemia Syndrome	10085219	4 (0.01)
Hyperprothrombinaemia	10067920	3 (0.01)
Hyperthrombinaemia	10058516	3 (0.01)
Factor Ii Inhibition	10075242	2 (0.00)
Factor X Inhibition	10075241	1 (0.00)
Pseudo-Heparin Resistance	10088924	1 (0.00)

thrombocytopenia, intravascular thrombosis, and ischemia-induced terminal organ damage (Izzedine and Perazella, 2015; Jodele et al., 2015). The chemotherapeutic drugs most frequently associated with coagulopathies are mitomycin-C and gemcitabine (Aklilu and Shirali, 2023). In our study, gemcitabine demonstrated the highest ROR value and risk intensity. Gemcitabine is a pyrimidine analog that promotes apoptosis in rapidly dividing cells by disrupting DNA synthesis (Pandit and Royzen, 2022). Numerous studies have reported gemcitabine-induced coagulopathies, and the use of gemcitabine may increase the incidence of cancer patients (Grall et al., 2021; Ishikawa et al., 2021; van der Heijden et al., 2023). While the mechanism of gemcitabine-induced coagulopathies remains unclear, it is hypothesized to involve microvascular endothelial damage and immune complex-mediated endothelial injury (Mini et al., 2006; Zupancic et al., 2007). Carboplatin, a second-generation platinum-based anticancer drug, is cell cycle non-specific and exerts anti-tumor effects by interfering with DNA synthesis and replication (Ettinger et al., 2022; Porter et al., 2023). It has been reported that carboplatin alone or in combination with other drugs can induce coagulopathies (Iams et al., 2013; Salhi et al., 2021). Given that many cancer patients are treated with multiple chemotherapy drugs, identifying the specific causative agent of coagulopathies can be challenging. Drug-induced coagulopathies may disrupt anti-tumor treatment in patients and increase the risk of cancer progression. Our study aims to discover drugs closely related to coagulopathies, which can help clinicians discover adverse drug reactions during treatment, support preventive measures and promote rational drug use in clinical practice.

Immunosuppressants-induced coagulopathies also accounted for a substantial proportion of cases in our study. Coagulopathies are a severe adverse reaction of immunosuppressants, mainly manifested as systemic platelet aggregation, thrombocytopenia, and mechanical damage to red blood cells (George and Nester,

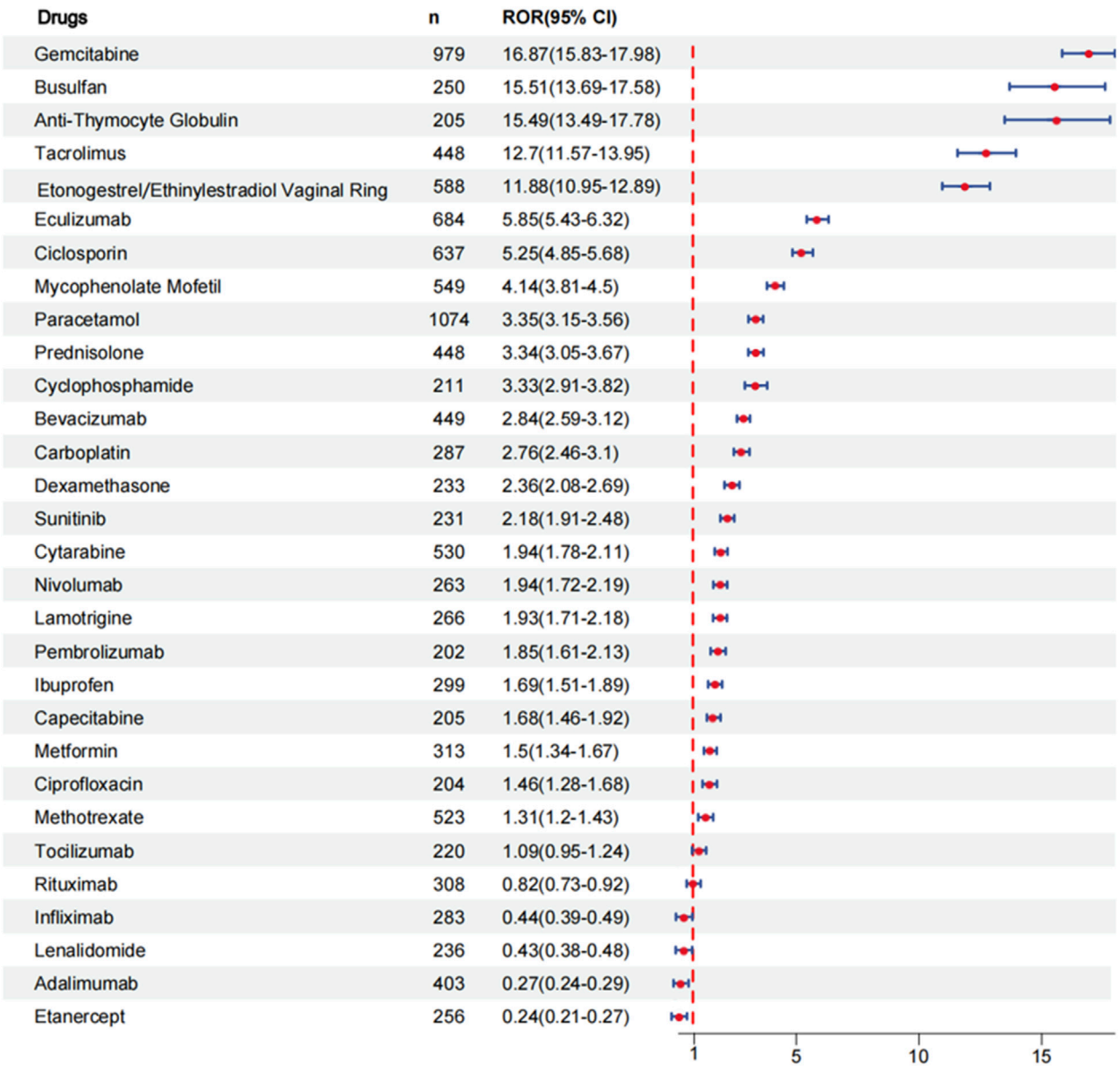


FIGURE 3
ROR for coagulopathies of single drug.

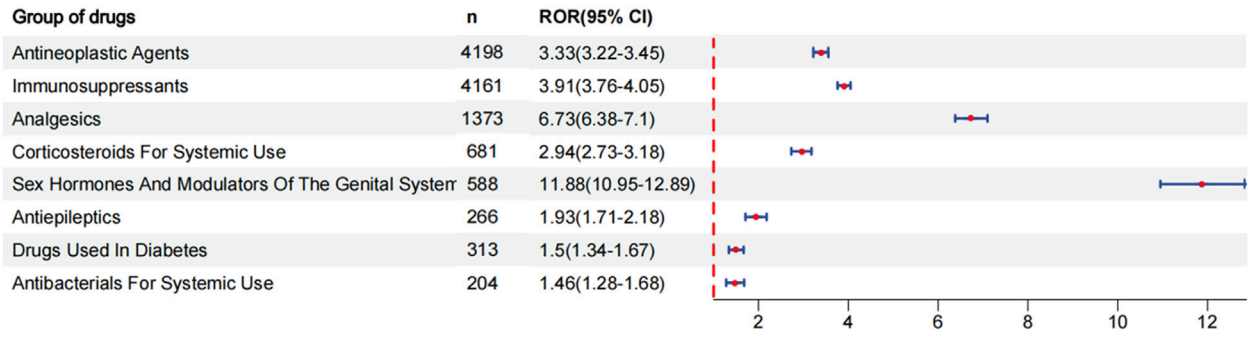


FIGURE 4
ROR for coagulopathies of each group of drugs.

2014). The mechanism behind immunosuppressant-induced coagulopathies may involve immune-mediated responses as well as dose- or duration-dependent toxicity (Bhavsar et al., 2016). Endothelial injury triggers the formation of microthrombi and platelet aggregation in the vascular system (Nwaba et al., 2013). Tacrolimus is a calcineurin inhibitor commonly used as an immunosuppressant post-solid organ transplants. There have been many reports on coagulopathies caused by tacrolimus (Nwaba et al., 2013; Cortina et al., 2015; Markan et al., 2021), and some have been fatal (Gill and Meghrajani, 2022). There are also some reports of coagulopathies caused by the combination of tacrolimus and ciclosporin; both drugs showed strong signals in our study (Pham et al., 2000). Recently, there have been reports that vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab can lead to coagulopathies. VEGF stimulates signaling pathways and transcription by activating its receptor VEG-FR2, which is crucial for angiogenesis. Bevacizumab disrupts this pathway, leading to thrombotic microvascular disease (Apte et al., 2019; Estrada et al., 2019).

Our study reveals that sex hormones and reproductive system regulators have the highest risk of inducing coagulopathies. Compelling evidence suggests that female hormone replacement therapies and combination oral contraceptives can induce coagulopathies and increase the risk of venous thromboembolism (Watson, 2007). The formation of coagulopathies may be related to the increased plasma concentrations of procoagulant proteins, reduced anticoagulant proteins, and altered fibrinolysis (Gialeraki et al., 2017; Teal and Edelman, 2021). Studies have shown that patients with oral contraceptives may face a significantly increased risk of developing coagulopathies during the perioperative period (Watson, 2007). Especially for patients with compound oral contraceptives, the probability of occurrence of coagulopathies is 2–4 times higher compared to patients who do not use them (Haverinen et al., 2022). The risk of coagulopathies is dose-dependent on the dose of sex hormones used (Weill et al., 2016). Excessive use of antipyretic and analgesic drugs can also lead to coagulopathies, characterized by an increased prothrombin time and international normalized ratio (Larson et al., 2005; Habib et al., 2013). Some antibiotics can increase the risk of coagulopathies, which has been confirmed in multiple studies, such as cefoperazone sulbactam, tigecycline, and linezolid (Routsi et al., 2015; Hakeam et al., 2018; Cui et al., 2019; Treml et al., 2021; Wu et al., 2021). Our study found that ciprofloxacin is associated with coagulopathies, although few studies have been conducted.

In our study, we identified some (OTC) drugs, such as paracetamol and ibuprofen, as potentially associated with coagulopathies, even though they can be purchased without a prescription. Patients should carefully read instructions before using OTC drugs, strictly follow the recommended dosage and frequency, and avoid altering the dosage or administration method (Sánchez-Sánchez et al., 2021). If symptoms of coagulopathies appear, such as severe bleeding or uncontrollable bleeding, patients should discontinue use immediately and seek medical attention (Tan et al., 2020). Pharmacists should assess patients on their health status, allergy history, medication history, and any concurrent treatments that could influence coagulopathy risk when dispensing OTC drugs. Governments, medical institutions, and pharmaceutical manufacturers can collaborate to raise awareness about the adverse reactions associated with OTC drugs and help to enhance patients' understanding of these potential risks (Gheorghe et al., 2019; Yousaf et al., 2020). Open communication between patients and healthcare providers is crucial to optimize patient care and ensure safety. Documenting the medical history of patient is a critical step in prevention, especially for those with a history of coagulopathies, who should exercise particular caution. For critically ill patients using these drugs, regular blood coagulation testing is particularly necessary (Song et al., 2020; Fan et al., 2024). In our study, monitoring cases of coagulopathies associated with any drug in the FAERS database was critical for helping clinicians properly diagnose and manage this condition. Comprehensive information enables healthcare providers to make informed treatment decisions and apply strategies to reduce the risk of drug-induced coagulopathies.

We found that many drugs with an elevated risk of coagulopathies, such as Mycophenolate Mofetil, Carboplatin, Cytarabine, Nivolumab, Metformin, Rituximab, and Infliximab, were not listed with coagulopathy risks in their instructions. Some drugs, such as Paracetamol, Prednisolone, Dexamethasone, and IbuProfen. In the instructions, only their use will affect the efficacy of oral anticoagulant drugs, but coagulopathies are not mentioned in adverse reactions. Although many drugs have been on the market for a long time, awareness of coagulopathy risks is limited, and data on the prevention and management of drug-induced coagulopathies remain sparse. Monitoring drug-induced coagulopathies is crucial, particularly for cancer and critically ill patients, as it may reduce mortality rates. With the advent of new drugs, especially anti-tumor drugs and immunosuppressants, continuous monitoring of drug-induced coagulopathies will better inform clinicians in making optimal treatment decisions.

This study has several limitations. First, the study established only the association between drugs and adverse events, while lacking definitive proof of the causal relationship between drug exposure and the reported event (Tobaiqy et al., 2010; Jain et al., 2023). Second, the FAERS data was based on spontaneous and voluntary reports, which may be influenced by recent research findings or media coverage (Fan et al., 2024; Jiang et al., 2024). Third, our study did not account for the impact of concomitant drugs and secondary suspect drugs (SS) on adverse reactions. Finally, this study did not assess whether coagulopathy-related adverse reactions are dose-dependent.

5 Conclusion

In summary, coagulopathies represent severe adverse reactions, with some cases leading to fatal outcomes, particularly among patients with severe illness and cancer. Despite the serious nature of coagulopathies, the risks have not been sufficiently assessed. In this study, we conducted a comprehensive evaluation of drugs related to coagulopathies using the FAERS database and systematically analyzed the top 30 drugs with strong risk signals. For clinical use, we recommend enhanced drug safety monitoring to reduce the risk of coagulopathies when administering these medications.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

YL: Data curation, Formal Analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing. QX: Data curation, Investigation, Writing–original draft. SZ: Data curation, Investigation, Writing–original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1486422/full#supplementary-material

References

Aklilu, A. M., and Shirali, A. C. (2023). Chemotherapy-associated thrombotic microangiopathy. *Kidney360* 4 (3), 409–422. doi:10.34067/kid.0000000000000061

Alenzi, K. A., Alsuhaibani, D., Batarfi, B., and Alshammari, T. M. (2024). Pancreatitis with use of new diabetic medications: a real-world data study using the post-marketing FDA adverse event reporting system (FAERS) database. *Front. Pharmacol.* 15, 1364110. doi:10.3389/fphar.2024.1364110

Al-Nouri, Z. L., Reese, J. A., Terrell, D. R., Vesely, S. K., and George, J. N. (2015). Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood* 125 (4), 616–618. doi:10.1182/blood-2014-11-611335

Apte, R. S., Chen, D. S., and Ferrara, N. (2019). VEGF in signaling and disease: beyond discovery and development. *Cell* 176 (6), 1248–1264. doi:10.1016/j.cell.2019.01.021

Bartoszko, J., and Karkouti, K. (2021). Managing the coagulopathy associated with cardiopulmonary bypass. *J. Thrombosis Haemostasis* 19 (3), 617–632. doi:10.1111/jth.15195

Bauer, A. T., Gorzelanny, C., Gebhardt, C., Pantel, K., and Schneider, S. W. (2022). Interplay between coagulation and inflammation in cancer: limitations and therapeutic opportunities. *Cancer Treat. Rev.* 102, 102322. doi:10.1016/j.ctrv.2021.102322

Bhavsar, K. V., Lin, S., Rahimy, E., Joseph, A., Freund, K. B., Sarraf, D., et al. (2016). Acute macular neuroretinopathy: a comprehensive review of the literature. *Surv. Ophthalmol.* 61 (5), 538–565. doi:10.1016/j.survophthal.2016.03.003

Cassar, K., Bachoo, P., Ford, I., Greaves, M., and Brittenden, J. (2005). Clopidogrel has no effect on D-dimer and thrombin-antithrombin III levels in patients with peripheral arterial disease undergoing peripheral percutaneous transluminal angioplasty. *J. Vasc. Surg.* 42 (2), 252–258. doi:10.1016/j.jvs.2005.04.027

Chai, P., and Babu, K. (2014). Toxin-induced coagulopathy. *Emerg. Med. Clin. N. Am.* 32 (1), 53–78. doi:10.1016/j.emc.2013.10.001

Cortina, G., Trojer, R., Waldegger, S., Schneeberger, S., Gut, N., and Hofer, J. (2015). *De novo* tacrolimus-induced thrombotic microangiopathy in the early stage after renal transplantation successfully treated with conversion to everolimus. *Pediatr. Nephrol.* 30 (4), 693–697. doi:10.1007/s00467-014-3036-8

Cui, N., Cai, H., Li, Z., Lu, Y., Wang, G., and Lu, A. (2019). Tigecycline-induced coagulopathy: a literature review. *Int. J. Clin. Pharm.* 41 (6), 1408–1413. doi:10.1007/s11096-019-00912-5

Estrada, C. C., Maldonado, A., and Mallipattu, S. K. (2019). Therapeutic inhibition of VEGF signaling and associated nephrotoxicities. *J. Am. Soc. Nephrol.* 30 (2), 187–200. doi:10.1681/asn.2018080853

Ettinger, D. S., Wood, D. E., Aisner, D. L., Akerley, W., Bauman, J. R., Bharat, A., et al. (2022). Non–small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J. Natl. Compr. Cancer Netw.* 20 (5), 497–530. doi:10.6004/jnccn.2022.0025

Evans, S. J. W., Waller, P. C., and Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol. Drug Saf.* 10 (6), 483–486. doi:10.1002/pds.677

Fan, M., Niu, K., Wu, X., and Shi, H. (2024). Risk of drug-induced angioedema: a pharmacovigilance study of FDA adverse event reporting system database. *Front. Pharmacol.* 15, 1417596. doi:10.3389/fphar.2024.1417596

Gando, S., Levi, M., and Toh, C.-H. (2016). Disseminated intravascular coagulation. *Nat. Rev. Dis. Prim.* 2 (1), 16037. doi:10.1038/nrdp.2016.37

George, J. N., and Nester, C. M. (2014). Syndromes of thrombotic microangiopathy. *N. Engl. J. Med.* 371 (7), 654–666. doi:10.1056/NEJMra1312353

Gheorghe, C.-M., Purcărea, V. L., and Gheorghe, I. R. (2019). Assessing the effectiveness of OTC Advertising on artificial tear drops from an experiential marketing perspective. *romanian J. Ophthalmol.* 63 (3), 297–305. doi:10.22336/rjo.2019.46

Gialeraki, A., Valsami, S., Pittaras, T., Panayiotakopoulos, G., and Politou, M. (2017). Oral contraceptives and HRT risk of thrombosis. *Clin. Appl. Thrombosis/Hemostasis* 24 (2), 217–225. doi:10.1177/1076029616683802

Gill, R., and Meghrajani, V. (2022). Tacrolimus-induced thrombotic microangiopathy after orthotopic heart transplant: a case report. *Cureus* 14, e25874. doi:10.7759/cureus.25874

Giustozzi, M., Ehrlinder, H., Bongiovanni, D., Borovac, J. A., Guerreiro, R. A., Gąsecka, A., et al. (2021). Coagulopathy and sepsis: pathophysiology, clinical manifestations and treatment. *Blood Rev.* 50, 100864. doi:10.1016/j.blre.2021.100864

Gómez-Mesa, J. E., Galindo-Coral, S., Montes, M. C., and Muñoz Martin, A. J. (2021). Thrombosis and coagulopathy in COVID-19. *Curr. Problems Cardiol.* 46 (3), 100742. doi:10.1016/j.cpcardiol.2020.100742

Grall, M., Daviet, F., Chiche, N. J., Provot, F., Presne, C., Coindre, J.-P., et al. (2021). Eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre. *BMC Nephrol.* 22 (1), 267. doi:10.1186/s12882-021-02470-3

Guo, M., Liang, J., Li, D., Zhao, Y., Xu, W., Wang, L., et al. (2022). Coagulation dysfunction events associated with tigecycline: a real-world study from FDA adverse event reporting system (FAERS) database. *Thrombosis J.* 20 (1), 12. doi:10.1186/s12959-022-00369-z

Habib, M., Roberts, L. N., Patel, R. K., Wendon, J., Bernal, W., and Arya, R. (2013). Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. *Liver Int.* 34 (5), 672–678. doi:10.1111/liv.12369

Hakeam, H. A., Al Duhailib, Z., Salahuddin, N., and Amin, T. (2018). Impact of tigecycline versus imipenem–cilastatin on fibrinogen levels following cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): a randomized-controlled study. *J. Chemother.* 30 (4), 224–232. doi:10.1080/1120009x.2018.1452333

Haverinen, A. H., Luiro, K. M., Szanto, T., Kangasniemi, M. H., Hiltunen, L., Sainio, S., et al. (2022). Combined oral contraceptives containing estradiol valerate vs ethinylestradiol on coagulation: a randomized clinical trial. *Acta Obstetricia Gynecol. Scand.* 101 (10), 1102–1111. doi:10.1111/aogs.14428

Helms, J., Iba, T., Connors, J. M., Gando, S., Levi, M., Meziani, F., et al. (2023). How to manage coagulopathies in critically ill patients. *Intensive Care Med.* 49 (3), 273–290. doi:10.1007/s00134-023-06980-6

Iams, W., Beckermann, K. E., Neff, A. T., Mayer, I. A., and Abramson, V. G. (2013). Thrombotic microangiopathy during docetaxel, trastuzumab, and carboplatin chemotherapy for early-stage HER2+ breast cancer: a case report. *Med. Oncol.* 30 (2), 568. doi:10.1007/s12032-013-0568-x

Iba, T., and Levy, J. H. (2020). Sepsis-induced coagulopathy and disseminated intravascular coagulation. *Anesthesiology* 132 (5), 1238–1245. doi:10.1097/aln.0000000000003122

Iba, T., Levy, J. H., Thachil, J., Wada, H., Levi, M., and Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis (2019a). The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. *Thrombosis Res.* 179, 11–14. doi:10.1016/j.thromres.2019.04.030

Iba, T., Levy, J. H., Warkentin, T. E., Thachil, J., van der Poll, T., Levi, M., et al. (2019b). Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J. Thrombosis Haemostasis* 17 (11), 1989–1994. doi:10.1111/jth.14578

Ishikawa, M., Nakayama, K., Razia, S., Ishida, A., Yamashita, H., Ishibashi, T., et al. (2021). Neutropenic enterocolitis-induced sepsis and disseminated intravascular coagulation after chemotherapy: a case report. *BMC Women's Health* 21 (1), 187. doi:10.1186/s12905-021-01302-8

Izzedine, H., and Perazella, M. A. (2015). Thrombotic microangiopathy, cancer, and cancer drugs. *Am. J. Kidney Dis.* 66 (5), 857–868. doi:10.1053/j.ajkd.2015.02.340

Jain, D., Sharma, G., and Kumar, A. (2023). Adverse effects of proton pump inhibitors (PPIs) on the renal system using data mining algorithms (DMAs). *Expert Opin. Drug Saf.* 22 (8), 741–752. doi:10.1080/14740338.2023.2189698

Javed, F., and Kumar, A. (2024). Identification of signal of clindamycin associated renal failure acute: a disproportionality analysis. *Curr. Drug Saf.* 19 (1), 123–128. doi:10.2174/1574886318666230228142856

Jiang, T., Su, H., Xu, J., Li, C., Zhang, N., Li, Y., et al. (2024). Drug-induced interstitial lung disease: a real-world pharmacovigilance study of the FDA Adverse Event Reporting System from 2004 to 2021. *Ther. Adv. Drug Saf.* 15, 20420986231224227. doi:10.1177/20420986231224227

Jodele, S., Laskin, B. L., Dandoy, C. E., Myers, K. C., El-Bietar, J., Davies, S. M., et al. (2015). A new paradigm: diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. *Blood Rev.* 29 (3), 191–204. doi:10.1016/j.blre.2014.11.001

Kleinveld, D. J. B., Hamada, S. R., and Sandroni, C. (2022). Trauma-induced coagulopathy. *Intensive Care Med.* 48 (11), 1642–1645. doi:10.1007/s00134-022-06834-7

Kubota, K., Koide, D., and Hirai, T. (2004). Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiol. Drug Saf.* 13 (6), 387–394. doi:10.1002/pds.964

Kumar, R., Vidaurre, J., and Gedela, S. (2019). Valproic acid–induced coagulopathy. *Pediatr. Neurol.* 98, 25–30. doi:10.1016/j.pediatrneurol.2019.04.019

Larson, A. M., Polson, J., Fontana, R. J., Davern, T. J., Lalani, E., Hynan, L. S., et al. (2005). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 42 (6), 1364–1372. doi:10.1002/hep.20948

Lechner, K., and Obermeier, H. L. (2012). Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. *Medicine* 91 (4), 195–205. doi:10.1097/MD.0b013e3182603598

Levi, M. (2014). Cancer-related coagulopathies. *Thrombosis Res.* 133, S70–S75. doi:10.1016/s0049-3848(14)50012-6

Li, D., Wang, H., Qin, C., Du, D., Wang, Y., Du, Q., et al. (2024). Drug-induced acute pancreatitis: a real-world pharmacovigilance study using the FDA adverse event reporting system database. *Clin. Pharmacol. and Ther.* 115 (3), 535–544. doi:10.1002/cpt.3139

Li, Y., Li, H., Wang, Y., Guo, J., and Zhang, D. (2023). Potential biomarkers for early diagnosis, evaluation, and prognosis of sepsis-induced coagulopathy. *Clin. Appl. Thrombosis/Hemostasis* 29, 10760296231195089. doi:10.1177/10760296231195089

Liu, M., Gu, L., Zhang, Y., Zhou, H., Wang, Y., and Xu, Z.-X. (2024). A real-world disproportionality analysis of mesalazine data mining of the public version of FDA adverse event reporting system. *Front. Pharmacol.* 15, 1290975. doi:10.3389/fphar.2024.1290975

Lockhart, E., Peterson-Layne, C., Ahmadzia, H., Grotegut, C., and James, A. (2016). Management of coagulopathy in postpartum hemorrhage. *Seminars Thrombosis Hemostasis* 42 (07), 724–731. doi:10.1055/s-0036-1593417

Markan, A., Ayyadurai, N., and Singh, R. (2021). Tacrolimus induced thrombotic microangiopathy (TMA) presenting as acute macular neuroretinopathy. *Ocular Immunol. Inflamm.* 31 (1), 231–232. doi:10.1080/09273948.2021.1998549

Mini, E., Nobili, S., Caciagli, B., Landini, I., and Mazzei, T. (2006). Cellular pharmacology of gemcitabine. *Ann. Oncol.* 17, v7–v12. doi:10.1093/annonc/mdj941

Moore, H. B., Gando, S., Iba, T., Kim, P. Y., Yeh, C. H., Brohi, K., et al. (2020). Defining trauma-induced coagulopathy with respect to future implications for patient management: communication from the SSC of the ISTH. *J. Thrombosis Haemostasis* 18 (3), 740–747. doi:10.1111/jth.14690

Noguchi, Y., Katsuno, H., Ueno, A., Otsubo, M., Yoshida, A., Kanematsu, Y., et al. (2018). Signals of gastroesophageal reflux disease caused by incretin-based drugs: a disproportionality analysis using the Japanese adverse drug event report database. *J. Pharm. Health Care Sci.* 4 (1), 15. doi:10.1186/s40780-018-0109-z

Novak, J., Mocikova, H., Pavlicek, P., Gaherova, L., and Kozak, T. (2012). Rituximab-induced coagulopathy. *Leukemia and Lymphoma* 53 (11), 2299–2301. doi:10.3109/10428194.2012.682313

Nwaba, A., MacQuillan, G., Adams, L. A., Garas, G., Delriviere, L., Augustson, B., et al. (2013). Tacrolimus-induced thrombotic microangiopathy in orthotopic liver transplant patients: case series of four patients. *Intern. Med. J.* 43 (3), 328–333. doi:10.1111/imj.12048

Pandit, B., and Royzen, M. (2022). Recent development of prodrugs of gemcitabine. *Genes* 13 (3), 466. doi:10.3390/genes13030466

Peralta, R., Thani, H. A., and Rizoli, S. (2019). Coagulopathy in the surgical patient: trauma-induced and drug-induced coagulopathies. *Curr. Opin. Crit. Care* 25 (6), 668–674. doi:10.1097/mcc.0000000000000676

Petros, S. (2019). Trauma-induced coagulopathy. *Hämostaseologie* 39 (01), 020–027. doi:10.1055/s-0039-1677853

Pham, P.-T. T., Peng, A., Wilkinson, A. H., Gritsch, H. A., Lassman, C., Pham, P.-C. T., et al. (2000). Cyclosporine and tacrolimus–associated thrombotic microangiopathy. *Am. J. Kidney Dis.* 36 (4), 844–850. doi:10.1053/ajkd.2000.17690

Poluzzi, E., Raschi, E., Moretti, U., and De Ponti, F. (2009). Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). *Pharmacoepidemiol. Drug Saf.* 18 (6), 512–518. doi:10.1002/pds.1746

Porter, L. H., Zhu, J. J., Lister, N. L., Harrison, S. G., Keerthikumar, S., Goode, D. L., et al. (2023). Low-dose carboplatin modifies the tumor microenvironment to augment CAR T cell efficacy in human prostate cancer models. *Nat. Commun.* 14 (1), 5346. doi:10.1038/s41467-023-40852-3

Raschi, E., Gatti, M., Gelsomino, F., Ardizzoni, A., Poluzzi, E., and De Ponti, F. (2020a). Lessons to be learnt from real-world studies on immune-related adverse events with checkpoint inhibitors: a clinical perspective from pharmacovigilance. *Target. Oncol.* 15 (4), 449–466. doi:10.1007/s11523-020-00738-6

Raschi, E., La Placa, M., Poluzzi, E., and De Ponti, F. (2020b). The value of case reports and spontaneous reporting systems for pharmacovigilance and clinical practice. *Br. J. Dermatology* 184 (3), 581–583. doi:10.1111/bjd.19677

Raschi, E., Mazzarella, A., Antonazzo, I. C., Bendinelli, N., Forcesi, E., Tuccori, M., et al. (2019). Toxicities with immune checkpoint inhibitors: emerging priorities from disproportionality analysis of the FDA adverse event reporting system. *Target. Oncol.* 14 (2), 205–221. doi:10.1007/s11523-019-00632-w

Rothman, K. J., Lanes, S., and Sacks, S. T. (2004). The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol. Drug Saf.* 13 (8), 519–523. doi:10.1002/pds.1001

Routsi, C., Kokkoris, S., Douka, E., Ekonomidou, F., Karaiskos, I., and Giamarellou, H. (2015). High-dose tigecycline-associated alterations in coagulation parameters in critically ill patients with severe infections. *Int. J. Antimicrob. Agents* 45 (1), 90–93. doi:10.1016/j.ijantimicag.2014.07.014

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Salhi, S., Ribes, D., and Faguer, S. (2021). Complement C5 inhibition reverses bleomycin-induced thrombotic microangiopathy. *Clin. Kidney J.* 14 (4), 1275–1276. doi:10.1093/ckj/sfaa101

Sánchez-Sánchez, E., Fernández-Cerezo, F. L., Díaz-Jimenez, J., Rosety-Rodriguez, M., Díaz, A. J., Ordonez, F. J., et al. (2021). Consumption of over-the-Counter drugs: prevalence and type of drugs. *Int. J. Environ. Res. Public Health* 18 (11), 5530. doi:10.3390/ijerph18115530

Sharma, A., and Kumar, A. (2022). Identification of novel signal of clobazam-associated drug reaction with eosinophilia and systemic symptoms syndrome: a disproportionality analysis. *Acta Neurol. Scand.* 146 (5), 623–627. doi:10.1111/ane.13690

Sharma, A., Roy, S., Sharma, R., and Kumar, A. (2023). Association of antiviral drugs and their possible mechanisms with DRESS syndrome using data mining algorithms. *J. Med. Virology* 95 (3), e28671. doi:10.1002/jmv.28671

Song, J.-C., Wang, G., Zhang, W., Zhang, Y., Li, W.-Q., Zhou, Z., et al. (2020). Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. *Mil. Med. Res.* 7 (1), 19. doi:10.1186/s40779-020-00247-7

Stensballe, J., Henriksen, H. H., and Johansson, P. I. (2017). Early haemorrhage control and management of trauma-induced coagulopathy: the importance of goal-directed therapy. *Curr. Opin. Crit. Care* 23 (6), 503–510. doi:10.1097/mcc.0000000000000466

Subeesh, V., Singh, H., Maheswari, E., and Beulah, E. (2017). Novel adverse events of vortioxetine: a disproportionality analysis in USFDA adverse event reporting system database. *Asian J. Psychiatry* 30, 152–156. doi:10.1016/j.ajp.2017.09.005

Tan, E., Braithwaite, I., McKinlay, C. J. D., and Dalziel, S. R. (2020). Comparison of acetaminophen (paracetamol) with ibuprofen for treatment of fever or pain in children younger than 2 Years: a systematic review and meta-analysis. *JAMA Netw. Open* 3 (10), e2022398. doi:10.1001/jamanetworkopen.2020.22398

Tang, S., Wu, Z., Xu, L., Wen, Q., and Zhang, X. (2022). Adverse reaction signals mining and hemorrhagic signals comparison of ticagrelor and clopidogrel: a pharmacovigilance study based on FAERS. *Front. Pharmacol.* 13, 970066. doi:10.3389/fphar.2022.970066

Teal, S., and Edelman, A. (2021). Contraception selection, effectiveness, and adverse effects: a review. *Jama* 326 (24), 2507–2518. doi:10.1001/jama.2021.21392

Tobaiqy, M., Stewart, D., Helms, P. J., Bond, C., Lee, A. J., Bateman, N., et al. (2010). A pilot study to evaluate a community pharmacy–based monitoring system to identify adverse drug reactions associated with paediatric medicines use. *Eur. J. Clin. Pharmacol.* 66 (6), 627–632. doi:10.1007/s00228-010-0790-9

Treml, B., Rajsic, S., Hell, T., Fries, D., and Bachler, M. (2021). Progression of fibrinogen decrease during high dose tigecycline therapy in critically ill patients: a retrospective analysis. *J. Clin. Med.* 10 (20), 4702. doi:10.3390/jcm10204702

van der Heijden, M. S., Sonpavde, G., Powles, T., Necchi, A., Burotto, M., Schenker, M., et al. (2023). Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma. *N. Engl. J. Med.* 389 (19), 1778–1789. doi:10.1056/NEJMoa2309863

Watson, H. G. (2007). Sex hormones and thrombosis. *Seminars Hematol.* 44 (2), 98–105. doi:10.1053/j.seminhematol.2007.01.004

Weill, A., Dalichampt, M., Raguideau, F., Ricordeau, P., Blotière, P.-O., Rudant, J., et al. (2016). Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *Bmj* 353, i2002. doi:10.1136/bmj.i2002

Wu, S., Wu, G., and Wu, H. (2021). A comparison of coagulation function in patients receiving aspirin and cefoperazone-sulbactam with and without vitamin K1: a retrospective, observational study. *Clin. Ther.* 43 (12), e335–e345. doi:10.1016/j.clinthera.2021.10.005

Xiao, Q., Ungerer, M., Li, Z., Baumgartner, C., Goebel, S., Vogelmann, J., et al. (2013). The GPVI – Fc fusion protein revacept reduces thrombus formation and improves vascular dysfunction in atherosclerosis without any impact on bleeding times. *PLoS ONE* 8 (8), e71193. doi:10.1371/journal.pone.0071193

Yang, Z., Lv, Y., Yu, M., Mei, M., Xiang, L., Zhao, S., et al. (2022). GLP-1 receptor agonist-associated tumor adverse events: a real-world study from 2004 to 2021 based on FAERS. *Front. Pharmacol.* 13, 925377. doi:10.3389/fphar.2022.925377

Yousaf, A., Hagen, R., Delaney, E., Davis, S., and Zinn, Z. (2020). The influence of social media on acne treatment: a cross-sectional survey. *Pediatr. Dermatol.* 37 (2), 301–304. doi:10.1111/pde.14091

Yu, R. J., Krantz, M. S., Phillips, E. J., and Stone, C. A. (2021). Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA adverse event reporting system (FAERS). *J. Allergy Clin. Immunol. Pract.* 9 (2), 819–829.e2. doi:10.1016/j.jaip.2020.09.021

Zhang, L., Mao, W., Liu, D., Hu, B., Lin, X., Ran, J., et al. (2023). Risk factors for drug-related acute pancreatitis: an analysis of the FDA adverse event reporting system (FAERS). *Front. Pharmacol.* 14, 1231320. doi:10.3389/fphar.2023.1231320

Zhang, X., Ren, X., Zhu, T., Zheng, W., Shen, C., and Lu, C. (2024). A real-world pharmacovigilance study of FDA adverse event reporting system (FAERS) events for sunitinib. *Front. Pharmacol.* 15, 1407709. doi:10.3389/fphar.2024.1407709

Zhao, Q.-Y., Liu, L.-P., Luo, J.-C., Luo, Y.-W., Wang, H., Zhang, Y.-J., et al. (2021). A machine-learning approach for dynamic prediction of sepsis-induced coagulopathy in critically ill patients with sepsis. *Front. Med.* 7, 637434. doi:10.3389/fmed.2020.637434

Zhou, Q., Du, Z., Qu, K., Shen, Y., Jiang, Y., Zhu, H., et al. (2023). Adverse events of epidiolex: a real-world drug safety surveillance study based on the FDA adverse event reporting system (FAERS) database. *Asian J. Psychiatry* 90, 103828. doi:10.1016/j.ajp.2023.103828

Zou, F., Zhu, C., Lou, S., Cui, Z., Wang, D., Ou, Y., et al. (2023). A real-world pharmacovigilance study of mepolizumab in the FDA adverse event reporting system (FAERS) database. *Front. Pharmacol.* 14, 1320458. doi:10.3389/fphar.2023.1320458

Zupancic, M., Shah, P. C., Shah-Khan, F., and Nagendra, S. (2007). Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol.* 8 (7), 634–641. doi:10.1016/s1470-2045(07)70203-6

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 03 January 2025
DOI 10.3389/fphar.2024.1505653

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Feng Shen,
Affiliated Hospital of Guizhou Medical University, China
Ermin Schadich,
Palacký University, Olomouc, Czechia

*CORRESPONDENCE
Xuping Yang,
634609985@qq.com
Yilan Huang,
hyl3160131@126.com

†These authors have contributed equally to this work

RECEIVED 03 October 2024
ACCEPTED 26 November 2024
PUBLISHED 03 January 2025

CITATION
Xu C, Zhu J, Tu K, Tang H, Zhou X, Li Q, Chen K, Yang X and Huang Y (2025) The clinical features and risk factors of coagulopathy associated with cefoperazone/sulbactam: a nomogram prediction model.
Front. Pharmacol. 15:1505653.
doi: 10.3389/fphar.2024.1505653

The clinical features and risk factors of coagulopathy associated with cefoperazone/sulbactam: a nomogram prediction model

Changjing Xu[1†], Junlong Zhu[2†], Kun Tu[3], Hui Tang[1], Xinxin Zhou[1], Qiuyu Li[3], Kun Chen[1], Xuping Yang[1*] and Yilan Huang[1*]

[1]Department of Pharmacy, The Affiliated Hospital of Southwest Medical University, Luzhou, China, [2]Department of Vascular Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China, [3]School of pharmacy, Southwest Medical University, Luzhou, China

Background: Cefoperazone/sulbactam (CPZ/SAM) is an important treatment option for infections caused by multidrug-resistant gram-negative bacteria. However, it is associated with an increased risk of coagulation disorders (CD) and causes severe bleeding in some instances. Early identification of risk factors and prediction of CD related to CPZ/SAM are crucial for prevention and treatment. This study aimed to explore the risk factors and developed a nomogram model for predicting the risk of coagulopathy in patients undergoing CPZ/SAM treatment.

Methods: A total of 1719 patients who underwent CPZ/SAM in the Affiliated Hospital of Southwest Medical University from August 2018 to August 2022, were recruited as the training cohort. For validation, 1,059 patients treated with CPZ/SAM from September 2022 to August 2024 were enrolled. Patients were divided into the CD and the N-CD groups. The occurrence of CD was designated as the dependent variable. The univariate and multivariate logistic regression analysis was performed to identify the risk factors of CD. A nomogram model was constructed from the multivariate logistic regression analysis and internally validated for model discrimination and calibration. The performance of the nomogram was estimated using the concordance index (C-index) and calibration curve.

Results: The multivariate logistic regression analysis resulted in the following independent risk factors for CD: baseline INR level (OR: 5.768, 95% CI: 0.484~11.372, p = 0.036), nutritional risk (OR:2.711, 95%CI: 1.495~4.125, p < 0.001), comorbidity of digestive system (OR:1.287, 95%CI: 0.434~2.215, p = 0.004), poor food intake (OR:1.261, 95%CI: 0.145~2.473, p = 0.032), ALB level (OR: −0.132, 95%CI: −0.229~-0.044, p = 0.005) and GFR< 30 mL/min (OR: 1.925, 95%CI: 0.704~3.337, p = 0.004). The internal validation confirmed the model's

Abbreviations: CPZ/SAM, cefoperazone/sulbactam; CD, coagulation disorders; NMTT, N-methylthiotetrazole; ADRs, adverse drug reactions; CTCAE, Common Terminology Criteria for Adverse Events; INR, international normalized ratio; APTT, activated partial thromboplastin time; ALT, alanine transaminase; TSB, total bilirubin; ALB, albumin; GFR, glomerular filtration rate; IQR, interquartile range; SD, standard deviation; OR, odds ratios; 95%CI, corresponding 95% confidence intervals; C-index, concordance index; AUC, receiver operating characteristic curve.

good performance (C-index, 0.905 [95% CI: 0.864~0.945]). The calibration plots in the nomogram model were of high quality. Validation further confirmed the reliability of the nomogram, with a C-index of 0.886 (95% CI: 0.832–0.940).

Conclusion: The nomogram model facilitated accurate prediction of CD in patients undergoing CPZ/SAM. And this could potentially contribute to reducing the incidence of CPZ/SAM-associated CD and consequently improving patients' outcomes.

KEYWORDS

cefoperazone/sulbactam, coagulation disorders, risk factor, nomogram, predictive model

1 Background

Cefoperazone/sulbactam (CPZ/SAM) is a therapeutic combination of the third-generation cephalosporin cefoperazone and the β-lactamase inhibitor sulbactam. It is widely used for treating moderate to severe infections at multiple body sites, such as respiratory tract infections, urinary tract infections, and intra-abdominal infections, due to its high efficacy and tolerability (Chen et al., 2021; Xin et al., 2013; Lan et al., 2021). In the context of the ongoing challenge faced by clinicians and medical institutions regarding the emergence and treatment of multidrug-resistant gram-negative bacteria infections, CPZ/SAM's broad-spectrum activity is significant. It is effective against multidrug-resistant gram-negative bacteria, including extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, ESBL-producing *Klebsiella pneumoniae*, and carbapenem-resistant *Acinetobacter baumannii* (Chang et al., 2018; Lai et al., 2019).

However, despite its general tolerability, increasing studies have indicated an association between CPZ/SAM and coagulation disorders (CD), which in some cases, can lead to severe bleeding (Wang et al., 2020; Cai et al., 2016; Hu, 2019). Two major mechanisms of coagulopathy associated with CPZ/SAM are as follows: (1) The chemical structure of CPZ contains an N-methylthio-tetrazole (NMTT) side chain, which can inhibits the vitamin K-dependent step in clotting factor synthesis (Lipsky, 1983; Lipsky, 1988). (2) Cefoperazone is not metabolized significantly and approximately 85% of the dose is excreted into the biliary tract (Greenfield et al., 1983), which can largely kill vitamin K-producing intestinal bacteria (Lipsky, 1988; Mulligan et al., 1982).

Given these potential adverse effects, early identification of risk factors and prediction of coagulation dysfunction related to CPZ/SAM are crucial for prevention and early intervention. However, limited research has been conducted on the risk factors, and no reliable models are currently available to predict the risk of coagulopathy in patients receiving CPZ/SAM treatment. A nomogram, which visually represents the prognostic strength of various factors from a multivariate model in a single diagram, can offer highly accurate risk estimation. This tool allows clinicians to standardize clinical decision-making based on evidence and personalize it for each individual (Shariat et al., 2009; Balachandran et al., 2015). Therefore, the objective of this study was to retrospectively analyze risk factors and develop a nomogram model to predict the risk of CD in patients undergoing CPZ/SAM treatment.

2 Methods

2.1 Study subjects

This retrospective case-control study analyzed the clinical data of patients aged 18 years and above who received CPZ/SAM (cefoperazone: sulbactam, 2:1) treatment from the Affiliated Hospital of Southwest Medical University. This hospital is a major academic tertiary hospital with 4,200 beds and more than 130,000 inpatients annually (Luo et al., 2022). Patients who met the above conditions were assigned to the training group from August 2018 to August 2002. A separate test cohort was recruited from patients who attended the same medical center from September 2022 to August 2024 to validate the reliability of the prediction model. The detailed patient data were retrieved from the hospital information system.

2.2 Definitions

Each patient receiving CPZ/SAM was evaluated for the causal association between the drug and coagulopathy adverse drug reactions (ADRs) using the Naranjo algorithm, which consists of ten questions and is scored as follows: scores between 9 and 10 indicate definite ADRs; 5–8, probable ADRs; 1–4, possible ADRs; and less than 1, doubtful ADRs (Naranjo et al., 1981; Son et al., 2011). In this study, cases meeting the first three selection criteria were adjudicated as coagulopathy associated with CPZ/SAM. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 was performed to evaluate the severity of coagulopathy ADRs. Serious ADRs were defined as CTCAE grade 3 or greater toxicities.

All of the patients had normal coagulation tests and no bleeding before CPZ/SAM therapy. We excluded patients who were concurrently receiving drugs affecting coagulation, including anticoagulants, anti-platelet agents, fibrinolysis or procoagulant drugs. Based on the occurrence of whether coagulation disorders (CD) after CPZ/SAM treatment, patients were divided into CD and the N-CD groups. For the CD group, the following criteria needed to be met: 1) The patients were adults over 18 years of age; 2) During the treatment, the indications, usage and dosage of CPZ/SAM were completely in accordance with the drug label and instruction; 3) CPZ/SAM treatment for more than 2 days; 4) Patients with complete medical records; 5) Patients without the basic diseases of blood and blood-forming organs, such as hemophilia; 6) Coagulation function was evaluated before, during, and after treatment. The study was

approved by the Ethics Committee of The Affiliated Hospital of Southwest Medical University (No.KY2022030), all methods used in this study were performed in accordance with relevant guidelines and regulations. And informed consent was not required for the retrospective analysis of patient data.

2.3 Data collection

Predictors were pre-set by clinical expertise and literature review. All predictors were assessed on the day before the start of CPZ/SAM. A pre-designed form was created to collect clinical data, including general information (age, sex, recent food intake), daily dose and duration of CPZ/SAM use, laboratory (international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, albumin (ALB), alanine transaminase (ALT), total bilirubin (TSB)) and glomerular filtration rate (GFR, Severe renal dysfunction was defined as a GFR less than or equal to 30 mL/min/1.73 m^2). Nutritional risk was assessed using the Nutritional Risk Screening 2002 (NRS-2002), with a total score above 3 indicating nutritional risk (Kondrup et al., 2003). Comobidities of digestive system included malignant tumors, gastroenteritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, peptic ulcer, acute pancreatitis, acute cholecystitis, acute cholangitis and so on.

2.4 Statistical analysis

Continuous variables were described using medians with interquartile range (IQR) or means with standard deviations (SD), while categorical variables were summarized as frequencies and percentages (n, %). For statistical analysis, $\chi 2$ test or Fisher exact test was used. Based on the univariate analysis results, multivariate logistic regression was conducted to identify independent risk factors for coagulation disorders. The effect of individual predictors on CD was reported as odds ratios (OR) with corresponding 95% confidence intervals (95%CI). We then used these significant independent factors to construct a nomogram for predicting coagulation disorders. The model's discriminative ability was assessed using the concordance index (C-index), which is analogous to the commonly reported area under the receiver operating characteristic curve (AUC). A C-index of 1 indicated perfect concordance; The C-index of most models is 0.7–0.85 (Balachandran et al., 2015), while the model's calibration was evaluated with a calibration curve. A DeLong test was used to evaluate the AUC difference between training set and test set. A two tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed in R version 4.3.6 (http://www.r-project.org/).

3 Results

3.1 Characteristics of the study population

7,279 infected patients were treated with CPZ/SAM (cefoperazone: sulbactam, 2:1) between August 2018 and August 2022, a total of 1719 patients who met the inclusion and exclusion criteria were divided into the training set. Among the selected patients, 110 (6.40%) exhibited CPZ/SAM associated CD and were assigned to the CD group. From the remaining 1,609 patients, 110 were randomly selected and included in the N-CD group using an Excel-generated random number table. The test set included 1,059 patients recruited based on the same criteria, with 72 (6.8%) developing CPZ/SAM-associated CD. The patient selection process was presented in Figures 1A, B.

The demographic and clinical data of the training and test cohorts were summarized in Table 1. The training set consisted 220 patients with an average baseline INR of 1.08 ± 0.093, 35.91% were aged ≥70years; 56.82% were male; 74.55% had nutritional risk. The test set comprised 144 patients with an average baseline INR of 1.06 ± 0.092, 39.58% were aged ≥70years; 61.11% were male; 65.97% had nutritional risk. Apart from the albumin level, there were no statistically significant differences in the characteristics between the two sets.

3.2 Summary of ADRs of training set

Coagulopathy ADRs occurred between 3 and 16 days after the initiation of CPZ/SAM treatment in training set, with a median onset of 7 days (interquartile range [IQR], 5–10). Among 110 patients with coagulopathy ADRs, 96 scored between 5 and 8 points on Naranjo algorithm were are rated as probable ADRs, 14 scored between 1 and 4 points were possible ADRs. Most ADRs were mild or moderate; however, 47 were classified as serious according to CTCAE Version 5.0. Overall, 104 cases (94.55%) exhibited prolonged INR, 41 (37.27%) showed prolonged APTT, 8 (7.27%) had decreased fibrinogen levels, and 20 (18.18%) experienced bleeding.

ADRs in 103 patients were successfully treated by discontinuing CPZ/SAM, administering intramuscular vitamin K1, and infusing fresh frozen plasma. For the remaining 7 patients, their families opted to discontinue further treatment due to serious underlying diseases, and one of them died in the hospital.

3.3 Univariate analysis of the occurrence of coagulopathy ADRs in patients receiving CPZ/SAM

All variables listed in Table 2 were used for univariate analysis. The univariate analysis results showed that there was no significant difference in gender between the CD group and N-CD group (p > 0.05). The CD group showed a higher likelihood of being aged 70 years or older, being at nutritional risk, having comorbidities of the digestive system, having poor food intake, receiving a daily dose of CPZ/SAM greater than 6g and receiving CPZ/SAM for more than 7 days (p < 0.05). The comparison of laboratory data found that there was no statistically significant difference in baseline APTT, ALT and TSB levels between the two groups (Table 2). However, ALB and GFR levels were significantly lower than those of N-CD group (p < 0.05). What's more, the baseline INR in CD group was significantly higher than that in N-CD group.

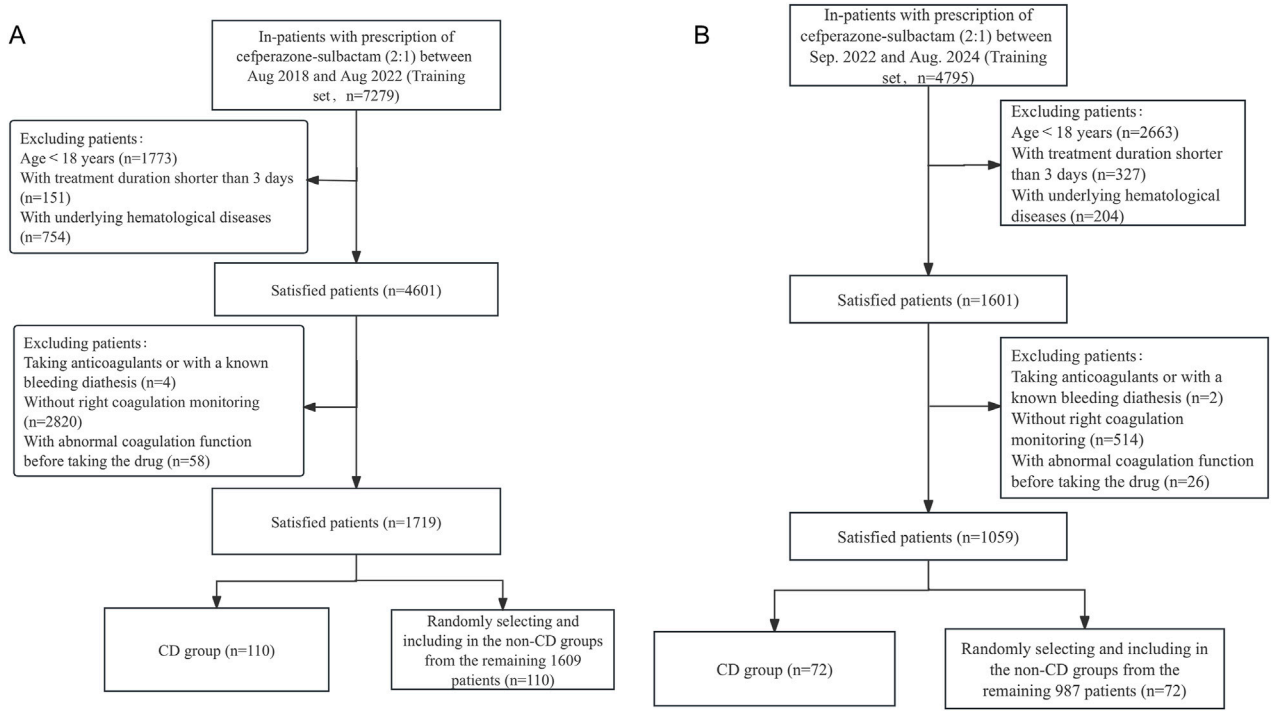


FIGURE 1
The flowchart of patient selection in the **(A)** training set and the **(B)** test set. CD, coagulation disorders.

TABLE 1 Characteristics of the study population and comparison of the training set and test set.

Variables	Training set (n = 220)	Test set (n = 144)	*p*-value
Age≥70 years, %	79 (35.91)	57 (39.58)	0.55
Male, %	125 (56.82)	88 (61.11)	0.481
Baseline INR	1.08 ± 0.093	1.06 ± 0.092	0.078
Baseline APTT (s)	31.12 ± 4.45	30.2 ± 4.52	0.436
Nutritional risk, %	164 (74.55)	95 (65.97)	0.10
Comorbidity of the digestive system, %	84 (38.18)	64 (44.44)	0.28
Poor food intake, %	169 (76.82)	114 (79.17)	0.691
Daily dose>6g, %	148 (67.27)	96 (66.67)	0.995
Treatment for ≥7 days, %	143 (65.00)	89 (61.81)	0.611
ALT>40U/L, %	56 (25.45)	36 (25.00)	1.00
TSB>34.2umol/L, %	20 (9.09)	16 (11.11)	0.651
GFR<30 mL/min, %	35 (15.91)	21 (14.58)	0.846
ALB (g/L)	31.13 ± 4.39	31.94 ± 5.17	0.024*

Abbreviations: INR, international normalized ratio; APTT, activated partial thromboplastin time; ALT, alanine transaminase; TSB: total bilirubin; GFR: glomerular filtration rate; ALB, albumin.
* p-value < 0.05.

3.4 Multivariate regression analysis of the occurrence of CD in patients receiving CPZ/SAM

All significant variables from the univariate analysis were considered as independent variables, and whether CD occurred was considered as dependent variable, then they were included in the multivariate logistic regression analysis (Table 3). The results showed that baseline INR level (OR: 5.768, 95% CI: 0.484~11.372, $p = 0.036$), nutritional risk (OR:2.711, 95%CI: 1.495~4.125, $p < 0.001$), comorbidity of digestive system (OR:1.287, 95%CI: 0.434 ~2.215, $p = 0.004$), poor food intake (OR:1.261, 95%CI: 0.145~2.473, $p = 0.032$), ALB level (OR:

TABLE 2 The results of Univariate analysis of training set and test set.

Variables	Training set			Test set		
	CD (n = 110)	N- CD (n = 110)	*p*-value	CD (n = 72)	N- CD (n = 72)	*p*-value
Age≥70 years, %	47 (42.73)	32 (29.09)	0.049*	35 (48.61)	22 (30.56)	0.041*
Male, %	66 (60)	59 (53.64)	0.058	41 (56.94)	47 (65.28)	0.393
Baseline INR	1.11 ± 0.11	1.05 ± 0.07	<0.001*	1.09 ± 0.10	1.03 ± 0.08	<0.001*
Baseline APTT (s)	31.84 ± 4.45	30.06 ± 4.78	0.09	30.56 ± 4.62	29.84 ± 4.39	0.35
Nutritional risk, %	106 (96.36)	58 (52.73)	<0.001*	61 (84.72)	34 (47.22)	<0.001*
Comorbidity of the digestive system, %	53 (48.18)	31 (28.18)	0.002*	40 (55.56)	24 (33.33)	0.012*
Poor food intake, %	103 (93.64)	66 (60)	<0.001*	66 (91.67)	48 (66.67)	<0.001*
Daily dose>6g, %	82 (74.55)	66 (60)	0.031*	55 (76.39)	41 (56.94)	0.022*
Treatment for ≥7 days, %	82 (74.55)	61 (55.45)	0.0045*	51 (70.83)	38 (52.78)	0.040*
ALT>40U/L, %	30 (27.27)	26 (23.64)	0.642	19 (26.39)	17 (23.61)	0.847
TSB>34.2umol/L, %	13 (11.82)	7 (6.36)	0.241	7 (9.72)	9 (12.5)	0.791
GFR<30 mL/min, %	28 (25.45)	7 (6.36)	<0.001*	17 (23.61)	4 (5.56)	0.005*
ALB (g/L)	31.13 ± 4.41	35.19 ± 4.46	<0.001*	29.75 ± 4.97	34.14 ± 4.37	<0.001*

Abbreviations: CD, coagulation disorders; INR, international normalized ratio; APTT, activated partial thromboplastin time; ALT, alanine transaminase; TSB: total bilirubin; GFR: glomerular filtration rate; ALB, albumin. * *p*-value < 0.05.

TABLE 3 The results of Multivariate logistic regression analysis of training set and test set.

Variables	Training set		Test set	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Age≥70 years	0.098 (−0.723~0.913)	0.813	0.908 (0.069~1.943)	0.074
Baseline INR	5.768 (0.484~11.372)	0.036*	6.36 (0.998~12.045)	0.023*
Nutritional risk	2.711 (1.495~4.125)	<0.001*	1.533 (0.479~2.686)	0.006*
Comorbidity of the digestive system	1.287 (0.434~2.215)	0.004*	1.572 (0.533~2.735)	0.005*
Poor food intake	1.261 (0.145~2.473)	0.032*	1.791 (0.547~3.216)	0.008*
Daily dose>6g	0.693 (−0.164~1.581)	0.117	0.815 (−0.218~1.897)	0.128
Treatment for ≥7 days	0.740 (−0.111~1.622)	0.092	0.811 (−0.215~1.889)	0.127
ALB (g/L)	−0.132 (−0.229~-0.044)	0.005*	−0.201 (−0.332~-0.091)	0.001*
GFR<30 mL/min	1.925 (0.704~3.337)	0.004*	1.639 (0.275~3.259)	0.028*

Abbreviations: INR, international normalized ratio; CPZ/SAM, cefoperazone/sulbactam; GFR: glomerular filtration rate; ALB, albumin. * *p*-value < 0.05.

−0.132, 95%CI: −0.229~-0.044, $p = 0.005$) and GFR < 30 mL/min (OR: 1.925, 95%CI: 0.704~3.337, $p = 0.004$) were the independent risk factors influencing the occurrence of CD in patients receiving CPZ/SAM.

3.5 The nomogram of CD occurrence and the performance evaluation of the nomogram

The six factors obtained from multivariate logistical regression analysis were used to establish a nomogram of the risk of CD (Figure 2). The ROC curve of prediction model was presented in Figure 3A, with an AUC of 0.905 (95% CI: 0.864~0.945), indicating high prediction accuracy. In the test set, the AUC was 0.886 (95% CI: 0.832~0.94) (Figure 3B). According to the DeLong test, the ROC AUC difference between training set and test set was not significant (p = 0.574). To verify the accuracy of the nomogram, internal validation was conducted using the bootstrap method with 1,000 resamples. Furthermore, the calibration curves in both sets demonstrated a high level of agreement between the predicted and ideal models (Figures 4A, B).

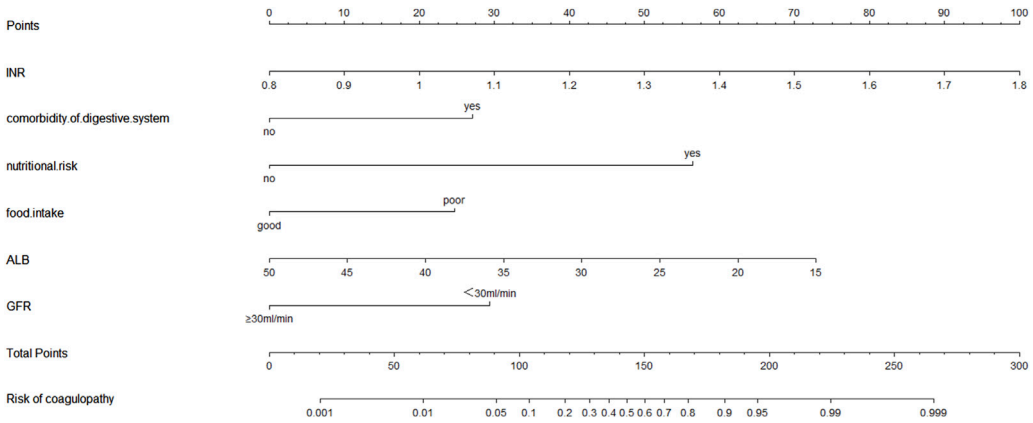


FIGURE 2
The nomogram for calculating the risk score and predicting the risk of CD in patients receiving CPZ/SAM treatment. To calculate total score and predicted probability of CD, points from individual variables are added and a vertical line is drawn from the total points line at the bottom downward to determine the predicted probability of CD due to CPZ/SAM. Abbreviations: CD, coagulation disorders; CPZ/SAM, cefoperazone/sulbactam; INR, international normalized ratio; CPZ/SAM, cefoperazone/sulbactam; GFR: glomerular filtration rate, mL/min; ALB, albumin, g/L.

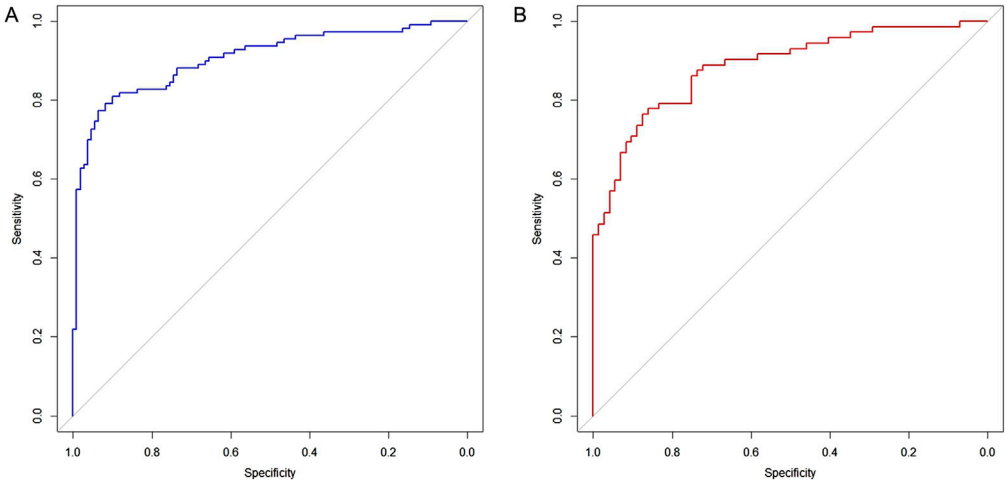


FIGURE 3
Receiver operating characteristic curves for evaluating the discrimination capability of plasma NSE and the final model. **(A)** Training set, AUC = 0.905 (95% CI: 0.864~0.945). **(B)** Test set, AUC = 0.886 (95% CI: 0.832~0.94).

4 Discussion

CPZ/SAM is widely used for the treatment of gram-negative bacilli infections (Ku and Yu, 2021). However, due to its unique chemical structure and pharmacokinetic characteristics, its treatment may be associated with a high risk of CD (Wang et al., 2020). In response to this, China's National Medical Products Administration requested modifications to drug labels in 2019 to include warnings about CD and bleeding risks. Despite the recognized risks, there have been few studies reported on the risk factors of CD in patients receiving CPZ/SAM. Thus, in this study, we used univariate analysis and multivariate logistic regression analysis to identify the risk factors for CD. Furthermore, we constructed a predictive nomogram to estimate the risk of CD for each patient treated with CPZ/SAM comprehensively and accurately.

Coagulopathy ADRs occurred at a median of 7 days (ranging from 3 to 16 days) after the start of CPZ/SAM treatment in this study, which was in agreement with prior report. Shao et al. (2023) showed that coagulopathy occurred at days 2–19 (7.380 ± 4.628) after administration of CPZ/SAM. Large amounts of CPZ in the gastrointestinal tract apparently alters vitamin K-producing gut flora, which may be the main cause of CD. This was confirmed by previous studies (Triger et al., 1988; Goss et al., 1992), they showed that treatment with other antibiotics containing a NMTT chain (e.g., cefotetan) did not significantly increase the risk of CD. In the present study, prothrombin time results are expressed as INR (Lee et al., 2017), CD in patients receiving CPZ/SAM was mainly

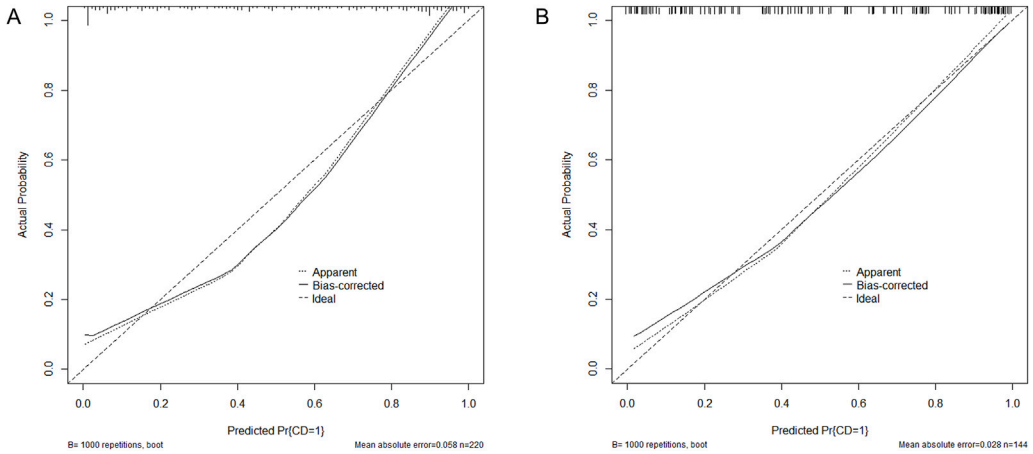


FIGURE 4
Calibration curves for the nomogram indicating good agreement between the predictors and observations. **(A)** Training set. **(B)** Test set. Pr, probability; CD, Coagulation disorders.

presented by an elevated INR, but rarely bleeding. This phenomenon was consistent with previous research findings. Wang et al. (2020) and Strom et al. (1999) found that cefoperazone was associated with a higher risk of PT prolongation.

In the study, we determined 6 factors related to the risk of CD in patients receiving CPZ/SAM through univariate and multivariate regression analysis, including baseline INR level, nutritional risk, comorbidity of digestive system, poor food intake, ALB level and GFR < 30 mL/min, all of which were used to establish a nomogram of the risk of PO. As far as we know, this was the first nomogram study for assessing the risk of CD in patients receiving CPZ/SAM. And based on AUC and calibration curve evaluation, the nomogram model showed good accuracy and consistency.

This study showed that baseline INR level, comorbidity of digestive system, poor food intake, nutritional risk, ALB level and GFR < 30 mL/min were independent risk factors for CD in patients receiving CPZ/SAM. It was observed that patients receiving CPZ/SAM with higher INR baseline level were more likely to develop CD. In some cases, the INR is considered as a vitamin K-dependent parameter, for example, patients on chronic warfarin therapy require close laboratory monitoring of their INR (Barnes et al., 2018). Thus, CD is more likely to occur when INR baseline level is high in patients receiving CPZ/SAM.

It's known that Vitamin K in the body is mainly obtained from diet and intestinal microbiome (Suttie and Booth, 2011; Zhang et al., 2021). Patients with comorbidity of digestive system often have inadequate absorption of vitamin K, and previous researches have also confirmed that malabsorption-related diseases resulted in vitamin K deficiency, like inflammatory bowel disease and primary biliary cholangitis (Nowak et al., 2014; Kuwabara et al., 2009; EASL Clinical Practice GuidelinesEuropean Association for the Study of the Liver, 2017). Therefore, poor food intake and comorbidity of digestive system contributed to vitamin K deficiency in patients receiving CPZ/SAM. Moreover, patients at nutritional risk were more likely to develop CD when receiving CPZ/SAM, and the mechanism was likely related to the inhibition of intestinal flora that synthesized vitamin K. The nutritional status of host affect the composition of the intestinal flora, simultaneously, changes in the gut nutritional environment and metabolic profile can markedly affect the activity of the gut microbiota (Dai et al., 2020; Fletcher et al., 2021).

In patients with hypoalbuminemia, the unbound proportion of highly protein-bound drugs increases due to the decrease in available binding sites. Furthermore, hypoalbuminemia is likely to increase the clearance (CL) of a drug (Ulldemolins et al., 2011; Parker et al., 2015). CPZ is a highly protein-bound drug with a binding rate of up to 90% (Peterson et al., 1989), it is excreted more quickly into the intestines through the biliary tract in patients with hypoalbuminemia. This action can affect the intestinal flora and maintenance of vitamin K. Gudivada KK et al. also showed that hypoalbuminemia was the risk factor for CPZ/SAM induced coagulopathy (Gudivada et al., 2023). CPZ is mainly excreted through feces (>75%), with less than 25% typically excreted through the kidneys. Previous study have indicated that no significant difference was observed in mean serum levels, half-life, and serum clearance between the groups with normal and severely impaired renal function (Greenfield et al., 1983). This may be because compared to normal patients, CPZ was excreted more via the feces in patients with severely impaired renal function when receiving an equivalent dose of CPZ/SAM, thus affecting the intestinal microecology.

Previous studies have suggested that the administration of vitamin K1 can somewhat reduce the occurrence of CD associated with CPZ/SAM (Shao et al., 2023; Wu et al., 2021; Ebid et al., 2024). However, research conducted by Gudivada KK et al. found that prophylactic vitamin K did not offer any benefit toward preventing INR elevation (Gudivada et al., 2023). In the current study, we also aimed to examine the preventive effects of prophylactic vitamin K on CD in patients receiving CPZ/SAM. Regrettably, few patients took vitamin K prophylaxis while taking CPZ/SAM in our unit. This will be further evaluated in our prospective study. However, given the inconsistent conclusions of previous studies, and the current model has demonstrated good prediction effects, we therefore

do not think that this will have a major impact on the final model.

Our study has several strengths. Firstly, we are the first to perform a multivariate logistic regression analysis to explore independent risk factors for CPZ/SAM associated with CD. Most previous studies were case reports and univariate analysis. Secondly, we developed a simple and visually effective prediction nomogram model for the first time, which contains six factors that affect the occurrence of CD in patients receiving CPZ/SAM. The concordance index (C-index) was used to assess the performance, which was graded as very good (0.80–1.00) (Luo et al., 2019). In the current study, the nomogram demonstrated good performance for prediction (C-index of 0.905), which may improve and provide new insights for the early identification and intervention of CD in patients receiving CPZ/SAM. On the other hand, for patients with more than two risk factors or an anticipated CD risk greater than 10%, we recommend more frequent monitoring of coagulation indicators or using alternative antibacterial drugs with less impact on coagulation to minimize the risk of bleeding.

This study still has some limitations. Firstly, this retrospective study was conducted based on reviewing medical records from a single institution and the sample size was relatively small. Secondly, the model was internally validated with good accuracy and reliability, and external validation was still necessary. Finally, due to missing data, some potentially meaningful factors, such as prophylactic vitamin K, were not included in the risk factor analysis. It is necessary to validate our results with those of other centers. In the future, a prospective multi-center in-sample study to further confirm the reliability of the nomogram is warranted.

5 Conclusion

In conclusion, we constructed and validated a novel prognostic nomogram to predict the risk of CPZ/SAM induced CD. Through this model, clinicians could potentially identify patients at a higher risk of developing CD early on, allowing for timely intervention and management. This could lead to a reduction in the occurrence of CD associated with CPZ/SAM, and consequently improve patients' outcomes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Hospital of Southwest Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CX: Data curation, Formal Analysis, Software, Writing–original draft, Conceptualization, Supervision, Writing–review and editing. JZ: Conceptualization, Writing–original draft, Writing–review and editing. KT: Data curation, Writing–review and editing. HT: Data curation, Writing–review and editing. XZ: Data curation, Writing–review and editing. QL: Data curation, Writing–review and editing. KC: Data curation, Funding acquisition, Writing–review and editing. XY: Writing–review and editing, Writing–original draft. YH: Conceptualization, Supervision, Writing–review and editing, Writing–original draft.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by research funding from Young Pharmacists Research Special Fund of Sichuan Hospital Association (No. 22033). Applied Basic Research Project Fund of Southwest Medical University (No. 2022QN008).

Acknowledgments

We would like to thank all the participants and their families who encouraged the production of this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

Balachandran, V. P., Gonen, M., Smith, J. J., and DeMatteo, R. P. (2015). Nomograms in oncology: more than meets the eye. *Lancet Oncol.* 16 (4), e173–e180. doi:10.1016/S1470-2045(14)71116-7

Barnes, G. D., Gu, X., Kline-Rogers, E., Graves, C., Puroll, E., Townsend, K., et al. (2018). Out-of-range INR results lead to increased health-care utilization in four large anticoagulation clinics. *Res. Pract. Thromb. Haemost.* 2 (3), 490–496. doi:10.1002/rth2.12110

Cai, Z., Yang, W., He, Y., Chen, Q., Wang, S., Luo, X., et al. (2016). Cefoperazone/sulbactam-induced abdominal wall hematoma and upper gastrointestinal bleeding: a case report and review of the literature. *Drug Saf. Case Rep.* 3 (1), 2. doi:10.1007/s40800-016-0025-9

Chang, P. C., Chen, C. C., Lu, Y. C., Lai, C. C., Huang, H. L., Chuang, Y. C., et al. (2018). The impact of inoculum size on the activity of cefoperazone-sulbactam against multidrug resistant organisms. *J. Microbiol. Immunol. Infect.* 51 (2), 207–213. doi:10.1016/j.jmii.2017.08.026

Chen, C. H., Tu, C. Y., Chen, W. C., Kuo, L. K., Wang, Y. T., Fu, P. K., et al. (2021). Clinical efficacy of cefoperazone-sulbactam versus piperacillin-tazobactam in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. *Infect. Drug Resist* 14, 2251–2258. doi:10.2147/IDR.S313828

Dai, D., Wu, S. G., Zhang, H. J., Qi, G. H., and Wang, J. (2020). Dynamic alterations in early intestinal development, microbiota and metabolome induced by in ovo feeding of L-arginine in a layer chick model. *J. Anim. Sci. Biotechnol.* 11, 19. doi:10.1186/s40104-020-0427-5

EASL Clinical Practice Guidelines European Association for the Study of the Liver (2017). EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J. Hepatol.* 67 (1), 145–172. Epub 2017 Apr 18. doi:10.1016/j.jhep.2017.03.022

Ebid, A. I., Abdeen, H. A., Muhammed Maher, R., and Mohamed-Abdel-Motaleb, S. M. (2024). Cefoperazone-sulbactam-induced coagulopathy in critically ill Egyptian patients: role of vitamin K prophylactic doses. *Hosp. Pharm.* 59 (5), 575–583. doi:10.1177/00185787241238310

Fletcher, J. R., Pike, C. M., Parsons, R. J., Rivera, A. J., Foley, M. H., McLaren, M. R., et al. (2021). Clostridioides difficile exploits toxin-mediated inflammation to alter the host nutritional landscape and exclude competitors from the gut microbiota. *Nat. Commun.* 12 (1), 462. doi:10.1038/s41467-020-20746-4

Goss, T. F., Walawander, C. A., Grasela, T. H., Jr., Meisel, S., Katona, B., and Jaynes, K. (1992). Prospective evaluation of risk factors for antibiotic-associated bleeding in critically III patients. *Pharmacotherapy* 12 (4), 283–291. doi:10.1002/j.1875-9114.1992.tb04462.x

Greenfield, R. A., Gerber, A. U., and Craig, W. A. (1983). Pharmacokinetics of cefoperazone in patients with normal and impaired hepatic and renal function. *Rev. Infect. Dis.* 5 (Suppl. 1), S127–S136. doi:10.1093/clinids/5-supplement_1.s127

Gudivada, K. K., Krishna, B., and Sampath, S. (2023). Cefoperazone-induced coagulopathy in critically ill patients admitted to intensive care unit. *Indian J. Crit. Care Med.* 27 (3), 183–189. doi:10.5005/jp-journals-10071-24417

Hu, H. R. (2019). Fatal vitamin K-dependent coagulopathy associated with cefoperazone/sulbactam: a case report. *Drug Saf. Case Rep.* 6 (1), 6. doi:10.1007/s40800-019-0100-0

Kondrup, J., Rasmussen, H. H., Hamberg, O., Stanga, Z., and Ad Hoc ESPEN Working Group (2003). Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin. Nutr.* 22 (3), 321–336. doi:10.1016/s0261-5614(02)00214-5

Ku, Y. H., and Yu, W. L. (2021). Cefoperazone/sulbactam: new composites against multiresistant gram negative bacteria? *Infect. Genet. Evol.* 88, 104707. doi:10.1016/j.meegid.2021.104707

Kuwabara, A., Tanaka, K., Tsugawa, N., Nakase, H., Tsuji, H., Shide, K., et al. (2009). High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease. *Osteoporos. Int.* 20 (6), 935–942. Epub 2008 Sep 30. doi:10.1007/s00198-008-0764-2

Lai, C. C., Chen, C. C., Lu, Y. C., Chuang, Y. C., and Tang, H. J. (2019). *In vitro* activity of cefoperazone and cefoperazone-sulbactam against carbapenem-resistant Acinetobacter baumannii and *Pseudomonas aeruginosa*. *Infect. Drug Resist* 12, 25–29. doi:10.2147/IDR.S181201

Lan, S. H., Chao, C. M., Chang, S. P., Lu, L. C., and Lai, C. C. (2021). Clinical efficacy and safety of cefoperazone-sulbactam in treatment of intra-abdominal infections: a systematic review and meta-analysis. *Surg. Infect. (Larchmt).* 22 (8), 763–770. doi:10.1089/sur.2020.468

Lee, S. H., Lee, W., Nguyen, T., Um, I. S., Bae, J. S., and Ma, E. (2017). Synthesis and thrombin, factor xa and U46619 inhibitory effects of non-amidino and amidino N^2-thiophenecarbonyl- and N^2-tosylanthranilamides. *Int. J. Mol. Sci.* 18 (6), 1144. doi:10.3390/ijms18061144

Lipsky, J. J. (1983). N-methyl-thio-tetrazole inhibition of the gamma carboxylation of glutamic acid: possible mechanism for antibiotic-associated hypoprothrombinaemia. *Lancet* 2 (8343), 192–193. doi:10.1016/s0140-6736(83)90174-5

Lipsky, J. J. (1988). Antibiotic-associated hypoprothrombinaemia. *J. Antimicrob. Chemother.* 21 (3), 281–300. doi:10.1093/jac/21.3.281

Luo, W. Q., Huang, Q. X., Huang, X. W., Hu, H. T., Zeng, F. Q., and Wang, W. (2019). Predicting breast cancer in breast imaging reporting and data system (BI-rads) ultrasound category 4 or 5 lesions: a nomogram combining radiomics and BI-rads. *Sci. Rep.* 9 (1), 11921. doi:10.1038/s41598-019-48488-4

Luo, Y., Fan, Q., Yu, Y., Zhang, L., Dong, L., and Luo, H. (2022). Efficacy of administrative intervention for neurosurgical patients with off-label use of alprostadil lipid microsphere. *Sci. Rep.* 12 (1), 15363. doi:10.1038/s41598-022-19717-0

Mulligan, M. E., Citron, D. M., McNamara, B. T., and Finegold, S. M. (1982). Impact of cefoperazone therapy on fecal flora. *Antimicrob. Agents Chemother.* 22 (2), 226–230. doi:10.1128/AAC.22.2.226

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., et al. (1981). A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* 30 (2), 239–245. doi:10.1038/clpt.1981.154

Nowak, J. K., Grzybowska-Chlebowczyk, U., Landowski, P., Szaflarska-Poplawska, A., Klincewicz, B., Adamczak, D., et al. (2014). Prevalence and correlates of vitamin K deficiency in children with inflammatory bowel disease. *Sci. Rep.* 4, 4768. doi:10.1038/srep04768

Parker, S. L., Sime, F. B., and Roberts, J. A. (2015). Optimizing dosing of antibiotics in critically ill patients. *Curr. Opin. Infect. Dis.* 28 (6), 497–504. doi:10.1097/QCO.0000000000000206

Peterson, L. R., Moody, J. A., Fasching, C. E., and Gerding, D. N. (1989). Influence of protein binding on therapeutic efficacy of cefoperazone. *Antimicrob. Agents Chemother.* 33 (4), 566–568. doi:10.1128/AAC.33.4.566

Shao, X., Ren, Y., Xie, N., Fan, K., Sun, H., Lu, J., et al. (2023). Effect of cefoperazone/sulbactam on blood coagulation function in infected emergency department patients and the necessity of vitamin K1 (VK1) preventive intervention: a single-center, retrospective analysis. *Med. Sci. Monit.* 29, e939203. doi:10.12659/MSM.939203

Shariat, S. F., Capitanio, U., Jeldres, C., and Karakiewicz, P. I. (2009). Can nomograms be superior to other prediction tools? *BJU Int.* 103 (4), 492–495. ; discussion 5-7. doi:10.1111/j.1464-410X.2008.08073.x

Son, Y. M., Lee, J. R., and Roh, J. Y. (2011). Causality assessment of cutaneous adverse drug reactions. *Ann. Dermatol* 23 (4), 432–438. doi:10.5021/ad.2011.23.4.432

Strom, B. L., Schinnar, R., Gibson, G. A., Brennan, P. J., and Berlin, J. A. (1999). Risk of bleeding and hypoprothrombinaemia associated with NMTT side chain antibiotics: using cefoperazone as a test case. *Pharmacoepidemiol Drug Saf.* 8 (2), 81–94. doi:10.1002/(SICI)1099-1557(199903/04)8:2<81::AID-PDS411>3.0.CO;2-G

Suttie, J. W., and Booth, S. L. (2011). Vitamin K. *Adv. Nutr.* 2 (5), 440–441. doi:10.3945/an.111.000786

Triger, D. R., Malia, R. G., and Preston, F. E. (1988). Platelet function and coagulation in patients with hepatobiliary disorders receiving cefotetan prophylaxis. *Infection* 16 (2), 105–108. doi:10.1007/BF01644314

Ulldemolins, M., Roberts, J. A., Rello, J., Paterson, D. L., and Lipman, J. (2011). The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin. Pharmacokinet.* 50 (2), 99–110. doi:10.2165/11539220-000000000-00000

Wang, W., Liu, Y., Yu, C., Tan, J., Xiong, W., Dong, D., et al. (2020). Cefoperazone-sulbactam and risk of coagulation disorders or bleeding: a retrospective cohort study. *Expert Opin. Drug Saf.* 19 (3), 339–347. doi:10.1080/14740338.2020.1713090

Wu, S., Wu, G., and Wu, H. (2021). A comparison of coagulation function in patients receiving aspirin and cefoperazone-sulbactam with and without vitamin K(1): a retrospective, observational study. *Clin. Ther.* 43 (12), e335–e345. doi:10.1016/j.clinthera.2021.10.005

Xin, X., Jian, L., Xia, X., Jia, B., Huang, W., Li, C., et al. (2013). A multicentre clinical study on the injection of ceftriaxone/sulbactam compared with cefoperazone/sulbactam in the treatment of respiratory and urinary tract infections. *Ann. Clin. Microbiol. Antimicrob.* 12, 38. doi:10.1186/1476-0711-12-38

Zhang, Z., Liu, L., Liu, C., Sun, Y., and Zhang, D. (2021). New aspects of microbial vitamin K2 production by expanding the product spectrum. *Microb. Cell Fact.* 20 (1), 84. doi:10.1186/s12934-021-01574-7

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 06 January 2025
DOI 10.3389/fphar.2024.1466875

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Isabel Silva,
University of Porto, Portugal
Moetaza M. Soliman,
Mansoura University, Egypt

*CORRESPONDENCE
Yuchuan Hou,
houyc@jlu.edu.cn

RECEIVED 18 July 2024
ACCEPTED 17 December 2024
PUBLISHED 06 January 2025

CITATION
Dai X, Yu K, Chang Y and Hou Y (2025) Drug-induced urinary retention: a real-world pharmacovigilance study using FDA and Canada vigilance databases.
Front. Pharmacol. 15:1466875.
doi: 10.3389/fphar.2024.1466875

Drug-induced urinary retention: a real-world pharmacovigilance study using FDA and Canada vigilance databases

Xianyu Dai[1], Kai Yu[1], Yu Chang[2] and Yuchuan Hou[1]*

[1]Department of Urology, The First Hospital of Jilin University, Changchun, China, [2]Department of Gastroenterology, The First Hospital of Jilin University, Changchun, China

Background: Urinary retention (UR) is a clinical condition where patients cannot fully empty their bladder. Although numerous drugs are associated with UR, comprehensive and reliable studies identifying drugs that induce UR are scarce.

Methods: This study leveraged data from the FDA Adverse Event Reporting System (FAERS) and the Canadian Vigilance Adverse Reaction (CVAR) database to explore adverse events (AEs) related to UR from 2004 to Q1 2024. The top 50 drugs were analyzed for annual reporting trends using linear regression. Disproportionality analysis using the reporting odds ratio (ROR) method, with *P*-values adjusted via Bonferroni correction, identified significant signals, which were then validated against drug labels and re-evaluated using the CVAR database. Time-to-onset analysis was also performed.

Results: From 2004 to Q1 2024, FAERS recorded 17,785,793 AEs, with 16,183 (0.09%) identified as UR cases. The median age among these cases was 65 years, with males comprising 53.4%. There were significant annual increases in UR reports associated with antineoplastic agents (0.19% per year) and antidiabetic drugs (0.09% per year), while reports linked to bronchodilators decreased (−0.53% per year). Disproportionality analysis revealed significant signals for 34 drugs (68%), with the highest RORs observed in Fesoterodine, Mirabegron, and Solifenacin. Initial signal detection identified potential new UR signals for Abiraterone, Valacyclovir, Fluoxetine, Empagliflozin, Clopidogrel, and Amlodipine, with CVAR confirming signals for Abiraterone, Fluoxetine, and Empagliflozin. The median time to onset of UR was 29 days, with over half of the cases occurring within 30 days of initiating medication.

Conclusion: The study identifies a rising trend in drug-related UR reports over the past 2 decades. The validation of new signals for Abiraterone, Fluoxetine, and Empagliflozin underscores the critical need for continuous drug safety monitoring and targeted research to better understand the mechanisms behind drug-induced UR.

KEYWORDS

urinary retention, adverse events, FAERS, Canadian Vigilance Adverse Reaction (CVAR), pharmacovigilance

1 Introduction

Urinary retention (UR) is a common yet serious clinical condition characterized by the inability of patients to completely empty their bladder. UR can be classified into acute and chronic types. Acute UR typically presents as sudden onset difficulty in urination and a sensation of bladder fullness, often requiring urgent medical interventions such as catheterization or surgical treatment (Thomas et al., 2004). Chronic UR may lead to bladder overdistension, recurrent urinary tract infections, and bladder stone formation, significantly reducing the patient's quality of life (Pape and Nitti, 2018).

The pathogenesis of UR is complex and may involve multiple factors such as bladder outlet obstruction, neurological dysfunction, urinary tract inflammation, or adverse drug effect (Selius and Subedi, 2008). Bladder outlet obstruction may be caused by conditions like benign prostatic hyperplasia or urethral stricture. Neurological dysfunctions that impair normal bladder contraction include diseases such as multiple sclerosis, Parkinson's disease, stroke, and spinal cord injuries (Moussa et al., 2020). Observational studies indicate that up to 10% of UR cases may be attributable to medication use (Verhamme et al., 2008). Previous reports have identified drugs associated with UR, including methamphetamine, sertraline, and buprenorphine (Edwards et al., 2014; Ojo et al., 2021; Jiang et al., 2022).

Crisafulli et al. previously utilized the Italian Spontaneous Reporting System database, which primarily collects and records reports from Italy, to explore drugs that might induce UR (Crisafulli et al., 2022). However, this study involved only 421 reports of adverse events (AEs) related to UR and lacked further validation from external databases, limiting its comprehensiveness and accuracy.

The aim of this study is to utilize two large databases, FDA Adverse Event Reporting System (FAERS, the world's largest post-marketing safety surveillance database) and Canadian Vigilance Adverse Reaction database (CVAR), to systematically and comprehensively investigate and analyze adverse drug reaction events related to UR. We also analyzed the onset time of AEs associated with drug-induced UR to further understand the temporal patterns of drug-induced UR. This study aims to provide a scientific basis for drug safety surveillance and to offer clinical references to improve medication safety for patients.

2 Materials and methods

2.1 Study design and data source

This study initially utilizes the FAERS database to extract reports of AEs related to UR. The top 50 drugs most commonly associated with UR were identified and categorized for annual reporting trend analysis. Disproportionality analysis was performed on these 50 drugs to explore UR-related AE signals, which were then matched against the drug labels to identify any discrepancies. For drugs without labeled UR, further validation was conducted using the CVAR database. FAERS contains millions of real-world AEs reports submitted by healthcare professionals, individual patients, lawyers, and drug manufacturers. The FAERS data files include seven types of datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse event coding (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start and end dates (THER), and indications for drug use (INDI) (Kadoyama et al., 2012). Each report categorizes the role of each drug in the AE: primary suspect (PS), secondary suspect (SS), interacting (I), or concomitant (C).

To ensure the reliability of results, we extracted UR-related AEs reports submitted by healthcare professionals (including physicians, pharmacists, and other health professionals) between 2004 and the first quarter of 2024. Considering the various sources of FDA data submissions, potential duplicate reports were handled following FDA guidelines: when CASEID was the same, we selected the latest FDA_DT and the highest PRIMARYID. The CVAR database, managed by Health Canada, has recorded post-market adverse reactions in Canada since 1965, including patient characteristics, drug usage, adverse reactions, and outcomes.

2.2 Identification of target AE reports

All reported AEs were coded in detail according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system. MedDRA's hierarchical structure includes five levels: System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lowest Level Term (LLT) (Mascolo et al., 2021). In this study, we extracted all AE reports containing the PT "urinary retention" and primarily focused on drugs listed as "PS".

2.3 Statistical analysis

This study evaluated annual reporting trends of the top 50 drug-related categories using time series plots and linear regression analysis, with *P*-values adjusted using the Bonferroni method. Disproportionality analysis, a common method in pharmacovigilance, based on the classical 2 × 2 contingency table (Table 1), was used to analyze the frequency of target drug and target AE occurrences relative to background frequencies, establishing statistical associations between drugs and AEs. The reporting odds ratio (ROR) algorithm was employed to detect drug-related AE signals. The ROR and its 95% confidence interval (CI) were calculated as follows:

$$\mathrm{ROR} = \frac{ad}{bc}, 95\%\ \mathrm{CI} = e^{ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

A positive AEs signal was identified when the lower limit of the 95% CI for the ROR was greater than 1.0, with at least 3 reports of the target AE (a ≥3) and P-adjust < 0.05. P-adjust is the *p*-value adjusted by chi-square test and Bonferroni correction. The ROR value also serves as an indicator to compare AEs risks among drugs; a higher ROR value suggests a higher risk of drug-induced UR (Yang et al., 2022). All analyses were conducted using R software version 4.2.3.

2.4 Time-to-onset analysis

The time-to-onset was defined as the interval from the therapy start date (START_DT in the THER file) to the event date (EVENT_

TABLE 1 2x2 contingency table for disproportionality analysis.

	Target AEs	All other AEs
Target drug	a	b
All other drugs	c	d

Notes: "a" represents the number of specific AEs, related to the target drug combination, "b" represents the number of other AEs related to the target drug, "c" represents the number of AEs related to other drugs involving the target AE, and "d" represents the number of other AEs unrelated to the target drug. AEs, adverse events.

TABLE 2 Basic characteristics of patients with drug-related UR from the FAERS database. UR, Urinary retention.

Characteristics	Drug-related UR (N = 16,183)
Gender	
Male	8,641 (53.4%)
Female	6,027 (37.2%)
Unknown	1,515 (9.4%)
Age (years)	
Median (Q1, Q3)	65.0 (47.0, 76.0)
Unknown	4,332 (26.8%)
Weight (kg)	
Median (Q1, Q3)	72.0 (59.0, 86.2)
Unknown	11,107 (68.6%)
Reported person	
Physician	8,399 (51.9%)
Pharmacist	1975 (12.2%)
Other health-professional	5,809 (35.9%)
Reported countries	
United States	5,348 (33.0%)
Japan	1712 (10.6%)
France	1,431 (8.8%)
United Kingdom	1,344 (8.3%)
Germany	976 (6.0%)
Canada	756 (4.7%)
Others[a]	4,616 (28.5%)
Reporting year	
2004–2008	1856 (11.5%)
2009–2013	2,717 (16.8%)
2014–2018	4,800 (29.7%)
2019–2023	6,473 (40.0%)
2024 Q1	337 (2.0%)

Notes:
[a]See Supplementary Table S1 for other countries.

DT in the DEMO file). Reports with input errors (e.g., EVENT_DT earlier than START_DT), inaccurate dates, and duplicates were excluded. In this study, the median and quartiles were used to describe the time-to-onset of AEs.

3 Results

3.1 Baseline characteristics of UR

During the study period from 2004 to Q1 2024, the FDA reported a total of 17,785,793 AEs, of which 16,183 (0.09%) were UR cases reported by healthcare professionals. Table 2 describes the baseline characteristics of patients with drug-related UR. Overall, reports of drug-related UR showed an increasing trend (Table 2; Figure 1A), with the highest number of reports in 2023 (1,397 cases, 8.63%). Among patients experiencing drug-related UR, males (53.4%) were more prevalent than females (37.2%), with a median age of 65 years (interquartile range [IQR] 47.0, 76.0) and a median weight of 72 kg (IQR 59.0, 86.2). Physicians accounted for the largest proportion of reports (51.9%), followed by other healthcare workers (35.9%). The United States reported the highest number of cases (33.0%), followed by Japan (10.6%), France (8.8%), the United Kingdom (8.3%), and Germany (6.0%). Details of case reports from other countries can be found in Supplementary Table S1.

3.2 Trend analysis of drug-related UR incidents

This study analyzed the top 50 drugs related to UR reported to the FDA (Supplementary Table S2). The drug categories included Immunomodulators (8/50), Antidepressants (7/50), Antipsychotics (6/50), Antineoplastic Agents (6/50), Analgesics and Antispasmodics (5/50), Urinary Antispasmodics (5/50), Anticoagulants (3/50), Antidiabetic Drugs (2/50), Bronchodilators (1/50), and Others (7/50). The time series of these drug reports is shown in Figure 1B. Additionally, linear regression analyses were conducted for each major drug category related to UR (Table 3). Regression for Antineoplastic Agents showed an average annual increase of 0.19% (95% CI: 0.10, 0.28, p-adjust = 0.004) from 0.30% in 2004 to 3% in 2023, a faster growth rate than any other drug category. Regression analysis for Antidiabetic Drugs also showed an average annual increase of 0.09% (95% CI: 0.06, 0.12, p-adjust < 0.001) in UR reports to the FDA. Conversely, the proportion of UR reports related to Bronchodilators showed a declining trend (−0.53% per year, 95% CI: −0.75, −0.31, p-adjust < 0.001). Other drug categories (Analgesics and Antispasmodics, Anticoagulants, Antidepressants, Antipsychotics, Immunomodulators, Urinary Antispasmodics) showed stable trends over time (*p*-adjust > 0.05).

3.3 Signal detection and validation

The ROR method was applied to the top 50 drugs for AE signal detection (Supplementary Table S2). The drugs with the most UR reports were Quetiapine (n = 336), followed by Tiotropium (n =

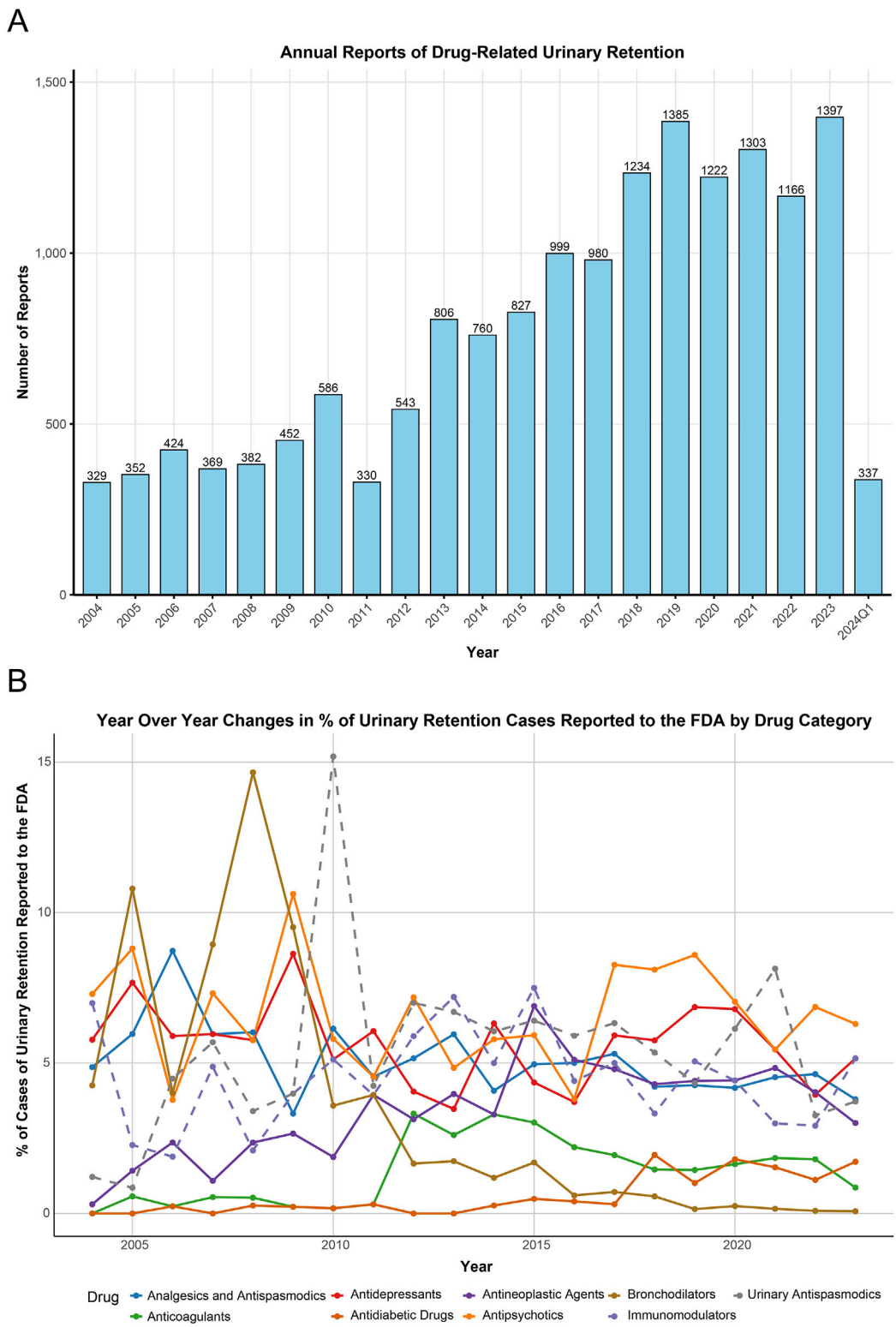


FIGURE 1
Annual reporting trends and time series plot. **(A)** The annual trend in the number of adverse event reports related to urinary retention from 2004 to the first quarter of 2024. **(B)** Changes in the percentage of urinary retention cases reported to the FAERS associated with various drug classes from 2004 to 2023. FAERS, FDA Adverse Event Reporting System.

10.3389/fphar.2024.1466875

TABLE 3 Linear regression analysis of the percentage of urinary retention cases associated with different drug classes. For each drug class, the slope, 95% CI, P-adjust, and the percentages in 2004 and 2023 are included. CI, confidence interval.

Reports of urinary retention to FDA from 2004 to 2023 by drug category					
Drug category	% change per year (95% CI)	% in 2004	% in 2023	*p*-value	p-adjust[a]
Analgesics and Antispasmodics	−0.11 (−0.19, −0.03)	4.86	3.79	0.012	0.105
Anticoagulants	0.08 (0.01, 0.16)	0	0.86	0.031	0.277
Antidepressants	−0.07 (−0.16, 0.03)	5.78	5.15	0.206	1.000
Antipsychotics	−0.01 (−0.15, 0.13)	7.29	6.30	0.905	1.000
Antineoplastic Agents	0.19 (0.10, 0.28)	0.30	3.00	<0.001	**0.004**
Antidiabetic Drugs	0.09 (0.06, 0.12)	0	1.72	<0.001	**<0.001**
Immunomodulators	0.01 (−0.11, 0.14)	6.99	5.15	0.843	1.000
Urinary Antispasmodics	0.09 (−0.14, 0.31)	1.22	3.72	0.463	1.000
Bronchodilators	−0.53 (−0.75, −0.31)	4.26	0.07	<0.001	**0.001**

Notes: [a] *P*-values were adjusted using the Bonferroni method. Bold values indicate statistically significant p-adjust.

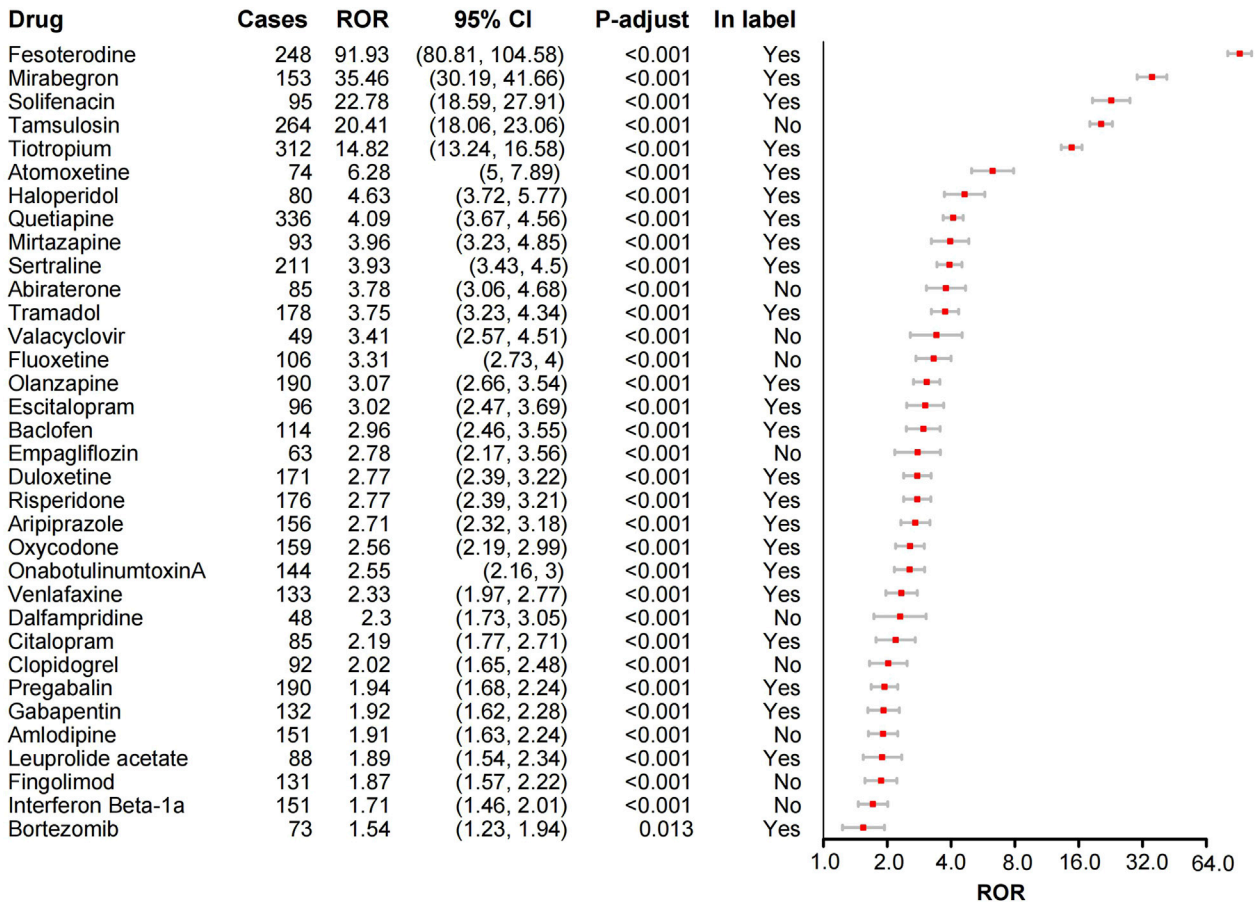


FIGURE 2
Forest plot of ROR analysis for 34 drugs with positive urinary retention signals and label information. ROR, Reporting odds ratio. CI, confidence interval. *P*-values were adjusted using the Bonferroni method.

312), Tamsulosin (n = 264), Fesoterodine (n = 248), and Lenalidomide (n = 246). After Bonferroni correction, 34 drugs (68%) exhibited significant signals for UR (Figure 2). The top five drugs by signal strength were Fesoterodine (ROR = 91.93), Mirabegron (ROR = 35.46), Solifenacin (ROR = 22.78), Tamsulosin (ROR = 20.41), and Tiotropium (ROR = 14.82). Notably, some

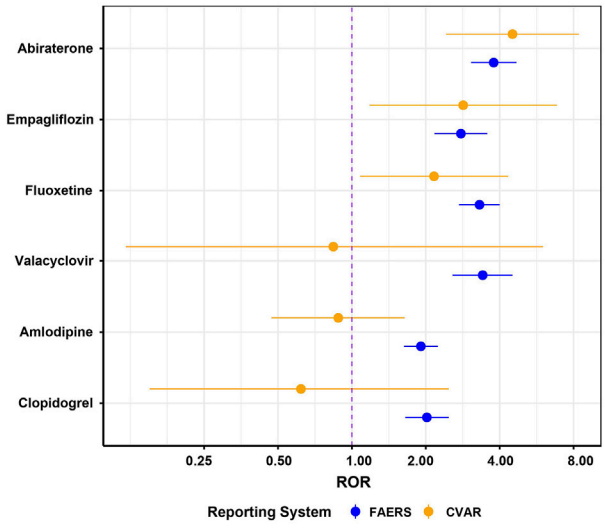


FIGURE 3
Analysis of ROR for drug adverse reactions related to urinary retention not covered in drug instructions, based on FAERS and CVAR. ROR, Reporting odds ratio. FAERS, FDA Adverse Event Reporting System. CVAR, Canada Vigilance Adverse Reaction Online Database.

drugs such as Fesoterodine, Mirtazapine, and Sertraline explicitly mentioned UR as a potential adverse reaction on their labels, consistent with our findings (Figure 2). Additionally, we discovered some drugs not listed for UR in their labels (Figure 2). However, certain drugs, like Tamsulosin for benign prostatic hyperplasia and Dalfampridine, Fingolimod, and Interferon Beta-1a for multiple sclerosis, are not considered new findings as their indications inherently risk UR. After screening, Abiraterone, Valacyclovir, Fluoxetine, Empagliflozin, Clopidogrel, and Amlodipine were identified as drugs with unexpected UR potential. Subsequently, we validated these unexpected findings using the CVAR database with the ROR method. Positive signals for Abiraterone, Fluoxetine, and Empagliflozin were confirmed (Figure 3), indicating a high risk of inducing UR.

3.4 Onset time of UR

After removing duplicates and erroneous reports, 4,790 reports provided onset time data. The median time to onset for drug-related UR was 29 days (IQR 6–183 days). Most cases of UR occurred within 30 days of medication initiation (n = 2,427, 50.7%), but UR could still occur over a year after starting the medication (n = 860, 18%), as shown in Figure 4.

4 Discussion

To our knowledge, this is the first study to jointly utilize the FAERS and CVAR databases to mine and analyze AEs related to drug-induced UR. Compared to previous studies based solely on the Italian spontaneous reporting system database (Crisafulli et al., 2022), our study features a larger sample size of AE reports (N = 16,183) and includes only data reported by healthcare professionals. Our findings were rigorously adjusted using the Bonferroni correction. This study reveals reporting trends of common drug categories associated with UR-related AEs from 2004 to 2023, using statistical methods to quantify these trends—an analysis that previous studies lacked. Further signal detection identified six drugs related to UR that were not mentioned on the product labels. Of these, three drugs—Abiraterone, Fluoxetine, and Empagliflozin—were further validated using the CVAR database, enhancing the reliability of our results.

During the past 2 decades, we observed a significant upward trend in reports of drug-related UR (Table 2, Figure 1A), with the number of reports increasing from 329 in 2004 to 1,397 in 2023. This trend may be attributed to factors such as an aging population, increased drug use, and improved AE monitoring (Verhamme et al., 2008). In our study, the proportion of male patients (53.4%) was higher than that of female patients (37.2%), consistent with previous findings (Verhamme et al., 2008; Crisafulli et al., 2022). Statistically, acute UR has an incidence rate of 4.5–6.8 per 1,000 men aged over 70 per year (Crisafulli et al., 2022), while in women, the incidence is about 0.07 per 1,000 (Klarskov et al., 1987). This discrepancy may be linked to men's higher susceptibility to prostate-related conditions, which increase the risk of UR (Crisafulli et al., 2022). In addition, we also observed that the top six countries in terms of reported cases listed in Table 2 are all developed countries. This may be attributed to their well-established pharmacovigilance systems, higher levels of public and physician awareness, and stricter legal and regulatory requirements.

Our study revealed that the proportion of UR reports related to Antineoplastic Agents and Antidiabetic Drugs showed a significant annual increase from 2004 to 2023 (p-adjust < 0.05), whereas reports related to Bronchodilators exhibited a significant decline. The increase in Antineoplastic Agent-related reports could be due to factors such as increased use, neurotoxicity of the drugs, side effects, and comorbidities in cancer patients (e.g., benign prostatic hyperplasia and diabetes) (Drake et al., 1998; Carbone et al., 2017; Alberti, 2019). The improved drug safety monitoring system and increased patient awareness may also contribute to the higher reporting numbers (Hazell and Shakir, 2006). The increasing proportion of reported UR associated with antidiabetic drugs over the past 20 years can be attributed to several factors. First, the global prevalence of diabetes, particularly the rising burden of type 2 diabetes, has driven a growing demand for antidiabetic medications (Ong et al., 2023). As the incidence of diabetes has increased, new drug classes, including glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors, have been rapidly developed and widely applied (Ahmad et al., 2022). While these drugs offer notable advantages in efficacy, their potential adverse effects, especially those impacting the autonomic nervous system and urinary tract, have not been fully recognized. Additionally, the widespread adoption of personalized treatment strategies has played a significant role. Updates to clinical guidelines, which focus on tailoring treatment plans based on patient characteristics, have led to a more diverse range of medications being prescribed, further increasing their use (Williams et al., 2022). Together, these factors, alongside continuous innovations in diabetes care, help explain the rise in

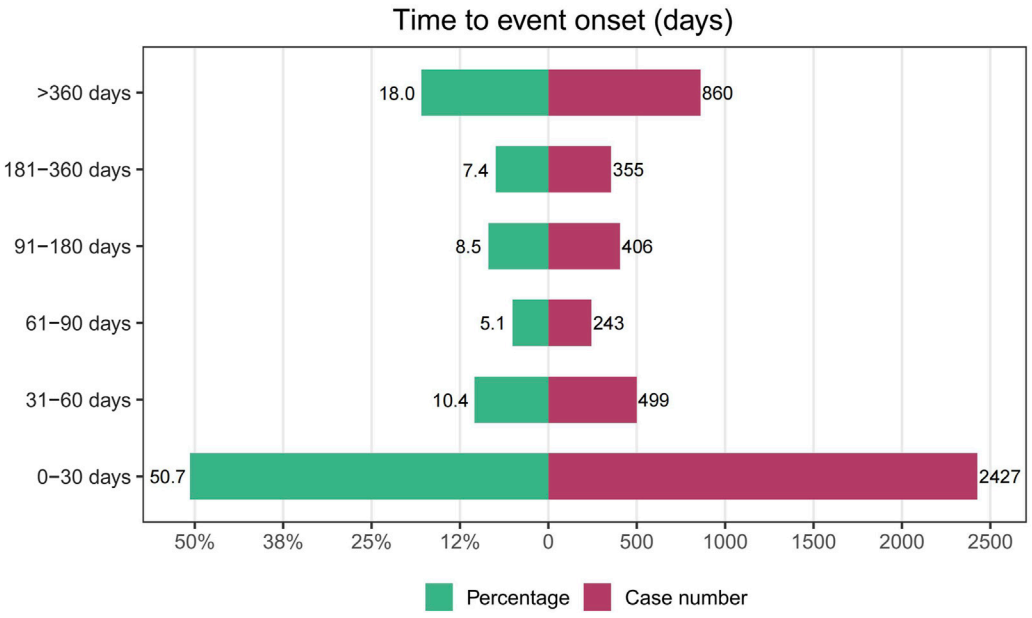


FIGURE 4
Time to onset of drug-related urinary retention.

UR reports associated with antidiabetic drugs in recent decades. In contrast, the decrease in Bronchodilator-related UR reports may be related to optimized treatment strategies, improved drug combinations, enhanced patient education, and better drug safety profiles (Rodrigo and Castro-Rodríguez, 2012; Cazzola and Matera, 2014). These findings underscore the importance of monitoring and managing drug-related AEs in clinical practice, especially for high-risk drugs and patient populations.

Certain antispasmodic drugs used for treating overactive bladder, including the anticholinergic agents Fesoterodine (ROR = 91.93) and Solifenacin (ROR = 22.78), and the β3-adrenergic receptor agonist Mirabegron (ROR = 35.46), exhibited high signal strength for UR AEs. Notably, UR is a known common adverse reaction for these drugs. This finding, consistent with their product labels, further validates the safety concerns associated with these drugs in clinical use. Therefore, clinicians should carefully evaluate patient risk factors when prescribing these medications and closely monitor for UR AEs.

Some drugs unexpectedly identified as potentially causing UR—Abiraterone, Fluoxetine, and Empagliflozin—showed positive AE signals in both the FAERS and CVAR databases. This finding is highly significant for drug safety monitoring and risk management, providing a scientific basis for improving drug labeling. Health professionals should exercise increased vigilance when prescribing these medications, particularly to high-risk populations such as older adults or individuals with comorbid conditions. Abiraterone, a selective androgen synthesis inhibitor, reduces androgen synthesis by inhibiting the enzyme cytochrome P450 c17 (CYP17), which is crucial in testosterone production in the adrenal glands, testes, and prostate tumors (de Bono et al., 2011). Beck et al. reported a case of a 74-year-old male developing UR and acute kidney injury with hypokalemia and metabolic alkalosis while on Abiraterone for metastatic prostate cancer. These symptoms resolved upon discontinuation of Abiraterone, suggesting a potential association (Beck et al., 2021), supporting our findings.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is effective and well-tolerated for treating depression and obsessive-compulsive disorder (Bulut et al., 2022). Previous studies have reported UR when Fluoxetine is combined with other antipsychotic or benzodiazepine drugs (Lock et al., 1990; Benazzi, 1996). There are also reports of UR with Fluoxetine monotherapy (Karadag et al., 2015; Bulut et al., 2022). For instance, a 17-year-old female developed UR within the first week of Fluoxetine (20 mg/day) treatment, which worsened to complete inability to urinate. Her symptoms resolved after discontinuing Fluoxetine (Karadag et al., 2015). BULUT also reported a case of chronic UR in a 15-year-old girl on Fluoxetine monotherapy (Bulut et al., 2022). The mechanism by which Fluoxetine causes UR is not fully understood, but several possible explanations exist. First, Fluoxetine may increase the activity of the external urethral sphincter by inhibiting the reuptake of serotonin around Onuf's nucleus motor neurons (Karadag et al., 2015). Second, blocking spinal 5-HT1a receptors can reduce bladder contractions, thereby promoting the development of UR (Le Poul et al., 2000; Burgard et al., 2003). Clinicians should be aware of the potential for Fluoxetine to cause UR and intervene promptly with timely diagnosis and treatment.

Empagliflozin, a potent selective SGLT2 inhibitor used to treat type 2 diabetes in adults, has a well-documented efficacy and tolerability profile (Frampton, 2018). Its label notes a higher incidence of urinary tract infections (UTIs) in patients, particularly those with a history of chronic or recurrent UTIs, but does not mention UR as a potential AE. Existing studies on Empagliflozin-related UR are scarce. Brock reported a case of asymptomatic UR and emphysematous cystitis in a 62-year-old male with type 2 diabetes on Empagliflozin (Brock et al., 2022). Another drug with a similar mechanism, Dapagliflozin, has been

reported to potentially cause UR (Crisafulli et al., 2022). The mechanism behind these drugs inducing UR is unclear but may be linked to their association with UTIs, leading to urethral edema and UR (Serlin et al., 2018). Additionally, diabetes itself can affect bladder nerves, causing bladder dysfunction and potentially leading to UR (Sakakibara et al., 2018). Future studies are needed to clarify whether this potential signal is due to Empagliflozin's independent effect or a synergistic effect with diabetes.

While Valacyclovir, Clopidogrel, and Amlodipine did not show positive signals for UR in the CVAR validation, this does not rule out their association with the AE. For example, Amlodipine, a calcium channel blocker (CCB), might cause UR by reducing the contractility of smooth muscles, including the bladder detrusor muscle, leading to incomplete bladder emptying (Serlin et al., 2018). Positive signals in the FAERS database suggest potential risks, but these signals may not replicate in validation databases due to sample size, observation time, or other variables. Therefore, clinical observation and further research and monitoring are needed to establish the relationship between these drugs and UR.

Our study found that the median time to onset for drug-related UR was 29 days. Over half of the patients experienced the target AE within the first 30 days of medication use (50.7%), indicating that drug-related UR primarily occurs early in the treatment course. This finding highlights the need for close monitoring of patients during this critical period and underscores the importance of educating patients about the early symptoms of UR to enable prompt intervention. However, it is important to note that UR can still occur over a year after starting the medication.

However, this study has several limitations. First, FAERS and CVAR are based on self-reporting systems, which carry the risks of underreporting, duplicate reporting, and inaccurate reporting. Although we conducted deduplication, the study results may still be biased. Second, there is a lack of overall information on the medication population, making it impossible to calculate the incidence of drug-related UR. Additionally, factors such as patient gender, age, race, comorbidities, and concomitant medications potentially influence the occurrence of AEs, but there are currently no established methods to account for these factors in disproportionality analysis. Furthermore, FAERS does not provide aggregated data for more than five drugs at a time (Giunchi et al., 2023), so our focus was limited to the top 50 drugs reporting UR AEs, a common practice in similar studies (Yu et al., 2021; Fei et al., 2023). Finally, our analysis is primarily hypothesis-generating; thus, the relationship between drugs and UR is correlational rather than causal. Potential safety signals need further evaluation through pharmacoepidemiological studies.

5 Conclusion

Our analysis of FAERS data reveals a consistent upward trend in reports of drug-induced UR over the past 2 decades. Notably, there has been a significant increase in UR reports associated with antineoplastic and antidiabetic drugs, while those linked to bronchodilators have decreased. The CVAR analysis has validated the newly identified signals for Abiraterone, Fluoxetine, and Empagliflozin. These findings are vital for healthcare providers, researchers, and regulatory authorities, highlighting the critical need for continuous monitoring and reassessment of drug safety to safeguard patient health. Furthermore, there is a pressing need for comprehensive clinical and pharmacoepidemiological studies to deepen our understanding of the mechanisms driving drug-induced UR.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

XD: Conceptualization, Data curation, Formal Analysis, Software, Writing–original draft. KY: Conceptualization, Visualization, Writing–review and editing. YC: Methodology, Writing–review and editing. YH: Funding acquisition, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (Grant No. 52173281).

Acknowledgments

We are grateful for the open policy and data provided by FAERS and CVAR, as well as the contributions of all participants in these studies.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1466875/full#supplementary-material

References

Ahmad, E., Lim, S., Lamptey, R., Webb, D. R., and Davies, M. J. (2022). Type 2 diabetes. *Lancet* 400 (10365), 1803–1820. doi:10.1016/s0140-6736(22)01655-5

Alberti, P. (2019). Platinum-drugs induced peripheral neurotoxicity: clinical course and preclinical evidence. *Expert Opin. Drug Metab. Toxicol.* 15 (6), 487–497. doi:10.1080/17425255.2019.1622679

Beck, N. M., Rizzolo, K., and Ambruso, S. L. (2021). Not just licorice: Abiraterone and apparent mineralocorticoid excess: PO1115. *J. Am. Soc. Nephrol.* 32 (10S), 368. doi:10.1681/ASN.20213210S1368b

Benazzi, F. (1996). Urinary retention with fluoxetine-haloperidol combination in a young patient. *Can. J. Psychiatry* 41 (9), 606–607. doi:10.1177/070674379604100922

Brock, G. M., Lane, S. M., and Roosevelt, T. S. (2022). Emphysematous cystitis and urinary retention in a male patient with diabetes mellitus type 2 treated with Empagliflozin. *AACE Clin. Case Rep.* 8 (4), 163–165. doi:10.1016/j.aace.2022.04.002

Bulut, Ö. F., Karayağmurlu, A., and Kaya, İ. (2022). Fluoxetine related urinary retention in a 15-year-old girl: a case report. *Noro Psikiyatr. Ars* 59 (3), 246–247. doi:10.29399/npa.27938

Burgard, E. C., Fraser, M. O., and Thor, K. B. (2003). Serotonergic modulation of bladder afferent pathways. *Urology* 62 (4 Suppl. 1), 10–15. doi:10.1016/s0090-4295(03)00590-9

Carbone, D. P., Reck, M., Paz-Ares, L., Creelan, B., Horn, L., Steins, M., et al. (2017). First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N. Engl. J. Med.* 376 (25), 2415–2426. doi:10.1056/NEJMoa1613493

Cazzola, M., and Matera, M. G. (2014). Bronchodilators: current and future. *Clin. Chest Med.* 35 (1), 191–201. doi:10.1016/j.ccm.2013.10.005

Crisafulli, S., Cutroneo, P. M., Verhamme, K., Ferrajolo, C., Ficarra, V., Sottosanti, L., et al. (2022). Drug-induced urinary retention: an analysis of a national spontaneous adverse drug reaction reporting database. *Eur. Urol. Focus* 8 (5), 1424–1432. doi:10.1016/j.euf.2021.07.001

de Bono, J. S., Logothetis, C. J., Molina, A., Fizazi, K., North, S., Chu, L., et al. (2011). Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* 364 (21), 1995–2005. doi:10.1056/NEJMoa1014618

Drake, M. J., Nixon, P. M., and Crew, J. P. (1998). Drug-induced bladder and urinary disorders. Incidence, prevention and management. *Drug Saf.* 19 (1), 45–55. doi:10.2165/00002018-199819010-00004

Edwards, R. T., McCormick-Deaton, C., and Hosanagar, A. (2014). Acute urinary retention secondary to buprenorphine administration. *Am. J. Emerg. Med.* 32 (1), 109.e1–109.e1092. doi:10.1016/j.ajem.2013.08.022

Fei, W., Shen, J., and Cai, H. (2023). Causes of drug-induced severe cutaneous adverse reaction epidermal necrolysis (EN): an analysis using FDA adverse event reporting system (FAERS) database. *Clin. Cosmet. Investig. Dermatol* 16, 2249–2257. doi:10.2147/ccid.S422928

Frampton, J. E. (2018). Empagliflozin: a review in type 2 diabetes. *Drugs* 78 (10), 1037–1048. doi:10.1007/s40265-018-0937-z

Giunchi, V., Fusaroli, M., Hauben, M., Raschi, E., and Poluzzi, E. (2023). Challenges and opportunities in accessing and analysing FAERS data: a call towards a collaborative approach. *Drug Saf.* 46 (10), 921–926. doi:10.1007/s40264-023-01345-w

Hazell, L., and Shakir, S. A. (2006). Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 29 (5), 385–396. doi:10.2165/00002018-200629050-00003

Jiang, S., Burke, H., Hernandez, M., and Ruth, L. (2022). Sertraline-induced urinary retention reversed by mirtazapine in an adolescent. *Prim. Care Companion CNS Disord.* 24 (6), 22cr03254. doi:10.4088/PCC.22cr03254

Kadoyama, K., Sakaeda, T., Tamon, A., and Okuno, Y. (2012). Adverse event profile of tigecycline: data mining of the public version of the U.S. Food and Drug Administration adverse event reporting system. *Biol. Pharm. Bull.* 35 (6), 967–970. doi:10.1248/bpb.35.967

Karadag, M., Gokcen, C., Bayar, H., and Aksoy, I. (2015). Urinary retention in an adolescent patient caused by fluoxetine alone. *J. Child. Adolesc. Psychopharmacol.* 25 (8), 658. doi:10.1089/cap.2015.0134

Klarskov, P., Andersen, J. T., Asmussen, C. F., Brenøe, J., Jensen, S. K., Jensen, I. L., et al. (1987). Acute urinary retention in women: a prospective study of 18 consecutive cases. *Scand. J. Urol. Nephrol.* 21 (1), 29–31. doi:10.3109/00365598709180286

Le Poul, E., Boni, C., Hanoun, N., Laporte, A. M., Laaris, N., Chauveau, J., et al. (2000). Differential adaptation of brain 5-HT1A and 5-HT1B receptors and 5-HT transporter in rats treated chronically with fluoxetine. *Neuropharmacology* 39 (1), 110–122. doi:10.1016/s0028-3908(99)00088-x

Lock, J. D., Gwirtsman, H. E., and Targ, E. F. (1990). Possible adverse drug interactions between fluoxetine and other psychotropics. *J. Clin. Psychopharmacol.* 10 (5), 383–384. doi:10.1097/00004714-199010000-00031

Mascolo, A., Scavone, C., Ferrajolo, C., Rafaniello, C., Danesi, R., Del Re, M., et al. (2021). Immune checkpoint inhibitors and cardiotoxicity: an analysis of spontaneous reports in eudravigilance. *Drug Saf.* 44 (9), 957–971. doi:10.1007/s40264-021-01086-8

Moussa, M., Papatsoris, A., Chakra, M. A., Fares, Y., and Dellis, A. (2020). Lower urinary tract dysfunction in common neurological diseases. *Turk J. Urol.* 46 (Suppl. 1), S70–s78. doi:10.5152/tud.2020.20092

Ojo, A. O., Ajasa, A. L., Oladipupo, R. B., and Aderinto, N. O. (2021). Urinary retention concomitant with methamphetamine use: a case report. *J. Med. Case Rep.* 15 (1), 183. doi:10.1186/s13256-021-02705-9

Ong, K. L., Stafford, L. K., McLaughlin, S. A., Boyko, E. J., Vollset, S. E., Smith, A. E., et al. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 402 (10397), 203–234. doi:10.1016/s0140-6736(23)01301-6

Pape, D. M., and Nitti, V. W. (2018). "Urinary retention and voiding dysfunction," in *Neuro-urology*. Editors R. Dmochowski and J. Heesakkers (Cham: Springer International Publishing), 207–231.

Rodrigo, G. J., and Castro-Rodríguez, J. A. (2012). Safety of long-acting β agonists for the treatment of asthma: clearing the air. *Thorax* 67 (4), 342–349. doi:10.1136/thx.2010.155648

Sakakibara, R., Takahashi, O., Nishimura, H., Tateno, F., Kishi, M., Tsuyusaki, Y., et al. (2018). The relationship between bladder, periarterial and somatic neuropathy in diabetes. *Intern Med.* 57 (15), 2165–2168. doi:10.2169/internalmedicine.9749-17

Selius, B. A., and Subedi, R. (2008). Urinary retention in adults: diagnosis and initial management. *Am. Fam. Physician* 77 (5), 643–650.

Serlin, D. C., Heidelbaugh, J. J., and Stoffel, J. T. (2018). Urinary retention in adults: evaluation and initial management. *Am. Fam. Physician* 98 (8), 496–503.

Thomas, K., Chow, K., and Kirby, R. S. (2004). Acute urinary retention: a review of the aetiology and management. *Prostate Cancer Prostatic Dis.* 7 (1), 32–37. doi:10.1038/sj.pcan.4500700

Verhamme, K. M., Sturkenboom, M. C., Stricker, B. H., and Bosch, R. (2008). Drug-induced urinary retention: incidence, management and prevention. *Drug Saf.* 31 (5), 373–388. doi:10.2165/00002018-200831050-00002

Williams, D. M., Jones, H., and Stephens, J. W. (2022). Personalized type 2 diabetes management: an update on recent advances and recommendations. *Diabetes Metab. Syndr. Obes.* 15, 281–295. doi:10.2147/dmso.S331654

Yang, Y., Shu, Y., Chen, G., Yin, Y., Li, F., and Li, J. (2022). A real-world pharmacovigilance study of FDA Adverse Event Reporting System (FAERS) events for venetoclax. *PLoS One* 17 (12), e0278725. doi:10.1371/journal.pone.0278725

Yu, R. J., Krantz, M. S., Phillips, E. J., and Stone, C. A. (2021). Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA adverse event reporting system (FAERS). *J. Allergy Clin. Immunol. Pract.* 9 (2), 819–829.e2. doi:10.1016/j.jaip.2020.09.021

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 10 January 2025
DOI 10.3389/fphar.2024.1517546

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Joanna Gdula-Argasinska,
Jagiellonian University Medical College, Poland
Liz Girardi Müller,
Regional Community University of Chapecó, Brazil

*CORRESPONDENCE
Jian Cai,
455320109@qq.com
Zhijun Xiao,
zhijxiao@126.com
Feng Xu,
xuf@smu.edu.cn

RECEIVED 26 October 2024
ACCEPTED 31 December 2024
PUBLISHED 10 January 2025

CITATION
Cao J, Chen Z, Wang Y, Ma Y, Yang Z, Cai J, Xiao Z and Xu F (2025) Overweight and glucose/lipid metabolism abnormality associated with SSRIs: a pharmacovigilance study based on the FDA adverse event reporting system. *Front. Pharmacol.* 15:1517546. doi: 10.3389/fphar.2024.1517546

Overweight and glucose/lipid metabolism abnormality associated with SSRIs: a pharmacovigilance study based on the FDA adverse event reporting system

Jinming Cao [1], Zhicong Chen [1], Yan Wang [2], Yunpeng Ma [2], Zhen Yang [2], Jian Cai [3]*, Zhijun Xiao [2]* and Feng Xu [1]*

[1]Fengxian Hospital, Southern Medical University, Shanghai, China, [2]Sixth People's Hospital South Campus, Shanghai Jiaotong University, Shanghai, China, [3]Fengxian Mental Health Center, Shanghai, China

Background: In the past few decades, selective serotonin reuptake inhibitors (SSRIs) became widely used antidepressants worldwide. Therefore, the adverse reactions of patients after SSRI administration became a public and clinical concern. In this study, we conducted a pharmacovigilance study using the Adverse Event Reporting System (FAERS) database of the US Food and Drug Administration. Our main goal was to evaluate adverse events related to SSRIs, with a particular focus on abnormal weight gain and glucose/lipid metabolism disorders.

Method: The adverse event data for representative SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) was extracted from the FAERS database from 2004Q1 to 2023Q4. The reporting odds ratio and proportional reporting ratio were employed to explore relevant adverse event reports (ADEs) signals. Univariate logistic regression analysis was utilized to explore factors associated with glucose/lipid metabolism abnormality following SSRIs treatment.

Results: We identified 143,744 ADE reports associated with SSRIs and revealed significant abnormal signals related to weight gain and glucose/lipid metabolism in depressed patients. Variations were observed among different SSRIs medications. Specifically, citalopram was associated with abnormal weight gain (ROR: 4, 95% CI: 3.1-5.2) and hepatic steatosis (ROR: 2.8, 95% CI: 2.1-3.6); escitalopram was correlated with gestational diabetes (ROR: 9.1, 95% CI: 6.6-12.4) and cholestasis (ROR: 2.4, 95% CI: 1.75-3.38); fluoxetine was associated with obesity (ROR: 2.8, 95% CI: 2.08-3.78); fluvoxamine was linked to arteriospasm coronary (ROR: 13.87, 95% CI: 4.47-43.1); and sertraline was implicated in neonatal jaundice (ROR: 16.1, 95% CI: 12.6-20.6). Females and younger age are important risk factors for the development of associated adverse effects.

Conclusion: Our study screened for adverse effects associated with abnormal glucose/lipid metabolism, such as abnormal body weight and fatty liver, in

depressed patients taking selective serotonin reuptake inhibitors by utilizing FAERS database. This provides valuable insights for healthcare professionals in accepting and managing patients treated with SSRIs.

KEYWORDS

selective serotonin reuptake inhibitors, FAERS, overweight, ADEs, glucose/lipid metabolism disorders

Introduction

With the increase of life pressure, the incidence rate of depression in all age groups has increased (Thapar et al., 2022; Gundersen and Bensadon, 2023). There are various factors that can lead to depression, including school or work stress, physical illness, strained relationships with family members, and financial stress in the family (Hammen, 2018). According to statistics from the World Health Organization, depression is expected to become one of the leading causes of death worldwide by 2030 (Miret et al., 2013).

Selective serotonin reuptake inhibitors (SSRIs) are widely used antidepressants for the treatment of depression and other related mental health disorders. The research on the mechanism of action of SSRIs in treating depression is constantly evolving. Early studies have shown that the expression level of brain-derived neurotrophic factor is significantly higher in patients with major depression after fluoxetine treatment (Ghosh et al., 2015). Some researchers have proposed that SSRIs exert their effects by increasing the concentration of the neurotransmitter serotonin between neurons, thereby regulating feelings and moods (Gothert et al., 2020). A study suggests that the use of sertraline significantly decrease interleukin-6 and tumor necrosis factor α in leukocytes of patients with depression (Galecki et al., 2018). In addition, some studies have shown that SSRIs improve mood disorders such as anxiety and depression by enhancing the neurotransmission of $GABA_A$ receptors (Pinna et al., 2009). Currently, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are the most used representative SSRIs for the treatment of depression. Among them, escitalopram is the s-enantiomer of citalopram, which has higher therapeutic efficacy and faster onset rate of action (Yin et al., 2023).

With the increasing use of SSRIs, public and clinical professionals are increasingly concerned about the adverse reactions of these antidepressants. In general, the common early adverse reactions encompass nausea, dizziness, headache, drowsiness, anxiety, and sexual dysfunction (Marjoribanks et al., 2013). For example, a survey indicate that SSRIs not only reduce sperm quantity and vitality in male depressive patients but also stimulate the fallopian tubes in female depressive patients, therefore negatively impacting fertility (Milosavljevic et al., 2022). In addition, SSRIs induce severe and rare adverse reactions such as gastrointestinal and intracranial hemorrhage in patients with depression (Yuet et al., 2019). However, the potential metabolic disorders after SSRI administration, such as overweight, glucose/lipid metabolism disorder, dyslipidemia and pregnancy diabetes, are still poorly understood.

The FDA Adverse Event Reporting System is maintained and managed by the US Food and Drug Administration (FDA), which supports the FDA's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. It includes adverse event reports received by FDA from manufacturers as required by regulation along with reports directly received from consumers (such as patients, family members, lawyers) and healthcare professionals (such as doctors, pharmacists, nurses), and facilitates the monitoring of drug safety and evaluation of potential medication risks. In this study, ADE data associated with SSRIs was extracted and analyzed from FAERS from the first quarter of 2004 to the fourth quarter of 2023. We aim to uncover and evaluate signals indicative of overweight and glucose/lipid metabolism disorders, and provide insights for clinical practitioners and researchers in the field.

Methods

Data source

ADE reporting data submitted to the FAERS from the first quarter of 2004 to the fourth quarter of 2023 was accessed and reviewed by authors. Each quarterly dataset includes information such as drug details (DRUG), patient demographics (DEMO), adverse events (REAC), and outcomes (OUTC).

Data processing

The generic name of the target drug was defined as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, and corresponding data are retrieved in FAERS. All quarterly DEMO, DRUG, REAC, and other report data were cleaned and organized. Subsequently, duplicate reports (retaining the latest version) were removed based on CaseID, patient name, age, country, generic names, brand names and primary suspected drug (PS). Finally, PT were identified by consulting MedDRA to further screen SSRIs-related adverse reaction reports, with emphasis on overweight, glucose/lipid metabolism disorder.

Signal mining and collation

This study utilized the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) methods for signal analysis, as delineated in Tables 1, 2. An adverse event signal was deemed significant if it met the following criteria: ADE reports >3, ROR >2, PRR >2, lower limit of the 95% confidence interval (CI) for ROR >1, lower limit of the 95% CI for PRR >1, and $\chi 2$ >4. Subsequently, manual screening was conducted to identify signals associated with overweight and glucose/lipid metabolism disorders. All data

TABLE 1 Disproportionality analysis.

Drugs	Number of targeted ADE reports	Number of other ADE reports	Total
Target drugs	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

TABLE 2 Formulas and threshold values of ROR and PRR.

	Formulas	Threshold
ROR	ad/bc	$exp(ln(ROR) \pm 1.96\ \sqrt{1/a + 1/b + 1/c + 1/d})$
PRR	a (a + b)/c (c + d)	$exp(ln(PRR) \pm 1.96\ \sqrt{1/a + 1/a + b + 1/c + 1/c + d})$

processing and signal mining calculations were performed using R software (version 4.2.2). P value less than 0.05 was considered statistically significant.

Results

ADE reports overview

Figure 1 illustrated the comprehensive data processing workflow of this study. A total of 20,755,634 ADE reports were extracted from FAERS. Following deduplication and data cleaning, a total of 143,746 reports were identified with SSRIs as the primary suspected (PS): 21,820 reports for citalopram, 19,288 for escitalopram, 21,456 for fluoxetine, 1,224 for fluvoxamine, 36,983 for paroxetine, and 42,975 for sertraline. After screening based on criteria such as ROR and PRR, a total of 6,588 PTs related to SSRIs were identified. Specifically, there were 1,227 PTs associated with citalopram, 1,091 with escitalopram, 1,248 with fluoxetine, 243 with fluvoxamine, 1,359 with paroxetine, and 1,420 with sertraline. Then, after reviewing the literature, 81 PTs related to weight and glucose/lipid metabolism were identified. Finally, we conducted a basic analysis of reports of PTs associated with SSRIs.

We visualized the number of reports for the 6 SSRIs by year (Figure 2A). The results showed a relatively smooth change in the number of ADE reports with escitalopram, citalopram, and fluvoxamine as the main suspected drugs. The number of ADE reports related to paroxetine showed an almost yearly decreasing trend. However, the number of ADE reports for sertraline increased

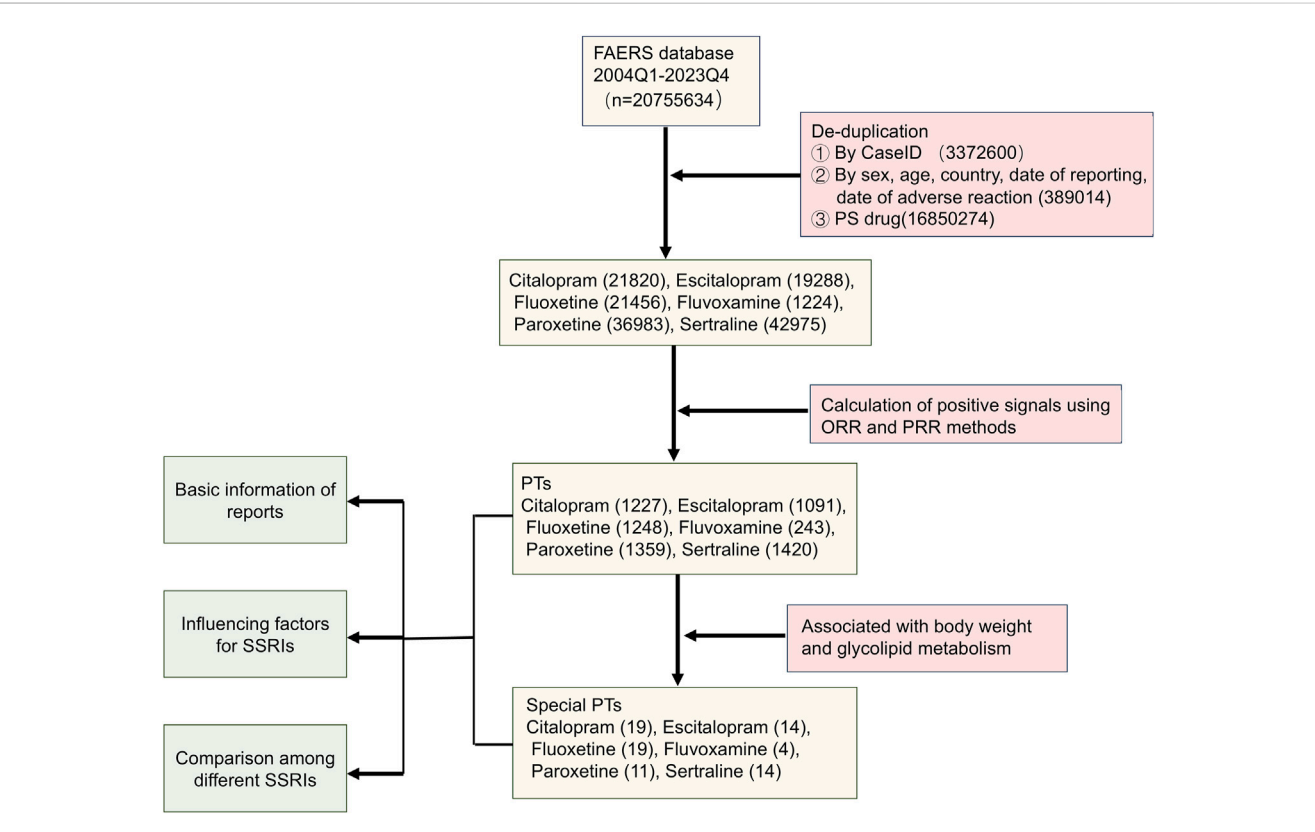


FIGURE 1
The flowchart for screening signals of overweight and glucose/lipid metabolism disorders associated with SSRIs.

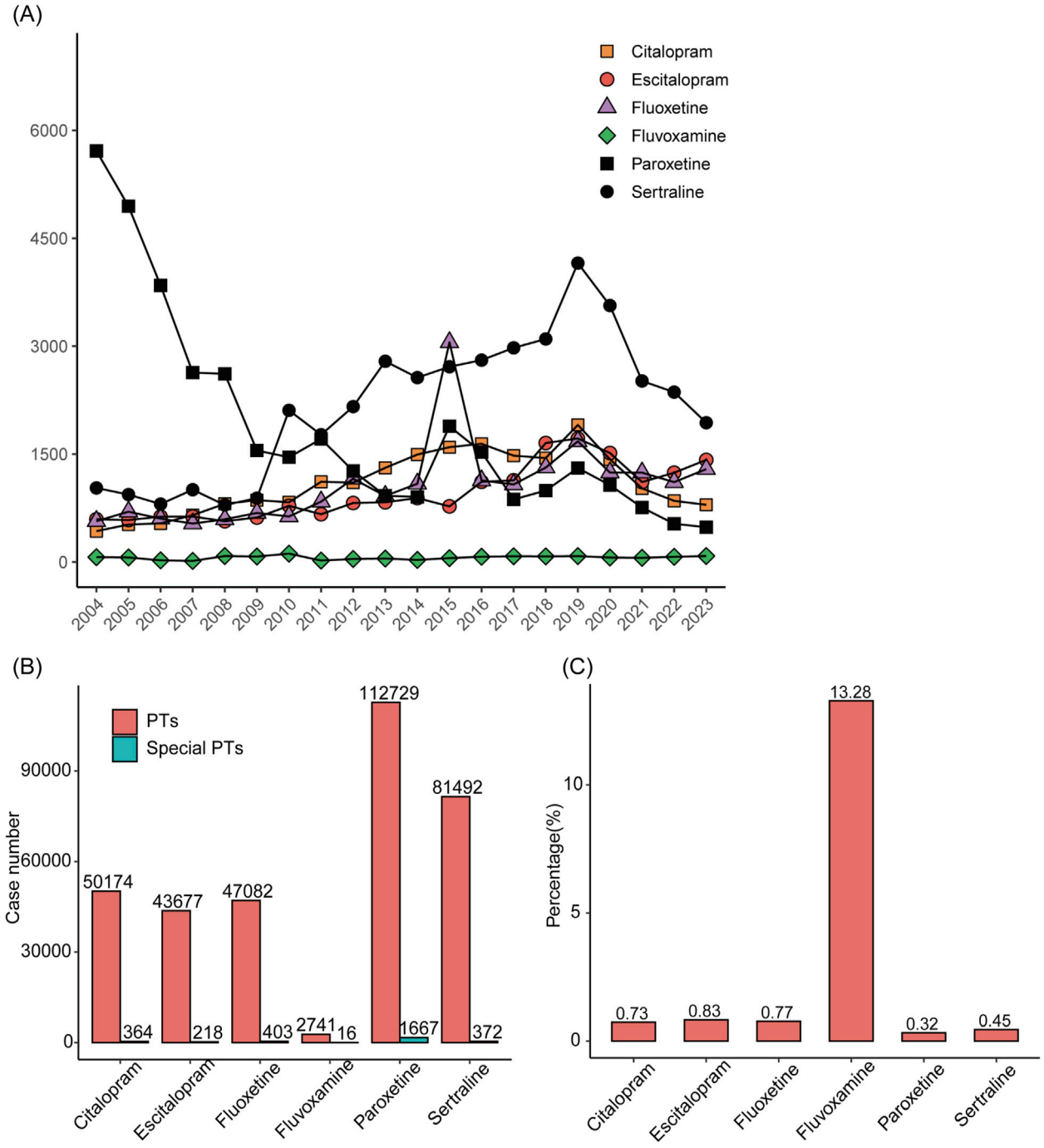


FIGURE 2
Statistics of reported diseases associated with abnormalities of glycolipid metabolism caused by treatment with SSRIs with and without SSRIs in FAERS between 2004 and 2023. **(A)** Annual ADE reports on SSRIs. **(B)** Total number of cases of adverse reactions after taking SSRIs and number of cases of adverse reactions related to disorders of glucolipid metabolism. **(C)** The proportions of reports with and without diseases associated with abnormalities of glycolipid metabolism for different SSRIs.

and then decreased, with large fluctuations. We then counted the number of reports of all ADE to SSRIs and the number of reports of ADE associated with disorders of glucolipid metabolism separately (Figure 2B). Paroxetine had the highest number of adverse reaction reports, followed by sertraline. Fluvoxamine had the lowest number of adverse reactions. In addition, we calculated the percentage of the number of adverse reactions reports related to disorders of glucolipid metabolism (Figure 2C), with fluvoxamine having the highest percentage (13.28%) and paroxetine having the lowest (0.32%).

In all relevant ADE reports, the proportion of women was higher than that of men, indicating that women might be more prone to adverse reactions compared to men after taking SSRIs. The age distribution of reports was divided into four stages. Compared to the other two age groups, the number of ADE reports was higher in the 20-40 and 40-

TABLE 3 Characteristics of cases occurred SSRIs-related ADE.

Characteristics		Citalopram (N = 21,820)	Escitalopram (N = 19,288)	Fluoxetine (N = 21,455)	Fluvoxamine (N = 1224)	Paroxetine (N = 36,982)	Sertraline (N = 42,975)
Gender [n (%)]	Female	11,699 (53.62)	11,020 (57.13)	12,261 (57.15)	599 (48.94)	21,275 (57.53)	24,282 (56.5)
	Male	7,034 (32.24)	5,959 (30.89)	5,691 (26.53)	512 (41.83)	11,997 (32.44)	12,792 (29.77)
	Unknown	3,087 (14.15)	2,307 (11.96)	3,503 (16.33)	113 (9.23)	3,710 (10.03)	5,901 (13.73)
Age [n (%)]	<20	1800 (8.25)	1707 (8.85)	3,257 (15.18)	185 (15.11)	3,364 (9.1)	5,269 (12.26)
	20–40	4,517 (20.7)	3,603 (18.68)	4,157 (19.38)	316 (25.82)	5,498 (14.87)	8,740 (20.34)
	40–60	4,872 (22.33)	3,833 (19.87)	4,325 (20.16)	244 (19.93)	5,832 (15.77)	7,758 (18.05)
	>60	4,317 (19.78)	3,638 (18.86)	2,690 (12.54)	211 (17.24)	4,699 (12.71)	7,364 (17.14)
	Unknown	6,314 (28.94)	6,507 (33.74)	7,026 (32.75)	268 (21.9)	17,589 (47.56)	13,844 (32.21)

TABLE 4 The occupational distribution and national source distribution of SSRI related ADE reporters.

	Citalopram (N = 21,820)		Escitalopram (N = 19,288)		Fluoxetine (N = 21,455)		Fluvoxamine (N = 1224)		Paroxetine (N = 36,982)		Sertraline (N = 42,975)	
Reporter [n (%)]	OT	7,209 (33.04)	CN	5,339 (27.68)	CN	7,269 (33.88)	MD	326 (26.63)	CN	21,295 (57.58)	CN	17,062 (39.7)
	CN	4,429 (20.3)	OT	5,249 (27.21)	OT	3,608 (16.82)	CN	238 (19.44)	MD	5,530 (14.95)	MD	9,139 (21.27)
	MD	4,347 (19.92)	MD	4,550 (23.59)	MD	5,724 (26.86)	OT	180 (14.71)	OT	3,339 (9.03)	OT	7,015 (16.32)
	Others	5,835 (26.74)	Others	4,150 (21.52)	Others	4,854 (22.62)	Others	480 (39.22)	Others	6,818 (18.44)	Others	9,759 (22.94)
Reporting country [n (%)]	US	5,980 (27.41)	US	7,293 (37.81)	US	10,475 (48.82)	US	393 (32.11)	US	16,432 (44.43)	US	19,254 (44.8)
	GB	5,046 (23.13)	DK	3,327 (17.25)	GB	3,534 (16.47)	JP	211 (17.24)	GB	3,856 (10.43)	GB	8,744 (20.35)
	DK	2,434 (11.15)	FR	1432 (7.42)	FR	1296 (6.04)	DE	124 (10.13)	JP	2077 (5.62)	DE	1730 (4.03)
	Others	8,360 (38.31)	Others	7,236 (37.52)	Others	6,150 (28.66)	Others	496 (40.52)	Others	14,617 (39.52)	Others	13,247 (30.82)

60 age groups (Table 3). Medical doctors (MD), occupational therapists (OT), and clinical nurses (CN) were the primary reporters. The majority of reports come from the United States (US), United Kingdom (GB), Denmark (DK), France (FR), Japan (JP), and Germany (DE) (Table 4).

ADE signal detection

The top-ranking PTs in ADE signal intensity for citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline were shown in Figures 3A–F. The frequency of PT reports related to overweight and glucose/lipid metabolism disorders for SSRIs were 364, 218, 403, 16, 1667, and 372, respectively, as delineated in Figures 4A–F. Specifically, with the exception of fluvoxamine, the remaining five SSRIs had a higher incidence of gestational diabetes in female patients. Citalopram, paroxetine and sertraline tend to cause abnormal weight gain in patients. In addition, hepatobiliary disorders such as "hepatic steatosis" and "cholestasis" caused by abnormalities in glucose and lipid metabolism were more common with citalopram, escitalopram and fluoxetine. For more details, please refer to Supplementary Tables S1–S6 (Sheet 1 and Special PTS, which respectively include all PTs related to citalopram, PTs related to glucose/lipid metabolism abnormality).

The number of adverse reactions caused by abnormalities in glucose/lipid metabolism was analyzed by gender (Figure 5). The results showed that, with the exception of "gestational diabetes", "abnormal increase" and "hepatic steatosis" were more likely to occur in female depressed patients, and coronary atherosclerosis was more likely to occur in male depressed patients.

Influencing factors for SSRIs-related glucose/lipid metabolism disorders

We further investigated demographic factors that may influence the occurrence of disorders associated with glucose/lipid

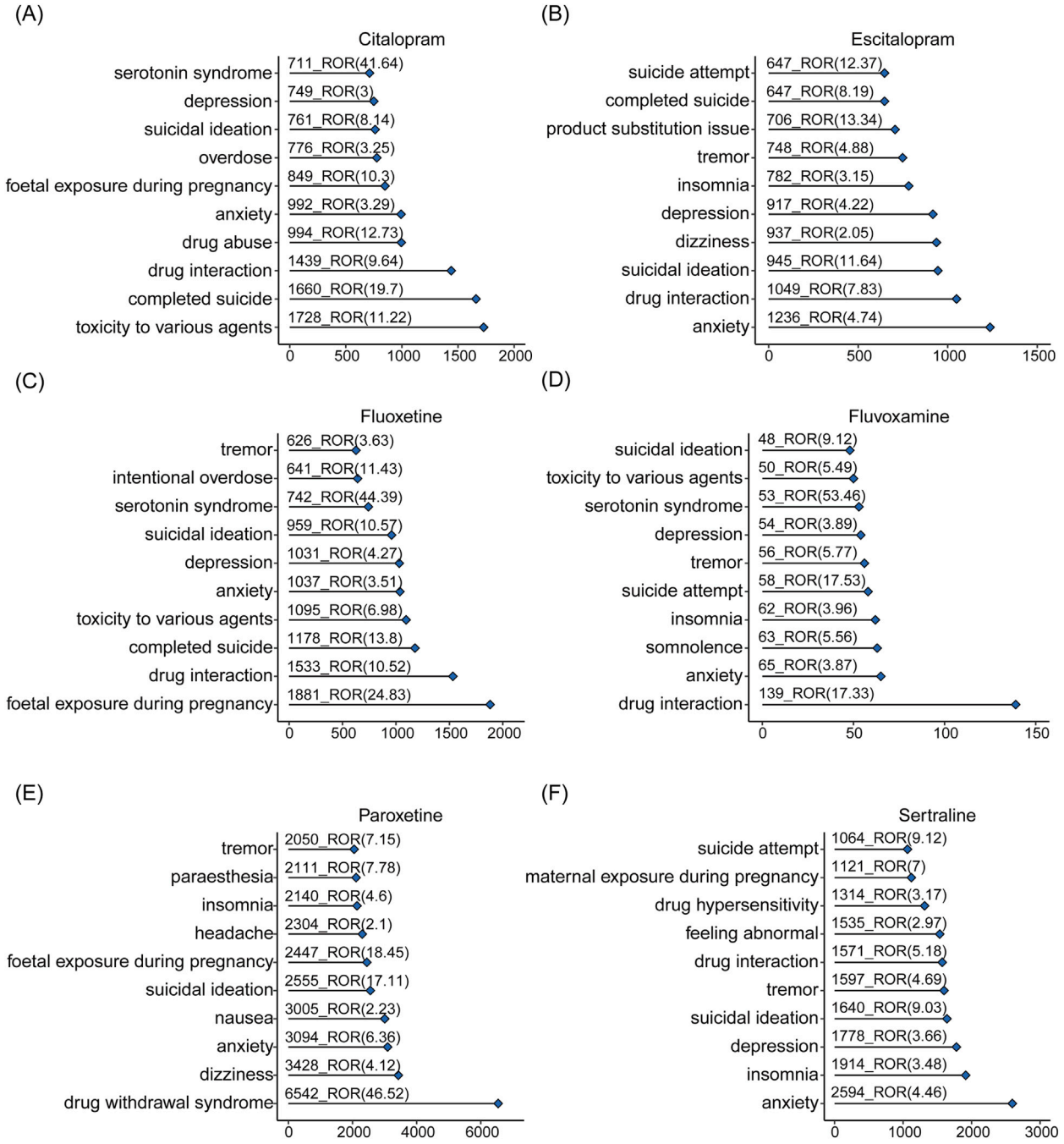


FIGURE 3
The overall signals of disorders associated with SSRIs. Adverse reactions related to citalopram **(A)**, escitalopram **(B)**, fluoxetine **(C)**, fluvoxamine **(D)**, paroxetine **(E)**, sertraline **(F)** and occurring in the top 10 numbers.

metabolism disorders using one-way logistic regression analyses based on case reports in which SSRIs were the primary suspected drug (Figure 6). Of these reports, only a total of 142,787 case reports of PTs associated with SSRIs all contained information on age, sex, and body weight, as detailed in Supplementary Table S7. Among all cases of SSRIs, female patients had a higher risk of glucose/lipid metabolism disorders-related disorders compared to males (OR = 1.63 [1.56, 1.71], P < 0.001). Patients aged 60–75 years were 1.27 times more likely to develop associated disorders compared to patients aged 75 years or older (OR = 1.27 [1.13, 1.42], P < 0.001), and patients younger than 60 years were 1.9 times more likely to develop associated disorders (OR = 1.90 [1.73, 2.09], P < 0.001). Patients weighing 60–75 kg and less than 60 kg had a reduced probability of developing the associated disease compared with patients weighing more than 75 kg. Subsequently, we analyzed each of the six SSRIs individually and showed that, consistent with the results of the overall analysis, both sex and age of the patients increased the probability of developing diseases associated

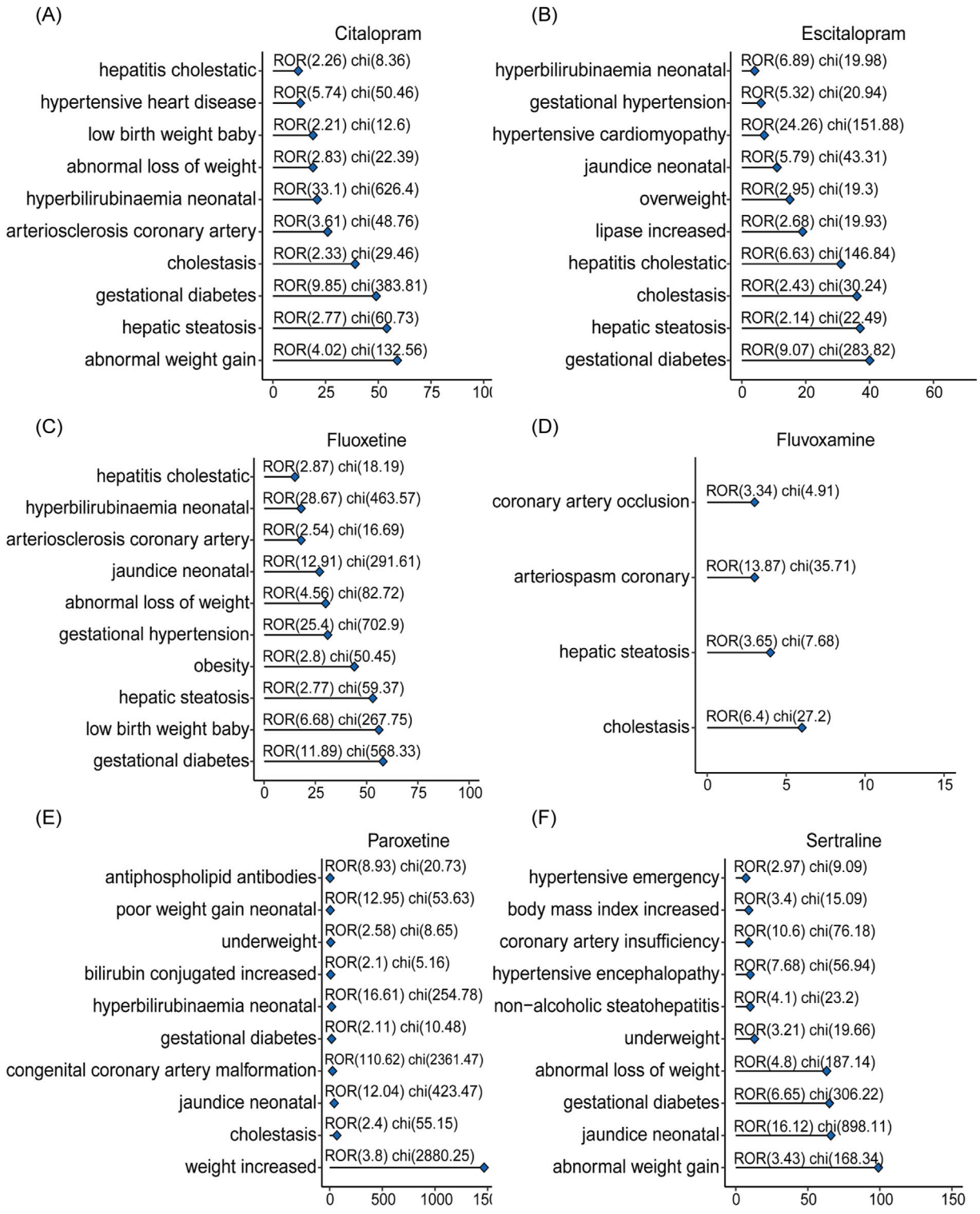


FIGURE 4
The signals of overweight and glucose/lipid metabolism disorders associated with SSRIs. Adverse reactions related to citalopram **(A)**, escitalopram **(B)**, fluoxetine **(C)**, fluvoxamine **(D)**, paroxetine **(E)**, sertraline **(F)** caused by abnormalities in glucolipid metabolism.

with glucose/lipid metabolism disorders. We were unable to perform one-way logistic regression analyses for case reports in which fluvoxamine was the primary suspect drug because of the lack of information and the insufficient number of reports associated with the occurrence of diseases related to glucose/lipid metabolism disorders.

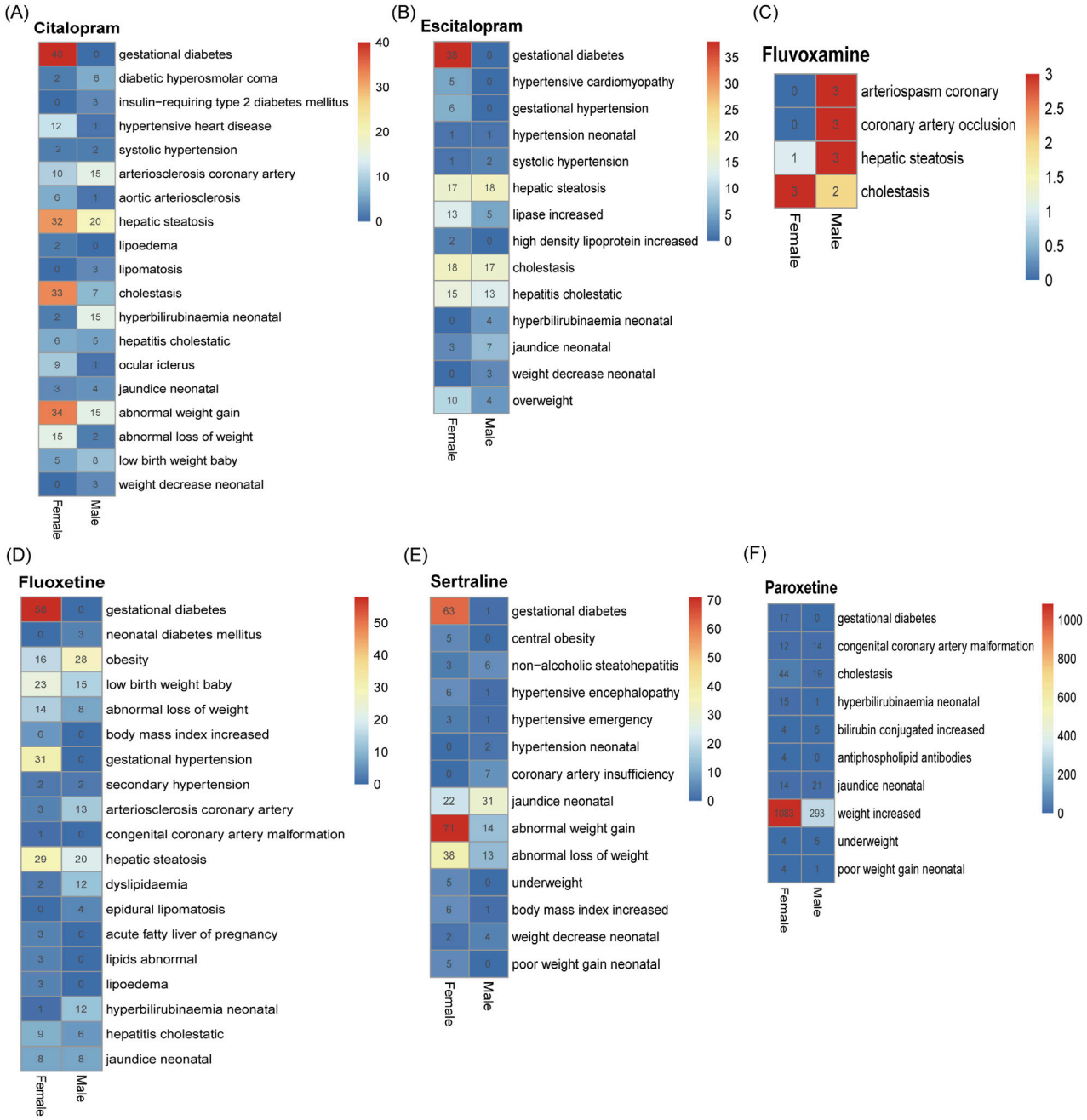


FIGURE 5
Differences in adverse reactions triggered by abnormalities in glucolipid metabolism in men and women after taking SSRIs. **(A)** Citalopram. **(B)** Escitalopram. **(C)** Fluvoxamine. **(D)** Fluoxetine. **(E)** Paroxetine. **(F)** Sertraline. The numerical values in the heatmap represent the number of specific PTs occurrences in males and females, respectively.

Discussion

Number of ADE reports

In this work, we conducted a pharmacovigilance study using the Adverse Event Reporting System (FAERS) database of the US Food and Drug Administration, focusing on representative SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) as well as signals of overweight and glucose-lipid metabolism disorders. Among representative SSRIs, citalopram and escitalopram were the main antidepressants for the treatment of moderate to severe depression, with the latter exhibiting superior efficacy (Cipriani et al., 2012; Yin et al., 2023). In addition, fluoxetine was indicated for patients with moderate depression but might have unsatisfied efficacy in severe cases (Kishi et al., 2023). These three antidepressants were the most widely used in clinical practice. Our work confirmed that there are more reports in the real world about ADE related to overweight and glucose/lipid metabolism disorders associated with citalopram, escitalopram, and fluoxetine. Clinical application of fluvoxamine was late, therefore there were

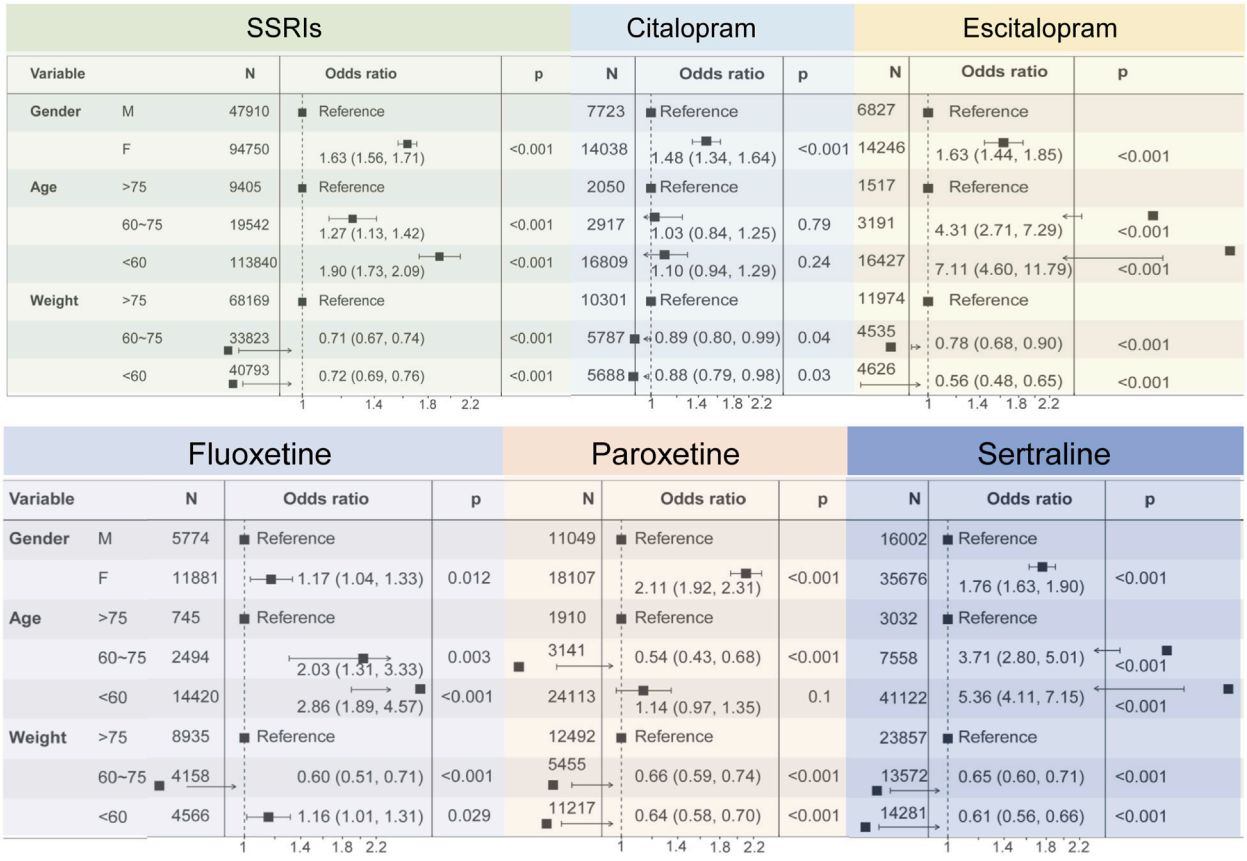


FIGURE 6
Forest plots showing the results of univariate logistic regression analyses regarding demographic factors affecting diseases caused by SSRIs-associated disorders of glucolipid metabolism.

significantly fewer ADE reports for fluvoxamine compared to the other five SSRIs. Relatively speaking, both paroxetine and sertraline were effective in the treatment of moderate to severe depression, with significant efficacy and good tolerability, and fewer reports of adverse events (Sanchez et al., 2014).

Abnormal bodyweight change, overweight or obesity

In this work, we noticed that SSRIs have various abnormal signals related to body weight. Patients taking citalopram and escitalopram might experience abnormal bodyweight change, overweight, even obesity. However, fluoxetine displayed a contrary pattern, with ADE reports of weight loss. The ADE reports of paroxetine and sertraline showed that after taking these two antidepressants, some patients gained weight while others lost weight. Currently, the mechanisms underlying abnormal bodyweight change, overweight or obesity associated with SSRIs medication remained unclear and warranted extensive research exploration. It might have been related to uncontrolled eating during depressive episodes or improvement in depressive symptoms (McCuen-Wurst et al., 2018; Yu et al., 2023). As to weight loss, a research found that three serotonin receptors (5-HT_{1B}, 5-$HT_{2C,}$ and 5-HT_6) might have been associated with abnormal weight loss in patients (Halford et al., 2005). Activation of 5-HT_{1B} and 5-HT_{2C} receptors could have led to reduced appetite, with the latter especially believed to induce satiety through endogenous hypothalamic serotonin subtypes (Lam et al., 2010). In addition, a meta-analysis integrating data from 15 studies involving 1,977,446 subjects found that prenatal depression patients who took SSRIs medication experienced newborn weight loss (Zhao et al., 2018). Although this study did not eliminate the influence of other confounding factors, its findings deserve careful attention. However, another study analyzed 238 pregnant women (71 severe depression patients with SSRIs exposed, 36 severe depression patients with SSRIs unexposed, 131 non-severe depression patients with SSRIs unexposed) and concluded that SSRIs medication was not associated with neonatal weight loss (Wisner et al., 2013). In summary, based on our findings from FAERS data analysis and other work, large-sample real world investigation was further needed to determine whether there was an association between body overweight and SSRIs drugs.

Gestational diabetes

Pregnant women were highly susceptible to depression and were often prescribed by physician with antidepressants for

treatment. Our results indicated a risk signal for gestational diabetes with all SSRIs except fluvoxamine. A study found that SSRIs not only activate the apoptosis of pancreatic β-cell, but also promote insulin resistance and thereby triggering diabetes (Isaac et al., 2018). Instead, a review summarized that SSRIs do not increase the risk of gestational diabetes (Lebin and Novick, 2022). Therefore, it should be vigilant to the risk of gestational diabetes for pregnant women with depression if they took SSRIs during pregnancy.

Gender differences

In this paper, our findings showed that gender was a risk factor for the occurrence of adverse reactions related to abnormalities of glycolipid metabolism after taking SSRIs. Women were more likely to experience adverse effects compared to men with depression. It was suggested that the high prevalence of depression in women may have been related to the interaction of a number of factors, including genetic, physiological, psychological, and social factors (Blanco et al., 2015; Sramek et al., 2016). These factors may have simultaneously affected women's sensitivity and tolerance to SSRI drugs, thereby increasing their risk of adverse effects. For different SSRIs drugs, the mechanism of inducing adverse effects may have varied. For example, it was shown that fluoxetine may have induced a series of adverse reactions by affecting various neurotransmitter systems such as the 5-hydroxytryptamine system, the norepinephrine system, and the dopamine system (Kobayashi et al., 2012; Edinoff et al., 2021). As for sertraline, it may have caused adverse reactions in patients by affecting molecular targets such as 5-HT receptors and NMDA receptors (Izumi et al., 2024). Therefore, further clarification of the specific mechanisms of different SSRIs in the treatment of depression was beneficial for healthcare professionals to more accurately judge and manage the occurrence of adverse reactions.

Lipid metabolism

Lipid metabolism was crucial for life activity in maintaining energy balance and hormone synthesis. Disorders in lipid metabolism could lead to various diseases such as obesity, hyperlipidemia, and cardiovascular diseases (Banzi et al., 2015). From our analysis on ADE reports, we found that SSRIs medications were highly prone to cause lipid metabolism disorders, such as hepatic steatosis, arteriosclerosis, cholestasis, and neonatal jaundice. However, there were not many reports on the risk signals of neonatal jaundice related to SSRIs. Although the impact of SSRIs during pregnancy on maternal and infant health was very important, the relevant research was not sufficient up to now.

Limitations

Although the FDA Adverse Event Reporting System serves as a critical repository for regulatory oversight, pharmaceutical surveillance, and public health monitoring, its utility is tempered by inherent limitations. FAERS relies on voluntary reporting, which introduces potential biases and underreporting. In addition, the database may suffer from data duplication and inaccuracies. Moreover, FAERS lacks comprehensive patient data, including detailed medical histories and comorbid conditions. It is imperative to recognize and address these limitations for clinicians and researchers to derive meaningful insights and make informed decisions based on FAERS data.

Conclusion

We used real-world data from the FAERS database to screen for adverse reactions associated with abnormalities in glucose/lipid metabolism. Through the proportional imbalance method, we identified PTs that were highly associated with SSRIs. In addition, there were differences in adverse reactions associated with abnormalities in glucose/lipid metabolism elicited by different SSRIs. Specifically, the adverse reactions associated with abnormalities of glycolipid metabolism associated with paroxetine were relatively low in percentage, while the absolute lowest number was fluvoxamine. Therefore, healthcare professionals should consider factors such as inter-drug variability, patient age, and gender when selecting drugs for SSRIs in order to more effectively manage the occurrence of adverse reactions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JnC: Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing–original draft, Writing–review and editing. ZC: Data curation, Supervision, Resources, Writing–review and editing. YW: Methodology, Supervision, Writing–review and editing. YM: Supervision, Validation, Writing–review and editing. ZY: Formal Analysis, Validation, Writing–review and editing. JaC: Resources, Supervision, Writing–review and editing. ZX: Conceptualization,

Data curation, Methodology, Software, Supervision, Writing–review and editing. FX: Methodology, Supervision, Visualization, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the China Medical Education Association Grant (CMEA2024001).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1517546/full#supplementary-material

References

Banzi, R., Cusi, C., Randazzo, C., Sterzi, R., Tedesco, D., and Moja, L. (2015). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. *Cochrane Database Syst. Rev.* 4 (4), CD002919. doi:10.1002/14651858.CD002919.pub3

Blanco, C., Hanania, J., Petry, N. M., Wall, M. M., Wang, S., Jin, C. J., et al. (2015). Towards a comprehensive developmental model of pathological gambling. *Addiction* 110 (8), 1340–1351. doi:10.1111/add.12946

Cipriani, A., Purgato, M., Furukawa, T. A., Trespidi, C., Imperadore, G., Signoretti, A., et al. (2012). Citalopram versus other anti-depressive agents for depression. *Cochrane Database Syst. Rev.* 7 (7), CD006534. doi:10.1002/14651858.CD006534.pub2

Edinoff, A. N., Akuly, H. A., Hanna, T. A., Ochoa, C. O., Patti, S. J., Ghaffar, Y. A., et al. (2021). Selective serotonin reuptake inhibitors and adverse effects: a narrative review. *Neurol. Int.* 13 (3), 387–401. doi:10.3390/neurolint13030038

Galecki, P., Mossakowska-Wojcik, J., and Talarowska, M. (2018). The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 80 (Pt C), 291–294. doi:10.1016/j.pnpbp.2017.03.016

Ghosh, R., Gupta, R., Bhatia, M. S., Tripathi, A. K., and Gupta, L. K. (2015). Comparison of efficacy, safety and brain derived neurotrophic factor (BDNF) levels in patients of major depressive disorder, treated with fluoxetine and desvenlafaxine. *Asian J. Psychiatr.* 18, 37–41. doi:10.1016/j.ajp.2015.10.006

Gothert, M., Bonisch, H., Malinowska, B., and Schlicker, E. (2020). Serotonin discovery and stepwise disclosure of 5-HT receptor complexity over four decades. Part II. Some contributions of Manfred Gothert. *Pharmacol. Rep.* 72 (2), 271–284. doi:10.1007/s43440-019-00047-4

Gundersen, E., and Bensadon, B. (2023). Geriatric depression. *Prim. Care* 50 (1), 143–158. doi:10.1016/j.pop.2022.10.010

Halford, J. C., Harrold, J. A., Lawton, C. L., and Blundell, J. E. (2005). Serotonin (5-HT) drugs: effects on appetite expression and use for the treatment of obesity. *Curr. Drug Targets* 6 (2), 201–213. doi:10.2174/1389450053174550

Hammen, C. (2018). Risk factors for depression: an autobiographical review. *Annu. Rev. Clin. Psychol.* 14, 1–28. doi:10.1146/annurev-clinpsy-050817-084811

Isaac, R., Boura-Halfon, S., Gurevitch, D., Shainskaya, A., Levkovitz, Y., and Zick, Y. (2018). Selective serotonin reuptake inhibitors (SSRIs) inhibit insulin secretion and action in pancreatic β cells. *J. Biol. Chem.* 293 (12), 4577–4578. doi:10.1074/jbc.AAC118.002476

Izumi, Y., Reiersen, A. M., Lenze, E. J., Mennerick, S. J., and Zorumski, C. F. (2024). Sertraline modulates hippocampal plasticity via sigma 1 receptors, cellular stress and neurosteroids. *Transl. Psychiatry* 14 (1), 474. doi:10.1038/s41398-024-03185-3

Kishi, T., Ikuta, T., Sakuma, K., Okuya, M., Hatano, M., Matsuda, Y., et al. (2023). Antidepressants for the treatment of adults with major depressive disorder in the maintenance phase: a systematic review and network meta-analysis. *Mol. Psychiatry* 28 (1), 402–409. doi:10.1038/s41380-022-01824-z

Kobayashi, K., Haneda, E., Higuchi, M., Suhara, T., and Suzuki, H. (2012). Chronic fluoxetine selectively upregulates dopamine D_1-like receptors in the hippocampus. *Neuropsychopharmacology* 37 (6), 1500–1508. doi:10.1038/npp.2011.335

Lam, D. D., Garfield, A. S., Marston, O. J., Shaw, J., and Heisler, L. K. (2010). Brain serotonin system in the coordination of food intake and body weight. *Pharmacol. Biochem. Behav.* 97 (1), 84–91. doi:10.1016/j.pbb.2010.09.003

Lebin, L. G., and Novick, A. M. (2022). Selective serotonin reuptake inhibitors (SSRIs) in pregnancy: an updated review on risks to mother, fetus, and child. *Curr. Psychiatry Rep.* 24 (11), 687–695. doi:10.1007/s11920-022-01372-x

Marjoribanks, J., Brown, J., O'brien, P. M., and Wyatt, K. (2013). Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst. Rev.* 2013 (6), CD001396. doi:10.1002/14651858.CD001396.pub3

Mccuen-Wurst, C., Ruggieri, M., and Allison, K. C. (2018). Disordered eating and obesity: associations between binge-eating disorder, night-eating syndrome, and weight-related comorbidities. *Ann. N. Y. Acad. Sci.* 1411 (1), 96–105. doi:10.1111/nyas.13467

Milosavljevic, J. Z., Milosavljevic, M. N., Arsenijevic, P. S., Milentijevic, M. N., and Stefanovic, S. M. (2022). The effects of selective serotonin reuptake inhibitors on male and female fertility: a brief literature review. *Int. J. Psychiatry Clin. Pract.* 26 (1), 43–49. doi:10.1080/13651501.2021.1872647

Miret, M., Ayuso-Mateos, J. L., Sanchez-Moreno, J., and Vieta, E. (2013). Depressive disorders and suicide: epidemiology, risk factors, and burden. *Neurosci. Biobehav Rev.* 37 (10 Pt 1), 2372–2374. doi:10.1016/j.neubiorev.2013.01.008

Pinna, G., Costa, E., and Guidotti, A. (2009). SSRIs act as selective brain steroidogenic stimulants (SBSSs) at low doses that are inactive on 5-HT reuptake. *Curr. Opin. Pharmacol.* 9 (1), 24–30. doi:10.1016/j.coph.2008.12.006

Sanchez, C., Reines, E. H., and Montgomery, S. A. (2014). A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? *Int. Clin. Psychopharmacol.* 29 (4), 185–196. doi:10.1097/YIC.0000000000000023

Sramek, J. J., Murphy, M. F., and Cutler, N. R. (2016). Sex differences in the psychopharmacological treatment of depression. *Dialogues Clin. Neurosci.* 18 (4), 447–457. doi:10.31887/DCNS.2016.18.4/ncutler

Thapar, A., Eyre, O., Patel, V., and Brent, D. (2022). Depression in young people. *Lancet* 400 (10352), 617–631. doi:10.1016/S0140-6736(22)01012-1

Wisner, K. L., Bogen, D. L., Sit, D., Mcshea, M., Hughes, C., Rizzo, D., et al. (2013). Does fetal exposure to SSRIs or maternal depression impact infant growth? *Am. J. Psychiatry* 170 (5), 485–493. doi:10.1176/appi.ajp.2012.11121873

Yin, J., Song, X., Wang, C., Lin, X., and Miao, M. (2023). Escitalopram versus other antidepressive agents for major depressive disorder: a systematic review and meta-analysis. *BMC Psychiatry* 23 (1), 876. doi:10.1186/s12888-023-05382-8

Yu, S., Zhang, Y., Shen, C., and Shao, F. (2023). Efficacy of pharmacotherapies for bulimia nervosa: a systematic review and meta-analysis. *BMC Pharmacol. Toxicol.* 24 (1), 72. doi:10.1186/s40360-023-00713-7

Yuet, W. C., Derasari, D., Sivoravong, J., Mason, D., and Jann, M. (2019). Selective serotonin reuptake inhibitor use and risk of gastrointestinal and intracranial bleeding. *J. Am. Osteopath Assoc.* 119 (2), 102–111. doi:10.7556/jaoa.2019.016

Zhao, X., Liu, Q., Cao, S., Pang, J., Zhang, H., Feng, T., et al. (2018). A meta-analysis of selective serotonin reuptake inhibitors (SSRIs) use during prenatal depression and risk of low birth weight and small for gestational age. *J. Affect Disord.* 241, 563–570. doi:10.1016/j.jad.2018.08.061

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 January 2025
DOI 10.3389/fphar.2025.1524702

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Daniele Mengato,
University Hospital of Padua, Italy
Ziran Li,
University of California, San Francisco, United States
Sarah Allegra,
San Luigi Gonzaga University Hospital, Italy
Moetaza M. Soliman,
Mansoura University, Egypt

*CORRESPONDENCE
Lingti Kong,
konglingti@163.com

RECEIVED 08 November 2024
ACCEPTED 09 January 2025
PUBLISHED 24 January 2025

CITATION
Li H, Jiang M, Pan X and Kong L (2025) Data mining and safety analysis of voriconazole in patients with a hematological malignant tumor based on the FAERS database: differences between children and adults.
Front. Pharmacol. 16:1524702.
doi: 10.3389/fphar.2025.1524702

Data mining and safety analysis of voriconazole in patients with a hematological malignant tumor based on the FAERS database: differences between children and adults

Hao Li[1,2], Manxue Jiang[1,2], Xiaona Pan[3] and Lingti Kong[1,2,4]*

[1]Department of Pharmacy, The First Affiliated Hospital of Bengbu Medical University, Bengbu, China, [2]School of Pharmacy, Bengbu Medical University, Bengbu, China, [3]School of Fundamental Sciences, Bengbu Medical University, Bengbu, China, [4]Institute of Emergency and Critical Care Medicine, The First Affiliated Hospital of Bengbu Medical University, Bengbu, China

Objective: Voriconazole is a broad-spectrum antifungal agent. It is used widely for the prevention and treatment of invasive fungal infections in patients with a hematological malignancy, but studies on its safety in this population are scarce. We assessed the adverse drug events (ADEs) of voriconazole in this population based on the US Food and Drug Administration Adverse Event Reporting System (FAERS) database to improve understanding of the safety of voriconazole.

Research design and methods: ADE reports for patients with a hematological malignant tumor using voriconazole between the first quarter of 2004 to the first quarter of 2024 were retrieved. Then, they were classified using the preferred terminology (PT) and system organ category (SOC) in the Medical Dictionary for Regulatory Activities. Data mining was done using reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS).

Results: A total of 605 ADEs were included: 116 (19.17%) in children and 489 (80.83%) in adults. The types of SOC involved in children and adults were 22 and 24, respectively. The only positive SOC signal that satisfied all four algorithms simultaneously in children was "psychiatric disorders", whereas in adults they were "endocrine disorders" and "hepatobiliary disorders". At the PT level, the types involved in children and adults were 28 and 74, respectively. The highest ROR signal intensities were found for "hallucinations, mixed" in children and "toxic optic neuropathy" in adults. The median time of onset of the ADE in children and adults was 11 and 8.5 days, respectively.

Conclusion: We used four algorithms (ROR, PRR, BCPNN, MGPS) to mine the signals of voriconazole in patients with a hematological malignant tumor, and compared the differences between children and adults. This study is important for targeting the monitoring, and could help to improve the safety of voriconazole.

KEYWORDS

data mining, voriconazole, hematological malignant tumor, FAERS, children, adults

1 Introduction

According to studies using cell lines involved in tumor transformation, the World Health Organization (WHO) classifies hematological malignant tumors into "myeloid tumours", "lymphoid tumours", "mast cell disorders", and "histiocyte tumours" (Arber et al., 2016; Mertowska et al., 2023; Swerdlow et al., 2016). In patients suffering from a hematological malignancy, due to the fact that their immune system may be suppressed by the disease or treatment, these patients are more susceptible to invasive fungal infections (IFIs). In addition, patients with hematological malignant tumors often require the use of central venous catheters to provide medication, fluids, or nutrition, which also increases the risk of infection. Therefore, these patients are a high-risk group for IFIs and require special prevention and treatment strategies (Jenks et al., 2020; Pagano et al., 2011).

Voriconazole is a broad-spectrum antifungal agent belonging to the triazole class. It inhibits ergosterol biosynthesis in the membranes of fungal cells. Voriconazole is active against a wide range of fungi, including *Aspergillus* spp, *Candida* spp, and several others (Fernández Ávila et al., 2021; Purkins et al., 2003; Xie et al., 2023). Voriconazole is used as first-line treatment for invasive aspergillosis. It can also be used for prophylaxis in high-risk patients with an IFI. Voriconazole is active against a wide range of fungi, but it produces adverse effects, including hepatotoxicity, visual disturbances, and rash (Eiden et al., 2007; Yasu et al., 2022; Kim et al., 2017; Mihăilă, 2015; Wu et al., 2021; Xie et al., 2023). Studies have shown that adjustments to dosing regimens for voriconazole based on therapeutic drug monitoring are beneficial for promoting its safety and efficacy (Luong et al., 2016; Valle-T-Figueras et al., 2021).

There are significant differences in physiology and pharmacokinetics between children and adults,but the dosage for children is usually extrapolated from the adult dose (Leroux et al., 2021; Sienkiewicz-Oleszkiewicz et al., 2023; Wei et al., 2019). Children and adults may have different sensitivity and tolerance to drugs, leading to differences in the types and incidence of adverse drug events (ADEs) (Kearns et al., 2003; Pasternak et al., 2019). Therefore, grouping patients in these two age groups can more accurately evaluate the safety and efficacy of voriconazole in patients with hematological malignancies, providing more specific guidance for clinical medication.

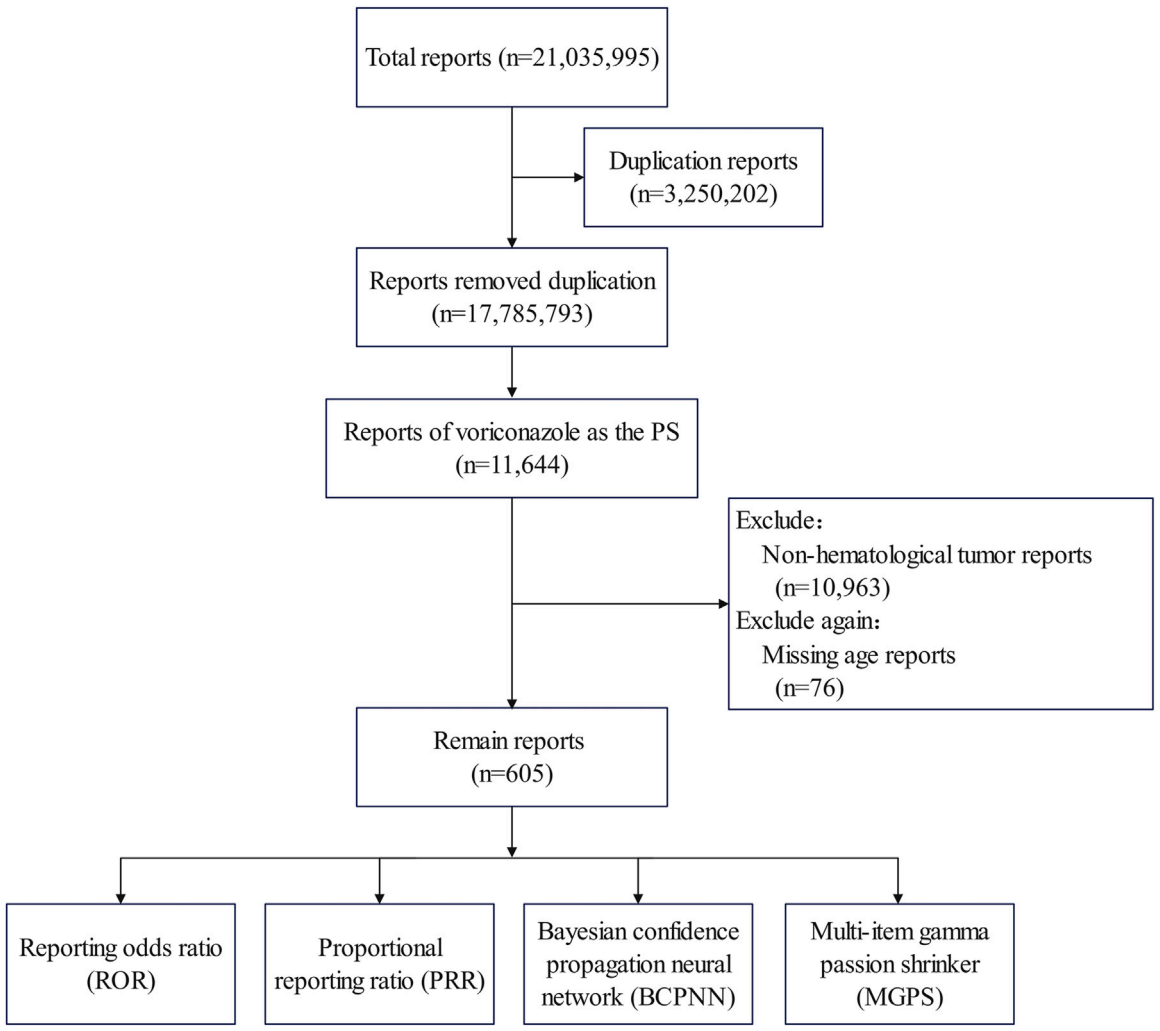


FIGURE 1
Flowchart showing data filtering.

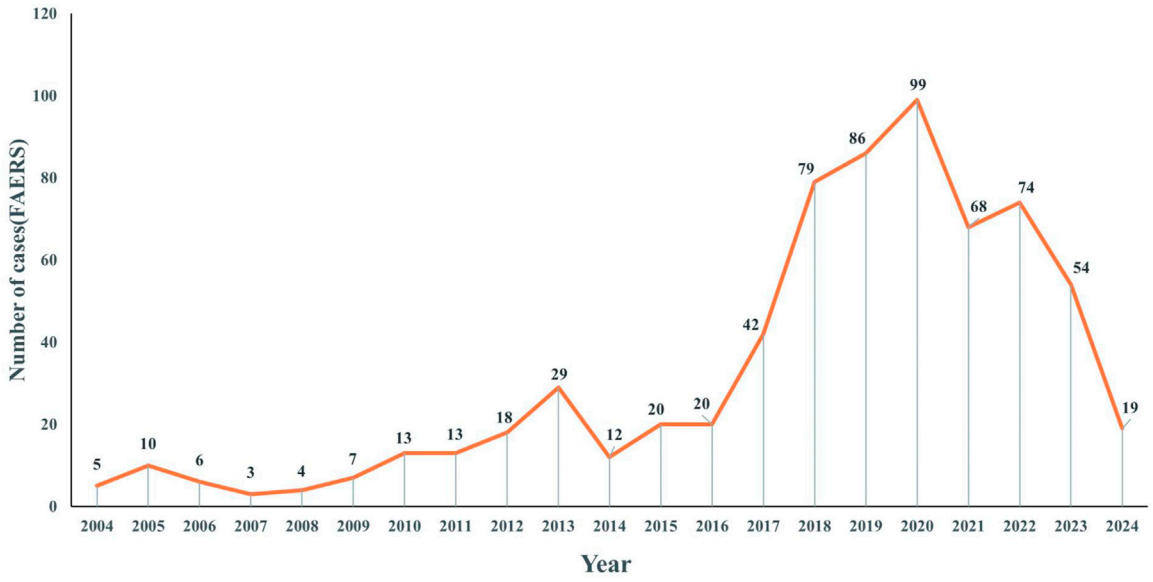


FIGURE 2
Distribution of reported trends in the use of voriconazole ADEs in patients with a hematological malignant tumor from Q1 2004 to Q1 2024.

The US Food and Drug Administration Adverse Event Reporting System (FAERS) is one of the major databases for the post-marketing surveillance of drugs (Cirmi et al., 2020; Feng et al., 2022). It is updated quarterly and publicly available for free download (Sakaeda et al., 2013). The database is used widely in pharmacovigilance studies to compensate for the limitations of the pre-marketing studies of drugs. FAERS plays an important part in updating drug inserts and releasing information on drug-safety alerts (Raisch et al., 2014).

Herein, we undertook data mining of ADEs with voriconazole in patients with a hematological malignancy using FAERS. We compared the differences between children and adults to provide information on the safety of voriconazole.

2 Materials and methods

2.1 Data sources

This study is based on data from FAERS from the first quarter of 2004 to the first quarter of 2024 (Zhai et al., 2019). FAERS consists of seven American Standard Code for Information Interchange data files: Demographic and Management Information, Adverse Drug Reaction Information, Patient Information, Drug Information, Date of Start and End of Treatment, Reporting Source Information, and Indication of Use/Diagnosis (Yu and Liu, 2024). The most recent FDA_DT with the same CASE ID, or a higher PRIMARY ID when the CASE ID and FDA_DT were identical, was selected to identify and remove duplicate reports (Huang et al., 2024; Zhou et al., 2022).

2.2 Data filtering

The search was carried out using the drug names (voriconazole or Vfend) as the primary suspect in the ROLE field. Only patients

TABLE 1 Demographic characteristics of ADEs reported in FAERS (first quarter of 2004 to first quarter of 2024) with voriconazole use as the main suspected drug in patients with a hematological malignancy.

Characteristic	Children	Adults
Sex		
Male	68 (58.62%)	304 (62.17%)
Female	47 (40.52%)	167 (34.15%)
Data missing	1 (0.86%)	18 (3.68%)
ADEs	116 (100%)	489 (100%)
Weight (kg)		
<50	19 (16.38%)	8 (1.64%)
50–100 g	4 (3.45%)	9 (1.84%)
>100	0 (0.00%)	104 (21.27%)
Data missing	93 (80.17%)	368 (75.26%)
Reporter country		
United States	16 (13.79%)	161 (32.92%)
France	8 (6.90%)	83 (16.97%)
German	1 (0.86%)	38 (7.77%)
Japan	13 (11.21%)	30 (6.13%)
Italy	5 (4.31%)	23 (4.70%)
Polish	4 (3.45%)	16 (3.27%)
China	7 (6.03%)	16 (3.27%)
Netherlands	13 (11.21%)	13 (2.66%)
Other	47 (40.52%)	103 (21.06%)
Data missing	2 (1.72%)	6 (1.23%)
Reporter type		
Physician	26 (22.41%)	162 (33.13%)
Pharmacist	7 (6.03%)	18 (3.68%)
Health-professional	76 (65.52%)	245 (50.10%)
Consumer	4 (3.45%)	57 (11.66%)
Data missing	3 (2.59%)	7 (1.43%)

Abbreviation: ADEs, adverse drug events.

TABLE 2 Frequency and signal intensity of ADEs in children at the level of system organ classifications (SOC).

SOCs	Frequency	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Psychiatric disorders	31	3.46 (2.4–4.98)	3.32 (50.05)	3.27 (2.41)	1.71 (0.04)
Skin and subcutaneous tissue disorders	47	3.08 (2.28–4.16)	2.91 (59.34)	2.87 (2.23)	1.52 (−0.15)
General disorders and administration site conditions	124	2.45 (2.01–2.99)	2.14 (82.35)	2.12 (1.79)	1.08 (-0.59)
Product issues	1	1.98 (0.27–14.26)	1.98 (0.48)	1.96 (0.38)	0.97 (-0.73)
Ear and labyrinth disorders	1	1.95 (0.27–14.06)	1.95 (0.46)	1.94 (0.37)	0.95 (-0.75)
Injury, poisoning and procedural complications	45	1.67 (1.23–2.26)	1.61 (10.9)	1.61 (1.24)	0.68 (-0.99)
Hepatobiliary disorders	22	1.35 (0.88–2.07)	1.34 (1.89)	1.33 (0.93)	0.41 (-1.26)
Renal and urinary disorders	15	1.23 (0.74–2.07)	1.23 (0.64)	1.23 (0.8)	0.29 (-1.38)
Infections and infestations	81	1.12 (0.88–1.42)	1.1 (0.89)	1.1 (0.91)	0.14 (-1.53)
Musculoskeletal and connective tissue disorders	12	1.04 (0.59–1.85)	1.04 (0.02)	1.04 (0.64)	0.05 (-1.62)
Gastrointestinal disorders	42	0.87 (0.63–1.19)	0.88 (0.81)	0.88 (0.67)	−0.19 (−1.86)
Cardiac disorders	10	0.82 (0.44–1.54)	0.83 (0.37)	0.83 (0.49)	−0.27 (−1.94)
Nervous system disorders	49	0.75 (0.56–1)	0.77 (3.76)	0.77 (0.6)	−0.37 (−2.05)
Investigations	34	0.67 (0.47–0.95)	0.69 (5.15)	0.69 (0.52)	−0.53 (−2.2)
Endocrine disorders	2	0.66 (0.16–2.64)	0.66 (0.35)	0.66 (0.21)	−0.6 (−2.27)
Respiratory, thoracic and mediastinal Disorders	13	0.51 (0.29–0.88)	0.52 (6.03)	0.52 (0.33)	−0.94 (−2.61)
Metabolism and nutrition disorders	10	0.48 (0.25–0.89)	0.49 (5.63)	0.49 (0.29)	−1.04 (−2.71)
Blood and lymphatic system disorders	25	0.37 (0.25–0.55)	0.39 (26.16)	0.4 (0.28)	−1.34 (−3.01)
Eye disorders	2	0.33 (0.08–1.33)	0.33 (2.69)	0.33 (0.1)	−1.58 (−3.25)
Vascular disorders	3	0.2 (0.07–0.63)	0.21 (9.37)	0.21 (0.08)	−2.27 (−3.94)
Immune system disorders	3	0.19 (0.06–0.58)	0.19 (10.7)	0.19 (0.07)	−2.39 (−4.06)
Neoplasms benign, malignant and unspecified (Incl Cysts And Polyps)	2	0.1 (0.02–0.38)	0.1 (16.99)	0.1 (0.03)	−3.33 (−5)

Abbreviations: SOCs, system organ classes; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; IC, information component; 95% CI, 95% confidence interval; χ2: Chi-squared.

identified as having a hematological malignant tumor were included. In addition, to compare the differences between adults and children, ADEs with missing ages were excluded (76 cases). The screening process for ADEs is shown in Figure 1.

ADEs were described and classified using the preferred terminology (PT) and the system organ category (SOC) in Medical Dictionary for Regulatory Activities v.26.0 (Romão et al., 2024).

2.3 Data mining

With respect to the safety evaluation of drugs, there are four commonly used signal-mining methods: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) (Jiang et al., 2024; Liu et al., 2024; Xiong et al., 2024). The calculation and judgment criteria for these four signal mining methods are shown in Supplementary Table S1. In this study, to remove bias, only those that met all the criteria of the four algorithms were considered to be positive signals (Zhang et al., 2024).

We also assessed the time-to-onset of the ADE, which was defined as the interval between the onset date (EVENT_DT) and start date (START_DT).

2.4 Statistical analyses

Data were analyzed using SPSS 26.0 (IBM, Armonk, NY, United States). Descriptive statistics were used. Variables are presented as numbers and percentages. R 4.3.1 (R Institute for Statistical Computing, Vienna, Austria) was employed for data visualization.

3 Results

3.1 Descriptive characteristics

Figure 2 presents the annual distribution of ADEs related to voriconazole use in patients with a hematological malignancy: there was a general upward trend until 2020.

TABLE 3 Frequency and signal intensity of ADEs in adults at the level of system organ classifications (SOC).

SOCs	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Endocrine disorders	18	5.82 (3.65–9.28)	5.78 (70.69)	5.74 (3.89)	2.52 (0.85)
Hepatobiliary disorders	77	3.46 (2.75–4.35)	3.36 (128.72)	3.35 (2.77)	1.74 (0.08)
Eye disorders	57	2.47 (1.9–3.21)	2.42 (48.14)	2.42 (1.94)	1.27 (−0.39)
Infections and infestations	365	1.89 (1.68–2.11)	1.72 (123.35)	1.72 (1.56)	0.78 (−0.89)
Psychiatric disorders	51	1.49 (1.13–1.97)	1.47 (7.92)	1.47 (1.17)	0.56 (−1.11)
General disorders and administration site conditions	374	1.38 (1.23–1.54)	1.31 (31.34)	1.31 (1.19)	0.38 (−1.28)
Cardiac disorders	72	1.13 (0.9–1.44)	1.13 (1.1)	1.13 (0.93)	0.18 (−1.49)
Nervous system disorders	144	1.07 (0.9–1.27)	1.07 (0.65)	1.07 (0.93)	0.09 (−1.57)
Injury, poisoning and procedural complications	131	1.03 (0.87–1.23)	1.03 (0.13)	1.03 (0.89)	0.04 (−1.62)
Investigations	179	1.01 (0.87–1.18)	1.01 (0.03)	1.01 (0.89)	0.02 (−1.65)
Renal and urinary disorders	35	0.86 (0.62–1.2)	0.86 (0.76)	0.86 (0.65)	−0.21 (−1.88)
Blood and lymphatic system disorders	104	0.81 (0.67–0.99)	0.82 (4.25)	0.82 (0.7)	−0.28 (−1.95)
Respiratory, thoracic and mediastinal disorders	84	0.78 (0.63–0.97)	0.79 (4.98)	0.79 (0.66)	−0.34 (−2.01)
Pregnancy, puerperium and perinatal conditions	1	0.78 (0.11–5.57)	0.78 (0.06)	0.78 (0.15)	−0.35 (−2.02)
Congenital, familial and genetic disorders	2	0.76 (0.19–3.04)	0.76 (0.15)	0.76 (0.24)	−0.4 (−2.07)
Immune system disorders	19	0.75 (0.48–1.17)	0.75 (1.61)	0.75 (0.51)	−0.42 (−2.08)
Vascular disorders	33	0.69 (0.49–0.97)	0.7 (4.5)	0.7 (0.52)	−0.52 (−2.19)
Reproductive system and breast disorders	3	0.64 (0.2–1.97)	0.64 (0.62)	0.64 (0.25)	−0.65 (−2.32)
Skin and subcutaneous tissue disorders	57	0.63 (0.48–0.82)	0.64 (11.91)	0.64 (0.52)	−0.64 (−2.31)
Metabolism and nutrition disorders	33	0.62 (0.44–0.88)	0.63 (7.42)	0.63 (0.47)	−0.67 (−2.34)
Neoplasms benign, malignant and unspecified (Incl Cysts and Polyps)	47	0.45 (0.33–0.6)	0.46 (31.53)	0.46 (0.36)	−1.12 (−2.79)
Gastrointestinal disorders	49	0.27 (0.21–0.36)	0.29 (92.49)	0.29 (0.23)	−1.78 (−3.45)
Musculoskeletal and connective tissue disorders	17	0.22 (0.14–0.36)	0.23 (45.21)	0.23 (0.16)	−2.11 (−3.78)
Surgical and medical procedures	2	0.11 (0.03–0.45)	0.11 (14.08)	0.11 (0.04)	−3.15 (−4.81)

Abbreviations: SOCs, system organ classes; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; IC, information component; 95% CI, 95% confidence interval; χ2, Chi-squared.

The number of children and adults was 116 (19.17%) and 489 (80.83%), respectively (Table 1). The study cohort comprised 214 females (35.37%), 372 males (61.49%), and 19 unspecified cases (3.14%). The country that provided the most ADEs was the USA, followed by France. The main reporter type was "professionals" (physician, pharmacist, health-professional), accounting for 88.26%, which greatly improved the reliability of ADE information.

3.2 Signal detects at the SOC level

At the SOC level (Tables 2, 3), the number of ADEs caused by voriconazole in children and adults was 22 and 24, respectively. The only positive signal that satisfied all four algorithms simultaneously in children was "psychiatric disorders", whereas in adults it was "endocrine disorders" and "hepatobiliary disorders".

Figure 3 shows the frequency of each SOC in children and adults as a percentage of the total SOC. The SOCs shown in group 1 were present in children and adults. The SOCs in group 2 were present in children or adults.

3.3 Signal detects at the PT level

Table 4 shows all positive PTs of voriconazole in the child group (ranked by ROR), totaling 28 types involving 13 SOCs. The top-five PTs were "hallucinations, mixed" (ROR: 363.94), "labelled drug-drug interaction medication error" (ROR: 170.43), "photosensitivity reaction" (ROR: 116.47), "steatohepatitis" (ROR: 116.25), and "drug level below therapeutic" (ROR: 109.37).

Table 5 shows all positive PTs of voriconazole in the adult group (ranked by ROR), totaling 74 types involving 17 SOCs. The top-five PTs were "toxic optic neuropathy" (ROR: 2722.79), "drug level below therapeutic" (ROR: 348.91), "vascular access site infection"

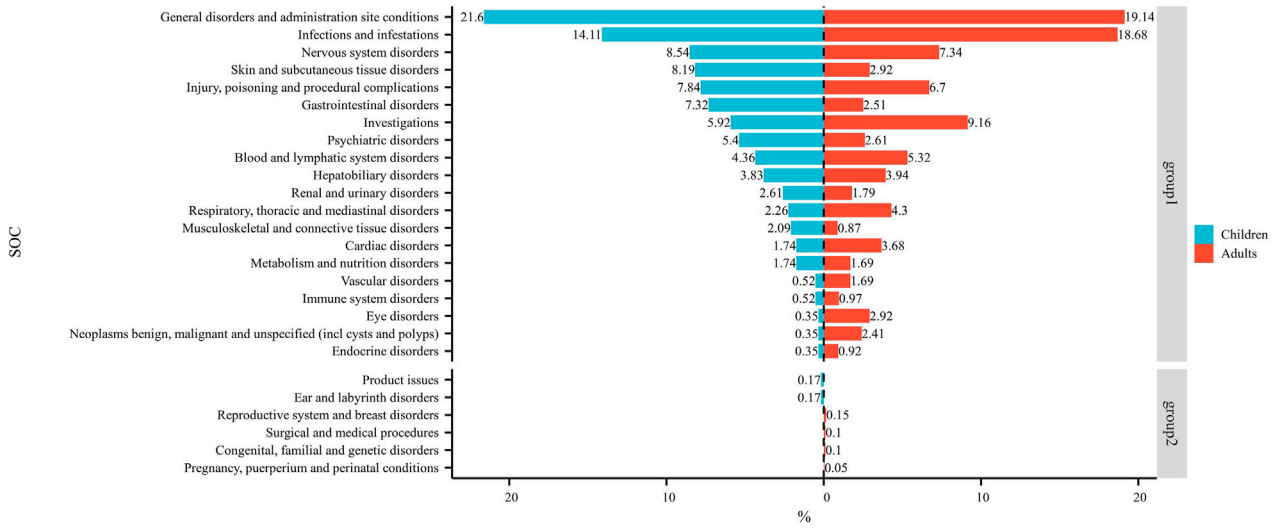


FIGURE 3
Dual-valued histograms plotted to depict the difference in SOCs between children and adults. *Note:* left: children; right: adult.

(ROR: 316.94), "peptic ulcer haemorrhage" (ROR: 308.45), and "drug level decreased" (ROR: 175.69).

We created a volcano plot to visualize the differences in positive PTs between children and adults (Figure 4). The *x*-axis of the volcano plot showed the magnitude of ROR values (log2), the *y*-axis height represented statistical significance, and higher points indicated lower p-values (which are more statistically significant results). Each point in the graph represents a relevant PT.

In the children group, the main terms were "hallucinations, mixed", "photosensitivity reaction", "drug interaction", "labelled drug–drug interaction medication error", "drug level below therapeutic", "steatohepatitis", and "cheilitis". In the adult group, the main terms were "toxic optic neuropathy", "drug interaction", "drug ineffective", "drug level below therapeutic", "vascular access site infection", "peptic ulcer haemorrhage", and "drug level decreased".

3.4 Time-of-onset of the ADEs

After excluding reports of missing or inaccurate start/onset date, 81 ADEs were collected, with most cases occurring within 0 and 30 days (n = 60, 74.07%), followed by 31–60 days (n = 11, 13.58%). The number of different time periods in children and adults is shown in Figure 5. The median time-of-onset of the ADE in children and adults was 11 and 8.5 days, respectively.

4 Discussion

Voriconazole underwent rigorous pre-marketing clinical trials to ensure its efficacy and safety in treating IFIs. However, the diversity and complexity of the patient population in actual clinical use suggest that there may be ADEs that have not been identified or evaluated fully. We conducted in-depth signal mining and evaluation to explore differences in ADEs between children and adults treated with voriconazole in patients with a hematological malignancy using FAERS. We aimed to provide important information for future clinical use.

Figure 2 showed an upward trend in the number of ADEs related to voriconazole from 2004 to 2020. This trend may have been related to the increased frequency of voriconazole use and increased awareness of ADEs. In particular, the number of reports peaked in 2020, which may have been associated with the coronavirus disease-2019 pandemic (Salmanton-García et al., 2024; Hlaing et al., 2023; Papakonstantinou et al., 2021). Since 2021, there has been a downward trend, which may be related to the development of individualized use of voriconazole in clinical practice.

At the SOC level, commonalities and differences were presented between child and adult groups. The only positive signal that satisfied all four algorithms simultaneously in children was "psychiatric disorders" (Table 2) whereas, in adults, the positive signals were "endocrine disorders" and "hepatobiliary disorders" (Table 3). The percentages of SOC that were significantly higher in children than in adults were "skin and subcutaneous tissue disorders", "gastrointestinal disorders", "psychiatric disorders", and "musculoskeletal and connective tissue disorders" (Figure 3). The percentages of SOC that were significantly higher in adults than in children were "investigations", "respiratory, thoracic and mediastinal disorders", "cardiac disorders", "eye disorders", and "neoplasms benign, malignant and unspecified (including cysts and polyps)". In addition, two SOCs were unique to the children group ("ear and labyrinth disorders" and "product issues"), four SOCs were unique to the adult group ("reproductive system and breast disorders", "congenital, familial and genetic disorders", "surgical and medical procedures", and "pregnancy, puerperium and perinatal conditions"). This phenomenon may have been due to the unique physiological state and drug-metabolism characteristics of children (children show greater systemic metabolism of voriconazole than adults) (Leroux et al., 2021).

TABLE 4 Frequency and signal intensity of ADEs in children at the level of preferred terms (PTs).

PTs	SOC	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Hallucinations, mixed	Psychiatric disorders	5	363.94 (70.46–1879.79)	360.78 (512.59)	103.79 (26.27)	6.7 (4.74)
Labelled drug-drug interaction medication error	Injury, poisoning and procedural complications	7	170.43 (57.1–508.72)	168.36 (537.59)	78.24 (31.34)	6.29 (4.45)
Photosensitivity reaction	Skin and subcutaneous tissue disorders	21	116.47 (65.45–207.26)	112.24 (1,303.1)	63.57 (39.25)	5.99 (4.27)
Steatohepatitis	Hepatobiliary disorders	4	116.25 (31.14–434.05)	115.45 (252.16)	64.58 (21.45)	6.01 (4.11)
Drug level below therapeutic	Investigations	6	109.37 (37.83–316.22)	108.23 (364.32)	62.28 (25.62)	5.96 (4.13)
Cheilitis	Gastrointestinal disorders	14	76.67 (39.99–147)	74.83 (671.9)	49.62 (28.78)	5.63 (3.9)
Photodermatosis	Skin and subcutaneous tissue disorders	3	72.53 (18.09–290.72)	72.16 (140.35)	48.44 (15.16)	5.6 (3.69)
Hallucination, auditory	Psychiatric disorders	4	48.43 (15.57–150.63)	48.1 (138.4)	36.33 (14.06)	5.18 (3.37)
Musculoskeletal pain	Musculoskeletal and connective tissue disorders	6	36.45 (14.84–89.51)	36.08 (163.77)	29.06 (13.7)	4.86 (3.11)
Hallucination, visual	Psychiatric disorders	5	30.32 (11.53–79.75)	30.06 (116.31)	25.05 (11.15)	4.65 (2.9)
Hypercalcaemia	Metabolism and nutrition disorders	5	29.11 (11.1–76.3)	28.86 (112.11)	24.22 (10.81)	4.6 (2.85)
Inflammation	General disorders and administration site conditions	7	25.55 (11.4–57.29)	25.25 (138.85)	21.64 (11.01)	4.44 (2.71)
Disorientation	Psychiatric disorders	6	19.01 (8.09–44.69)	18.82 (89.63)	16.77 (8.2)	4.07 (2.35)
Rash macular	Skin and subcutaneous tissue disorders	3	18.92 (5.66–63.18)	18.82 (44.8)	16.77 (6.11)	4.07 (2.31)
Neuralgia	Nervous system disorders	7	17.93 (8.14–39.48)	17.72 (98.45)	15.89 (8.21)	3.99 (2.28)
Drug interaction	General disorders and administration site conditions	43	13.84 (10.01–19.12)	12.87 (435.1)	11.9 (9.08)	3.57 (1.9)
Hypoaesthesia	Nervous system disorders	6	10.93 (4.75–25.15)	10.82 (49.81)	10.14 (5.05)	3.34 (1.64)
Therapeutic response decreased	General disorders and administration site conditions	4	10.56 (3.81–29.24)	10.5 (32.06)	9.85 (4.2)	3.3 (1.59)
Drug level increased	Investigations	5	7.73 (3.13–19.09)	7.68 (27.6)	7.34 (3.45)	2.88 (1.18)
Agranulocytosis	Blood and lymphatic system disorders	4	6.67 (2.44–18.25)	6.64 (18.32)	6.39 (2.75)	2.68 (0.98)
Drug-induced liver injury	Hepatobiliary disorders	4	6.18 (2.26–16.86)	6.14 (16.53)	5.93 (2.56)	2.57 (0.87)
Condition aggravated	General disorders and administration site conditions	8	6.12 (3–12.47)	6.04 (32.4)	5.84 (3.22)	2.55 (0.86)
Arthralgia	Musculoskeletal and connective tissue disorders	4	5.38 (1.97–14.63)	5.34 (13.64)	5.19 (2.25)	2.38 (0.68)
Treatment failure	General disorders and administration site conditions	5	5.34 (2.18–13.09)	5.31 (16.88)	5.15 (2.43)	2.37 (0.68)
Respiratory distress	Respiratory, thoracic and mediastinal disorders	7	5.13 (2.4–10.94)	5.08 (22.19)	4.94 (2.62)	2.3 (0.62)
Confusional state	Psychiatric disorders	6	4.82 (2.13–10.93)	4.78 (17.42)	4.66 (2.35)	2.22 (0.54)
Drug ineffective	General disorders and administration site conditions	21	4.78 (3.07–7.44)	4.64 (58.59)	4.53 (3.13)	2.18 (0.5)

(Continued on following page)

TABLE 4 (*Continued*) Frequency and signal intensity of ADEs in children at the level of preferred terms (PTs).

PTs	SOC	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Septic shock	Infections and infestations	8	3.85 (1.9–7.81)	3.81 (16.22)	3.74 (2.07)	1.9 (0.22)

Abbreviations: PTs, preferred terms; SOC, system organ class; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; IC, information component; 95% CI, 95% confidence interval; χ2, Chi-squared.

TABLE 5 Frequency and signal intensity of ADEs in adults at the level of preferred terms (PTs).

PTs	SOC	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Toxic optic neuropathy	Eye disorders	11	2,722.79 (759.01–9,767.45)	2,707.47 (6,377.23)	580.96 (199.5)	9.18 (7.36)
Drug level below therapeutic	Investigations	8	348.91 (150.4–809.42)	347.48 (1879.47)	236.61 (117.01)	7.89 (6.13)
Vascular access site infection	Infections and infestations	3	316.94 (81.9–1,226.57)	316.46 (660.37)	221.82 (71.49)	7.79 (5.91)
Peptic ulcer haemorrhage	Gastrointestinal disorders	5	308.45 (108.56–876.39)	307.67 (1,078.85)	217.47 (90.77)	7.76 (5.96)
Drug level decreased	Investigations	9	175.69 (84.84–363.82)	174.88 (1,258.09)	141.59 (77)	7.15 (5.43)
Endophthalmitis	Infections and infestations	6	113.95 (48.19–269.45)	113.6 (580.38)	98.59 (47.98)	6.62 (4.9)
Intentional overdose	Injury, poisoning and procedural complications	4	75.89 (27.09–212.56)	75.73 (267.55)	68.78 (29.05)	6.1 (4.38)
Superinfection bacterial	Infections and infestations	4	62.97 (22.67–174.94)	62.84 (224.35)	57.99 (24.66)	5.86 (4.14)
Hallucination, visual	Psychiatric disorders	9	49.45 (25.15–97.24)	49.23 (398.69)	46.21 (26.24)	5.53 (3.85)
Eastern cooperative oncology group performance status worsened	Investigations	3	46.22 (14.38–148.51)	46.15 (124.72)	43.49 (16.38)	5.44 (3.73)
Drug interaction	General disorders and administration site conditions	92	34.04 (27.49–42.15)	32.49 (2,693.48)	31.16 (26.06)	4.96 (3.29)
Drug level increased	Investigations	14	33.05 (19.31–56.55)	32.82 (413.59)	31.46 (20.07)	4.98 (3.3)
Contraindicated product administered	Injury, poisoning and procedural complications	5	32.75 (13.36–80.31)	32.67 (147.02)	31.33 (14.79)	4.97 (3.28)
Neurological decompensation	Nervous system disorders	7	32.62 (15.28–69.63)	32.51 (204.78)	31.18 (16.53)	4.96 (3.28)
Torsade de pointes	Cardiac disorders	6	30.65 (13.53–69.43)	30.55 (164.72)	29.38 (14.82)	4.88 (3.19)
Nephrotic syndrome	Renal and urinary disorders	7	29.14 (13.67–62.09)	29.04 (182.36)	27.98 (14.86)	4.81 (3.13)
Photosensitivity reaction	Skin and subcutaneous tissue disorders	9	28.28 (14.51–55.12)	28.16 (227.13)	27.16 (15.54)	4.76 (3.09)
Intervertebral discitis	Infections and infestations	4	26.66 (9.82–72.36)	26.61 (95.16)	25.72 (11.15)	4.68 (3)
Brain abscess	Infections and infestations	4	23.12 (8.54–62.61)	23.07 (81.92)	22.41 (9.74)	4.49 (2.8)
Central nervous system lesion	Nervous system disorders	6	22.79 (10.1–51.41)	22.72 (120.88)	22.07 (11.17)	4.46 (2.78)
Psychotic disorder	Psychiatric disorders	5	21.64 (8.88–52.72)	21.59 (95.41)	21.01 (9.97)	4.39 (2.71)
Pathogen resistance	Infections and infestations	6	21.16 (9.39–47.69)	21.1 (111.69)	20.54 (10.4)	4.36 (2.68)

(Continued on following page)

TABLE 5 (*Continued*) Frequency and signal intensity of ADEs in adults at the level of preferred terms (PTs).

PTs	SOC	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Generalised tonic-clonic seizure	Nervous system disorders	8	20.81 (10.29–42.07)	20.73 (146.13)	20.19 (11.2)	4.34 (2.66)
Bacterial test positive	Investigations	3	20.17 (6.4–63.55)	20.14 (53.12)	19.63 (7.51)	4.29 (2.61)
Prescribed overdose	Injury, poisoning and procedural complications	3	19.81 (6.29–62.4)	19.78 (52.1)	19.29 (7.38)	4.27 (2.58)
Hallucination	Psychiatric disorders	17	19.41 (11.97–31.49)	19.25 (286.84)	18.79 (12.54)	4.23 (2.56)
Cholecystitis acute	Hepatobiliary disorders	6	16.83 (7.48–37.85)	16.78 (87.09)	16.43 (8.34)	4.04 (2.36)
Neurological symptom	Nervous system disorders	5	15.42 (6.35–37.43)	15.38 (65.88)	15.09 (7.19)	3.92 (2.24)
Hypertransaminasaemia	Hepatobiliary disorders	5	15.17 (6.25–36.81)	15.13 (64.67)	14.85 (7.07)	3.89 (2.22)
Nephropathy	Renal and urinary disorders	3	14.89 (4.74–46.73)	14.87 (38.04)	14.59 (5.6)	3.87 (2.18)
Hemiparesis	Nervous system disorders	7	13.51 (6.39–28.56)	13.46 (79.32)	13.24 (7.07)	3.73 (2.05)
Spinal cord compression	Nervous system disorders	4	13.45 (5–36.19)	13.43 (45.19)	13.2 (5.77)	3.72 (2.04)
Treatment failure	General disorders and administration site conditions	17	13.03 (8.05–21.09)	12.93 (183.99)	12.72 (8.5)	3.67 (2)
Nail disorder	Skin and subcutaneous tissue disorders	3	12.82 (4.09–40.18)	12.8 (32.1)	12.6 (4.85)	3.66 (1.97)
Ventricular hypokinesia	Cardiac disorders	3	12.82 (4.09–40.18)	12.8 (32.1)	12.6 (4.85)	3.66 (1.97)
Necrosis	General disorders and administration site conditions	3	12.26 (3.91–38.39)	12.24 (30.46)	12.06 (4.64)	3.59 (1.91)
Acute hepatic failure	Hepatobiliary disorders	6	11.94 (5.32–26.79)	11.91 (59.03)	11.74 (5.97)	3.55 (1.88)
Cardiovascular disorder	Cardiac disorders	5	11.86 (4.9–28.73)	11.83 (48.82)	11.66 (5.56)	3.54 (1.87)
Brain oedema	Nervous system disorders	5	11.71 (4.84–28.36)	11.68 (48.1)	11.52 (5.49)	3.53 (1.85)
Oral disorder	Gastrointestinal disorders	4	11.29 (4.2–30.35)	11.27 (36.89)	11.12 (4.86)	3.47 (1.8)
Neutrophil count increased	Investigations	4	10.27 (3.83–27.59)	10.26 (32.96)	10.13 (4.43)	3.34 (1.66)
Ventricular extrasystoles	Cardiac disorders	4	10.1 (3.76–27.12)	10.08 (32.28)	9.96 (4.36)	3.32 (1.64)
Inappropriate antidiuretic hormone secretion	Endocrine disorders	4	9.7 (3.61–26.04)	9.68 (30.75)	9.57 (4.19)	3.26 (1.58)
Herpes simplex	Infections and infestations	4	9.67 (3.6–25.96)	9.65 (30.63)	9.54 (4.18)	3.25 (1.58)
Hepatic cytolysis	Hepatobiliary disorders	7	8.94 (4.24–18.86)	8.91 (48.6)	8.82 (4.72)	3.14 (1.47)
Eyelid oedema	Eye disorders	3	8.87 (2.84–27.72)	8.86 (20.68)	8.77 (3.38)	3.13 (1.46)
Pulmonary mass	Respiratory, thoracic and mediastinal disorders	6	8.68 (3.88–19.43)	8.65 (40.16)	8.56 (4.36)	3.1 (1.43)
Ileus paralytic	Gastrointestinal disorders	4	8.55 (3.19–22.94)	8.54 (26.32)	8.45 (3.7)	3.08 (1.4)
Drug ineffective for unapproved indication	General disorders and administration site conditions	5	8.47 (3.5–20.47)	8.45 (32.47)	8.36 (4)	3.06 (1.39)
Hepatotoxicity	Hepatobiliary disorders	10	8.13 (4.35–15.19)	8.1 (61.56)	8.02 (4.75)	3 (1.33)
Ventricular fibrillation	Cardiac disorders	3	7.92 (2.54–24.73)	7.91 (17.92)	7.84 (3.02)	2.97 (1.29)
Haemoptysis	Respiratory, thoracic and mediastinal disorders	8	7.62 (3.79–15.31)	7.59 (45.35)	7.53 (4.2)	2.91 (1.24)
Electrocardiogram qt prolonged	Investigations	11	7.55 (4.16–13.7)	7.51 (61.54)	7.45 (4.52)	2.9 (1.23)
Cholestasis	Hepatobiliary disorders	7	7.49 (3.55–15.8)	7.47 (38.85)	7.4 (3.97)	2.89 (1.22)

(Continued on following page)

TABLE 5 (*Continued*) Frequency and signal intensity of ADEs in adults at the level of preferred terms (PTs).

PTs	SOC	Frequency	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Hypothyroidism	Endocrine disorders	6	7.48 (3.34–16.73)	7.46 (33.23)	7.39 (3.77)	2.89 (1.22)
Pulmonary haemorrhage	Respiratory, thoracic and mediastinal disorders	4	7.27 (2.71–19.48)	7.26 (21.38)	7.2 (3.15)	2.85 (1.17)
Blood alkaline phosphatase increased	Investigations	9	7.08 (3.66–13.66)	7.05 (46.29)	6.99 (4.03)	2.81 (1.14)
Ventricular tachycardia	Cardiac disorders	4	7.01 (2.62–18.79)	7 (20.38)	6.94 (3.04)	2.8 (1.12)
Respiratory disorder	Respiratory, thoracic and mediastinal disorders	7	6.92 (3.28–14.59)	6.9 (35.01)	6.85 (3.67)	2.78 (1.1)
Nephropathy toxic	Renal and urinary disorders	3	6.89 (2.21–21.49)	6.88 (14.94)	6.83 (2.63)	2.77 (1.1)
Drug ineffective	General disorders and administration site conditions	94	6.85 (5.56–8.43)	6.57 (443.05)	6.52 (5.48)	2.7 (1.04)
Skin infection	Infections and infestations	4	6.8 (2.54–18.22)	6.79 (19.57)	6.74 (2.95)	2.75 (1.08)
Guillain-barre syndrome	Nervous system disorders	3	6.8 (2.18–21.22)	6.8 (14.69)	6.74 (2.6)	2.75 (1.08)
Hepatocellular injury	Hepatobiliary disorders	6	6.3 (2.82–14.09)	6.28 (26.45)	6.24 (3.18)	2.64 (0.97)
Immunosuppression	Immune system disorders	4	6.2 (2.32–16.61)	6.19 (17.28)	6.15 (2.7)	2.62 (0.95)
Metabolic acidosis	Metabolism and nutrition disorders	4	6.1 (2.28–16.34)	6.09 (16.88)	6.05 (2.65)	2.6 (0.92)
Skin lesion	Skin and subcutaneous tissue disorders	8	5.72 (2.85–11.49)	5.7 (30.8)	5.67 (3.16)	2.5 (0.83)
Drug-induced liver injury	Hepatobiliary disorders	4	5.66 (2.11–15.14)	5.65 (15.19)	5.61 (2.46)	2.49 (0.82)
Left ventricular dysfunction	Cardiac disorders	3	5.57 (1.79–17.37)	5.57 (11.16)	5.53 (2.14)	2.47 (0.79)
Hepatitis	Hepatobiliary disorders	5	5.46 (2.26–13.19)	5.45 (18.06)	5.42 (2.59)	2.44 (0.77)
Product use in unapproved indication	Injury, poisoning and procedural complications	31	5.26 (3.69–7.51)	5.2 (104.61)	5.17 (3.83)	2.37 (0.7)
Thrombotic microangiopathy	Blood and lymphatic system disorders	4	5.09 (1.9–13.63)	5.08 (13.04)	5.06 (2.22)	2.34 (0.67)
Condition aggravated	General disorders and administration site conditions	16	4.79 (2.92–7.84)	4.75 (47.21)	4.73 (3.13)	2.24 (0.57)
Graft versus host disease	Immune system disorders	5	4.51 (1.87–10.87)	4.5 (13.52)	4.48 (2.14)	2.16 (0.49)

Abbreviations: PTs, preferred terms; SOC, system organ class; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; IC, information component; 95% CI, 95% confidence interval; χ2, Chi-squared.

At the PT level, "photosensitivity reactions" is a more common dermatological complication of voriconazole than in other azole antifungal agents (Malani and Aronoff, 2008). We found that the ROR signal intensity of this PT was higher in children and significant compared with that in adults (Figure 4). This finding provides additional evidence of the need for caution when prescribing voriconazole in children.

In the children group, "hallucinations, mixed" was the PT signal with the highest ROR signal intensity (Table 4). In an observational study of 72 patients aged 14–76 years treated with voriconazole, hallucinations occurred in 12 cases (16.67%). Half of these patients did not report their hallucinations spontaneously. They showed reluctance to describe them, possibly due to embarrassment and other contributing factors (Zonios et al., 2008). A case report and literature review of voriconazole-induced hallucinations and visual disturbances reported 42 cases, three of whom were children (Zheng et al., 2021). In a recent study, a search of multiple databases on drug-induced musical hallucinations identified 27 cases and 21 triggering drugs. Among them, three patients (11.11%) had musical hallucinations induced by voriconazole (Bakewell et al., 2024; Zonios et al., 2008). Voriconazole treatment-related hallucinations may be overlooked by physicians. There are few reports of hallucinations associated with voriconazole in children. However, given the high ROR in the current study, we suggest that whether children experience hallucinations deserves more clinical attention.

In the adult group, "toxic optic neuropathy" had an unusually high ROR signal intensity and high statistical significance (Figure 4). One study revealed six cases of toxic optic neuropathy induced by voriconazole in pharmacovigilance databases (e.g., VigiAcess), and voriconazole was the only drug suspected in two cases (Orssaud et al., 2021). Mounier et al. reported a case of ophthalmic complications possibly caused by toxic optic neuropathy (Mounier et al., 2018). Understanding the mechanism leading to

10.3389/fphar.2025.1524702

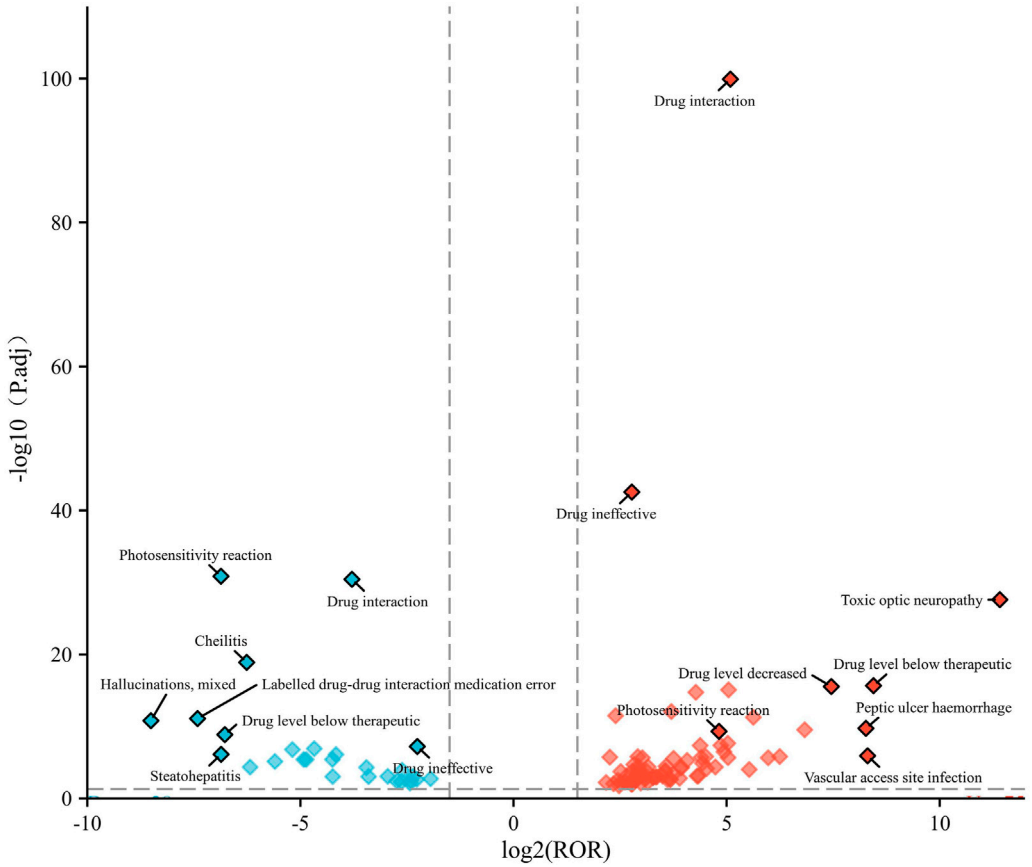


FIGURE 4
Volcano plot of age-differentiated risk signals for voriconazole in patients with a hematological malignant tumor. *Note:* Horizontal coordinates indicate log2 ROR (left: children; right: adult) and vertical coordinates indicate –log10-transformed adjusted p-values. Significant signals are highlighted in color. p-values are adjusted using the false discovery rate.

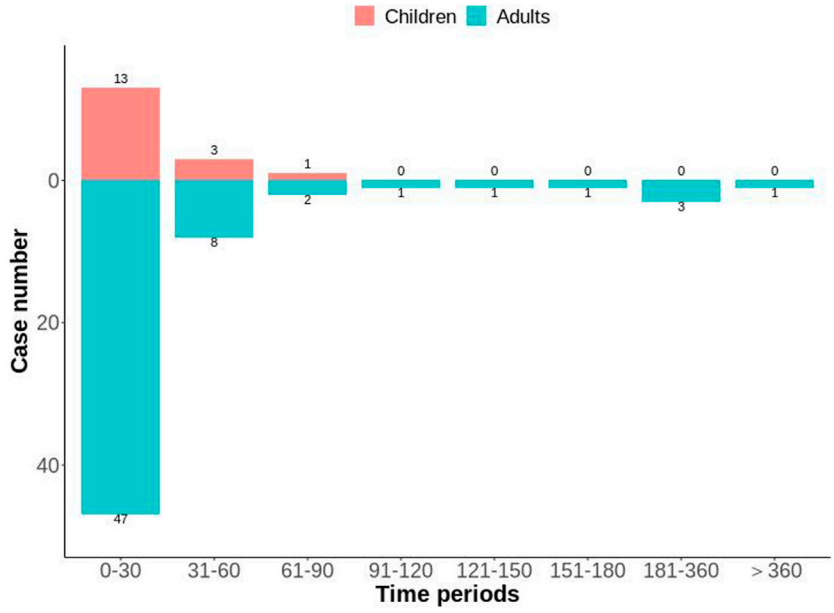


FIGURE 5
Distribution of time-to-onset of voriconazole-associated adverse reactions in child and adult patients with a hematological malignant tumor.

this neuro-ophthalmic adverse effect is crucial for clinical practice. One meta-analysis indicated a trough concentration >3.0 mg/L to be associated with an increased risk of moderate-to-severe hepatotoxicity, and >4.0 mg/L to be associated with an increased risk of neurotoxicity (Jin et al., 2016). Those data suggest a need for close monitoring of the therapeutic concentrations of voriconazole during treatment. Notably, there were "drug interactions", "drug level below therapeutic", and "drug level increased" in children and adults in our study. Studies have shown interactions between voriconazole and carbamazepine, cyclophosphamide, aprepitant, tacrolimus, and letermovir, which are related to the induction or inhibition of metabolic enzymes such as CYP2C19, 3A4, 3a5-2D6. Multiple guidelines recommend monitoring the drug concentration during voriconazole treatment to improve safety and efficacy, preferably with prospective dose optimization based on genotype.

We identified new PTs that were not previously listed in the drug label, such as "generalised tonic–clonic seizures" (Table 5) and "disorientation" (Table 4). This finding: (i) suggests that certain patient groups may be at risk; (ii) demonstrates the importance of ongoing post-marketing surveillance and signal mining for ADEs.

Analyses of time-to-onset of the ADE showed that most ADEs occurred within 0 days and 30 days of dosing (Figure 5). The median time-to-onset of the ADE was 11 days in the children group and 8.5 days in the adult group. These data suggested that close monitoring should be carried out during the initial stage of voriconazole treatment. However, one case occurred in the adult group after 1 year of treatment with voriconazole.

Our study had two main limitations. First, FAERS faces inherent challenges, including incomplete, inaccurate, inconsistent, and delayed reporting of ADEs. These factors may have affected the relevance and accuracy of our results. Second, our analysis was affected by the uneven distribution of cases in FAERS, with more adult patients but a significantly smaller number of children. This uneven distribution of cases may have introduced a bias and limited the applicability of our findings. Further prospective clinical studies are needed to overcome these limitations and provide more reliable insights.

5 Conclusion

We used four algorithms (ROR, PRR, BCPNN, MGPS) to mine the signals of voriconazole in patients with a hematological malignant tumor. We found similarities and differences in SOC/PT signals between children and adults, but also identified some new PT signals not included in the drug label. In the future clinical use, differentiated pharmaceutical monitoring should be carried out for children and adults, and personalized dosing measures, such as therapeutic drug monitoring, should be combined to optimize the dosage, in order to improve the safety of voriconazole in patients with hematological malignancies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HL: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Supervision, Validation, Visualization, Writing–original draft. MJ: Data curation, Methodology, Supervision, Validation, Writing–original draft. XP: Data curation, Formal Analysis, Writing–original draft. LK: Conceptualization, Formal Analysis, Project administration, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Natural Science Foundation of Bengbu Medical University (No. 2023byzd060), and Anhui Province Key Clinical Specialty Construction Project (No. 2023-320).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1524702/full#supplementary-material

References

Arber, D. A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M. J., Le Beau, M. M., et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 127 (20), 2391–2405. doi:10.1182/blood-2016-03-643544

Bakewell, B., Johnson, M., Lee, M., Tchernogorova, E., Taysom, J., and Zhong, Q. (2024). Drug-induced musical hallucination. *Front. Pharmacol.* 15, 1401237. doi:10.3389/fphar.2024.1401237

Cirmi, S., El Abd, A., Letinier, L., Navarra, M., and Salvo, F. (2020). Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). *Cancers (Basel)* 12 (4), 826. doi:10.3390/cancers12040826

Eiden, C., Peyrière, H., Cociglio, M., Djezzar, S., Hansel, S., Blayac, J.-P., et al. (2007). Adverse effects of voriconazole: analysis of the French Pharmacovigilance Database. *Ann. Pharmacother.* 41 (5), 755–763. doi:10.1345/aph.1H671

Feng, Z., Li, X., Tong, W. K., He, Q., Zhu, X., Xiang, X., et al. (2022). Real-world safety of PCSK9 inhibitors: a pharmacovigilance study based on spontaneous reports in FAERS. *Front. Pharmacol.* 13, 894685. doi:10.3389/fphar.2022.894685

Fernández Ávila, D. C., Diehl, M., Degrave, A. M., Buttazzoni, M., Pereira, T., Aguirre, M. A., et al. (2021). Voriconazole-induced periostitis. *Reumatismo* 73 (1), 44–47. doi:10.4081/reumatismo.2021.1368

Hlaing, K. M., Monday, L. M., Nucci, M., Nouér, S. A., and Revankar, S. G. (2023). Invasive fungal infections associated with COVID-19. *J. Fungi* 9 (6), 667. doi:10.3390/jof9060667

Huang, F., San, X., Liu, Q., Zhu, H., and Xu, W. (2024). Signal mining and risk analysis of Alprazolam adverse events based on the FAERS database. *Sci. Rep.* 14 (1), 7489. doi:10.1038/s41598-024-57909-y

Jenks, J. D., Cornely, O. A., Chen, S. C., Thompson, G. R., 3rd, and Hoenigl, M. (2020). Breakthrough invasive fungal infections: who is at risk? *Mycoses* 63 (10), 1021–1032. doi:10.1111/myc.13148

Jiang, Y., Lu, R., Zhou, Q., Shen, Y., and Zhu, H. (2024). Analysis of post-market adverse events of istradefylline: a real-world study base on FAERS database. *Sci. Rep.* 14 (1), 7659. doi:10.1038/s41598-024-58460-6

Jin, H., Wang, T., Falcione, B. A., Olsen, K. M., Chen, K., Tang, H., et al. (2016). Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* 71 (7), 1772–1785. doi:10.1093/jac/dkw045

Kearns, G. L., Abdel-Rahman, S. M., Alander, S. W., Blowey, D. L., Leeder, J. S., and Kauffman, R. E. (2003). Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* 349 (12), 1157–1167. doi:10.1056/NEJMra035092

Kim, S. B., Cho, S.-Y., Lee, D.-G., Choi, J.-K., Lee, H.-J., Kim, S.-H., et al. (2017). Breakthrough invasive fungal diseases during voriconazole treatment for aspergillosis: a 5-year retrospective cohort study. *Med. Mycol.* 55 (3), 237–245. doi:10.1093/mmy/myw067

Leroux, S., Mechinaud-Heloury, F., and Jacqz-Aigrain, E. (2021). Contribution of population pharmacokinetics of glycopeptides and antifungals to dosage adaptation in paediatric onco-hematological malignancies: a review. *Front. Pharmacol.* 12, 635345. doi:10.3389/fphar.2021.635345

Liu, D., Mao, W., Hu, B., Li, X., Zhao, Q., Zhang, L., et al. (2024). A real-world pharmacovigilance study of polatuzumab vedotin based on the FDA adverse event reporting system (FAERS). *Front. Pharmacol.* 15, 1405023. doi:10.3389/fphar.2024.1405023

Luong, M.-L., Al-Dabbagh, M., Groll, A. H., Racil, Z., Nannya, Y., Mitsani, D., et al. (2016). Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J. Antimicrob. Chemother.* 71 (7), 1786–1799. doi:10.1093/jac/dkw099

Malani, A. N., and Aronoff, D. M. (2008). Voriconazole-induced photosensitivity. *Clin. Med. Res.* 6 (2), 83–85. doi:10.3121/cmr.2008.806

Mertowska, P., Mertowski, S., Smolak, K., Kita, A., Kita, G., Guz, K., et al. (2023). Immune checkpoint pathway expression in lymphocyte subpopulations in patients with common variable immunodeficiency and chronic lymphocytic leukemia. *Cancers (Basel)* 15 (21), 5184. doi:10.3390/cancers15215184

Mihăilă, R.-G. (2015). Voriconazole and the liver. *World J. Hepatol.* 7 (14), 1828–1833. doi:10.4254/wjh.v7.i14.1828

Mounier, A., Agard, E., Douma, I., Chehab, H. E., Vie, A. L., Dot, J. M., et al. (2018). Macular toxicity and blind spot enlargement during a treatment by voriconazole: a case report. *Eur. J. Ophthalmol.* 28 (4), NP11–NP14. doi:10.1177/1120672117750051

Orssaud, C., Guillemain, R., and Lillo Le Louet, A. (2021). Toxic optic neuropathy due to voriconazole: possible potentiation by reduction of CYP2C19 activity. *Eur. Rev. Med. Pharmacol. Sci.* 25 (24), 7823–7828. doi:10.26355/eurrev_202112_27628

Pagano, L., Akova, M., Dimopoulos, G., Herbrecht, R., Drgona, L., and Blijlevens, N. (2011). Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *J. Antimicrob. Chemother.* 66 (Suppl. 1), i5–i14. doi:10.1093/jac/dkq437

Papakonstantinou, E., Dragoumani, K., Efthimiadou, A., Palaiogeorgou, A. M., Pierouli, K., Mitsis, T., et al. (2021). Haematological malignancies implications during the times of the COVID-19 pandemic. *Oncol. Lett.* 22 (6), 856. doi:10.3892/ol.2021.13117

Pasternak, Y., Shechter, N., Loebstein, R., Markovits, N., Gueta, I., Halkin, H., et al. (2019). Voriconazole-induced QTc prolongation in a paediatric population. *Acta Paediatr.* 108 (6), 1128–1132. doi:10.1111/apa.14652

Purkins, L., Wood, N., Greenhalgh, K., Allen, M. J., and Oliver, S. D. (2003). Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. *Br. J. Clin. Pharmacol.* 56 (Suppl. 1), 10–16. doi:10.1046/j.1365-2125.2003.01993.x

Raisch, D. W., Garg, V., Arabyat, R., Shen, X., Edwards, B. J., Miller, F. H., et al. (2014). Anaphylaxis associated with gadolinium-based contrast agents: data from the Food and Drug Administration's Adverse Event Reporting System and review of case reports in the literature. *Expert Opin. Drug Saf.* 13 (1), 15–23. doi:10.1517/14740338.2013.832752

Romão, B. M. S., Duval, F. V., Lima, E. C., da Silva, F. A. B., and de Matos, G. C. (2024). Detection of potential safety signals related to the use of remdesivir and tocilizumab in the COVID era during pregnancy, resorting to open data from the FDA adverse event reporting system (FAERS). *Front. Pharmacol.* 15, 1349543. doi:10.3389/fphar.2024.1349543

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Salmanton-García, J., Marchesi, F., Farina, F., Weinbergerová, B., Itri, F., Dávila-Valls, J., et al. (2024). Decoding the historical tale: COVID-19 impact on haematological malignancy patients-EPICOVIDEHA insights from 2020 to 2022. *EClinMedicine* 71, 102553. doi:10.1016/j.eclinm.2024.102553

Sienkiewicz-Oleszkiewicz, B., Salamonowicz-Bodzioch, M., Słonka, J., and Kałwak, K. (2023). Antifungal drug-drug interactions with commonly used pharmaceutics in European pediatric patients with acute lymphoblastic leukemia. *J. Clin. Med.* 12 (14), 4637. doi:10.3390/jcm12144637

Swerdlow, S. H., Campo, E., Pileri, S. A., Harris, N. L., Stein, H., Siebert, R., et al. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 127 (20), 2375–2390. doi:10.1182/blood-2016-01-643569

Valle-T-Figueras, J. M., Renedo Miró, B., Benítez Carabante, M. I., Díaz-de-Heredia, C., Vima Bofarull, J., Mendoza-Palomar, N., et al. (2021). Voriconazole use in children: therapeutic drug monitoring and control of inflammation as Key points for optimal treatment. *J. Fungi* 7 (6), 456. doi:10.3390/jof7060456

Wei, X., Zhao, M., Fu, P., and Xiao, X. (2019). Risk factors associated with insufficient and potentially toxic voriconazole plasma concentrations: an observational study. *J. Chemother.* 31 (7-8), 401–407. doi:10.1080/1120009X.2019.1646974

Wu, J., Chen, N., Yao, Y., Zhou, J., and Zhou, H. (2021). Hyperlipidemia caused by voriconazole: a case report. *Infect. Drug Resist.* 14, 483–487. doi:10.2147/IDR.S301198

Xie, G.-L., Wang, X.-S., Hu, L.-Y., Wang, Y., Gu, X., and Xu, Y.-Q. (2023). Myelodysplastic syndrome-like response after voriconazole treatment of systemic lupus erythematosus complicated with fungal infection: a case report. *Front. Med. (Lausanne)* 10, 1286649. doi:10.3389/fmed.2023.1286649

Xiong, S., Gou, R., Liang, X., Wu, H., Qin, S., Li, B., et al. (2024). Adverse events of oral GLP-1 receptor agonist (semaglutide tablets): a real-world study based on FAERS from 2019 to 2023. *Diabetes Ther.* 15 (8), 1717–1733. doi:10.1007/s13300-024-01594-7

Yasu, T., Nomura, Y., Gando, Y., Matsumoto, Y., Sugita, T., Kosugi, N., et al. (2022). High-performance liquid chromatography for ultra-simple determination of plasma voriconazole concentration. *J. Fungi* 8 (10), 1035. doi:10.3390/jof8101035

Yu, L., and Liu, L. (2024). Exploration of adverse events associated with risdiplam use: retrospective cases from the US Food and drug administration adverse event reporting system (FAERS) database. *PLoS One* 19 (3), e0298609. doi:10.1371/journal.pone.0298609

Zhai, Y., Ye, X., Hu, F., Xu, J., Guo, X., Zhuang, Y., et al. (2019). Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. *J. Immunother. Cancer* 7 (1), 286. doi:10.1186/s40425-019-0754-2

Zhang, W., Wang, Y., Jiang, X., Zhao, H., Jia, X., Wang, Q., et al. (2024). Newly identified adverse events for gemcitabine using the Food and drug administration adverse event reporting system. *Expert Opin. Drug Saf.* 23 (7), 917–923. doi:10.1080/14740338.2023.2284989

Zheng, R., Li, Y., Guo, C., Pei, Y., Ke, Z., and Huang, L. (2021). Voriconazole induced hallucinations and visual disturbances in a female child: a case report and literature review. *Front. Pediatr.* 9, 655327. doi:10.3389/fped.2021.655327

Zhou, J., Wei, Z., Xu, B., Liu, M., Xu, R., and Wu, X. (2022). Pharmacovigilance of triazole antifungal agents: analysis of the FDA adverse event reporting system (FAERS) database. *Front. Pharmacol.* 13, 1039867. doi:10.3389/fphar.2022.1039867

Zonios, D. I., Gea-Banacloche, J., Childs, R., and Bennett, J. E. (2008). Hallucinations during voriconazole therapy. *Clin. Infect. Dis.* 47 (1), e7–e10. doi:10.1086/588844

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 13 February 2025
DOI 10.3389/fphar.2025.1524159

OPEN ACCESS

EDITED BY
Linan Zeng,
McMaster University, Canada

REVIEWED BY
Daniele Mengato,
University Hospital of Padua, Italy
Josipa Bukić,
University of Split, Croatia

*CORRESPONDENCE
Yixiang Lian,
1394625382@qq.com
Quanyou Lai,
laiqy@pku.org.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 07 November 2024
ACCEPTED 20 January 2025
PUBLISHED 13 February 2025

CITATION
Jia P, Zhou Y, Gao Y, Wang S, Yin J, Lian Y and Lai Q (2025) Real-world pharmacovigilance investigation of imipenem/cilastatin: signal detection using the FDA Adverse Event Reporting System (FAERS) database. *Front. Pharmacol.* 16:1524159. doi: 10.3389/fphar.2025.1524159

Real-world pharmacovigilance investigation of imipenem/cilastatin: signal detection using the FDA Adverse Event Reporting System (FAERS) database

Peng Jia[1†], Yusen Zhou[2†], Yuan Gao[1], Shangyu Wang[1], Jiangliu Yin[2], Yixiang Lian[3*] and Quanyou Lai[1*]

[1]Department of Hepato-Biliary and Pancreato-Splenic Surgery, Xijing Hospital, Air Force Military Medical University, Xi'an, China, [2]Department of Neurosurgery, The Affiliated Changsha Central Hospital, University of South China, Changsha, China, [3]Department of Pathology, The Affiliated Changsha Central Hospital, University of South China, Changsha, China

Background: Although imipenem/cilastatin (IMI/CIL) has demonstrated favorable therapeutic efficacy against various infections, the incidence of potential adverse events (AEs) has escalated in parallel with its increased utilization and has been documented in clinical trials. However, a comprehensive understanding of real-world implications remains lacking.

Methods: By conducting a comprehensive search in the FDA Adverse Event Reporting System (FAERS) database, AE reports associated with IMI/CIL as the primary suspect (PS) were selected for analysis, spanning from the first quarter of 2004 to the fourth quarter of 2023. Utilizing disproportionality analysis techniques, potential signals of AE s were identified through reported odds ratio (ROR), proportional report ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric mean (EBGM). The obtained results were systematically classified using Medical Dictionary for Regulatory Activities (MedDRA).

Result: From the first quarter of 2004 to the fourth quarter of 2023, a total of 2,574 reports documenting AEs associated with IMI/CIL were obtained, with more than half (n = 1,517, 58.94%) involving individuals aged over 60 years old. Descriptive analysis was conducted based on age groups and time to onset, revealing that the majority of AEs occurred within 3 days. Adverse drug reactions caused by IMI/CIL were classified into 24 system organ classes (SOCs) at the preferred term (PT) level. Furthermore, previously unreported and clinically significant AEs such as cerebral atrophy, and delirium were also identified at the PT level.

Conclusion: This study offers a more comprehensive insight into the monitoring, supervision, and management of adverse drug reactions associated with IMI/CIL. Clinicians should pay further attention to the implications of numerous AEs and their corresponding signal intensities, as well as unrecorded signals of severe AEs. This holds significant value in enhancing the clinical safety profile of IMI/CIL.

KEYWORDS

imipenem/cilastatin, FAERS, pharmacovigilance, real-world data analysis, adverse events, carbapenem

1 Introduction

To address the issue of limited antimicrobial options due to resistance to β-lactam drugs, an atypical β-lactam antibiotic that is stable against β-lactamase, namely, carbapenems, has been identified (Bush and Bradford, 2020; Drawz and Bonomo, 2010). Carbapenems exhibit stability against the majority of β-lactamases, including AmpC, β-lactamases, and extended-spectrum β-lactamases (ESBL), and can serve as a feasible therapeutic alternative to third-generation cephalosporins (Zhanel et al., 2007; Bradley et al., 1999). Since the mid-1980s, carbapenems have been extensively utilized in clinical practice and are regarded as the preferred drugs for multi-drug-resistant infections. Imipenem (IMI) is the first carbapenem antibiotic to be approved (Paterson and Bonomo, 2005; Paterson, 2000). Compared with other β-lactam drugs, it possesses a broader spectrum of antibacterial activity and post-antibiotic effect (PAE) against both Gram-positive and Gram-negative bacteria (MacKenzie et al., 1994). IMI is metabolized by dehydropeptidase-1 (DHP-1) produced by proximal renal tubules and is rapidly inactivated. Cilastatin (CIL), a DHP-1 inhibitor, were formulated in a fixed 1: 1 ratio to delay the metabolism of imipenem *in vivo* and prevent the inherent nephrotoxicity of imipenem. Clinical experience has demonstrated that imipenem/cilastatin (IMI/CIL) demonstrates excellent efficacy in the treatment of moderate to severe infections in various systems and is frequently employed as empirical treatment for febrile neutropenia and other serious infections caused by multi-drug resistant pathogens (Balfour et al., 1996).

In the 1980s, Calandra et al. conducted a comparative analysis of the efficacy and safety of IMI/CIL and cephalosporins in two multicenter clinical trials conducted in North America and Europe. The results indicated that the safety of IMI/CIL was comparable to that of conventional β-lactam antibiotics (Calandra et al., 1983). Besides, Calandra et al. also conducted a review of case reports involving approximately 3,500 patients following the use of IMI/CIL, and the data indicated that common adverse effects (AEs) included local reactions at the site of intravenous infusion (such as phlebitis and local pain), gastrointestinal symptoms (including nausea, vomiting, and diarrhea), impaired liver function, elevated eosinophils, skin symptoms (such as rash, pruritus, and urticaria), seizures, oral mucosal changes, fever, and dizziness (Calandra et al., 1988a). Additionally, rare AEs associated with IMI/CIL included severe neutropenia (Fariñas et al., 1993), thrombocytopenia (Qiao et al., 2022), persistent hiccups unrelated to central nervous system diseases (Lucena et al., 1992), and exacerbation of myasthenia gravis (O'Riordan et al., 1994). Some experiments have demonstrated the potential of IMI/CIL to induce nephrotoxicity (Tahri et al., 2018). The potential toxic effects of high doses of IMI/CIL on the gonads and male reproductive organs require further investigation (Tahri et al., 2017; Cherif et al., 2019). As a classic carbapenem, IMI/CIL continues to hold significant value in contemporary clinical practice. However, the escalating utilization of IMI/CIL has brought to light potential AEs. Although Ge et al. performed an overall pharmacovigilance analysis of carbapenems using the FARES database, a comprehensive understanding of the real-world safety profile of IMI/CIL has not been achievable due to the long history and the small number of included reports (Ge et al., 2021). Not only that, over the past decade, no study has been capable of systematically summarizing its AEs, and the existing studies are merely confined to a single symptom of AEs, which severely restricts clinicians' ability to identify and respond to other related AEs.

The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, the largest global repository of spontaneously reported AEs, systematically collects and monitors AEs associated with a wide range of approved drugs from manufacturers, healthcare professionals, and members of the public. This study comprehensively evaluates the potential risks of IMI/CIL in clinical application through signal mining of the FAERS database, providing valuable insights into its safety profile for clinical practice.

2 Materials and methods

2.1 Data sources

Since 2004, the FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), supervised by the FDA, has remained consistently accessible to the public, amassing a substantial volume of AE reports from real-world populations and evolving into a pivotal post-marketing safety monitoring database. This study encompasses data on reported adverse events associated with IMI/CIL spanning from Q1 2004 to Q4 2023. To ensure precision and consistency, SAS and MYSQL software were employed for data preprocessing. Individual Safety Reports (ISRs) were utilized to eliminate duplicate entries.

2.2 Standardization of drug names and adverse drug reactions

The American Standard Code for Information Interchange (ASCII) was extracted from the FAERS database and imported into SAS and MYSQL software for data cleansing. AE reports with IMI/CIL as the primary suspect (PS) were meticulously sorted. The RxNorm standard was utilized to accurately encode drug names, followed by the use of the latest MedDRA (25.0) to precisely match the preferred term (PT) of IMI/CIL-related AEs and categorize them into corresponding system organ classes (SOCs), thus establishing a comprehensive framework for ADR analysis. Basic clinical information of patients in the AE reports, including age, sex, country, reporter, time to onset, and outcomes of AEs such as hospitalization, death, life-threatening and disability were obtained to comprehensively evaluate drug safety. This auxiliary information provides a thorough understanding of IMI/CIL's safety profile and potential risks in real-world settings as well as regional and national usage characteristics.

2.3 Signal mining algorithm

The analysis of disproportionality holds significant value in pharmacovigilance research. In this study, we employed four distinct algorithms simultaneously to meticulously identify signals of AEs associated with IMI/CIL. These algorithms encompass reported odds ratio (ROR), Proportional report ratio (PRR), Bayesian Confidence propagation Neural Network (BCPNN), and empirical Bayesian geometric mean (EBGM). The specific algorithm utilized aligns with previous research findings (Zhang et al., 2024).

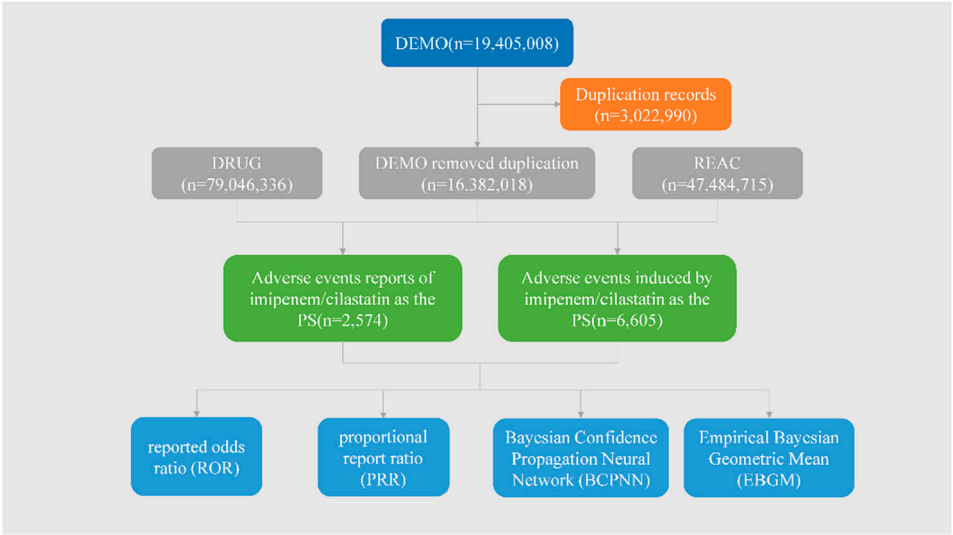


FIGURE 1
The flow diagram of selecting IMI/CIL-related AEs from FAERS database.

Utilizing four methods for the identification and quantification of AE signals can substantially enhance result stability and diminish the occurrence of false positive signals. To ensure the precision of ADR study results, the criteria for detecting positive safety signals were set as follows: ROR ≥ 3 (95% CI > 1), PRR ≥ 2 (95% CI > 1), IC025 > 1, and EBGM05 > 2.

3 Result

3.1 The basic clinical characteristics of IMI/CIL-related AEs

In this study, a total of 19, 405, 008 ADR reports related to IMI/CIL from 2004Q1-2023Q4 were retrieved, resulting in 16, 382, 018 unique reports after the removal of 3,022,990 duplicates. Among these reports, IMI/CIL was identified as the PS drug in 2,574 reports which encompassed a total of 6,605 AEs (Figure 1). The annual line chart illustrates a gradual increase in ADR reports over time (Figure 2). Table 1 presents detailed clinical characteristics associated with reports of ADR. In the ADR reports, there was a significantly higher proportion of male patients (n = 1,490, 57.89%) compared to female patients (n = 1,026, 39.86%). More than half of the reports were over 60 years old (n = 1,517, 58.94%), which were more likely to experience AEs due to weaker organ function and increased underlying diseases. The majority of ADR reported for IMI/CIL were from pharmacists (n = 1,422, 55.24%), physician (n = 268, 10.41%), and other health-professional (n = 716, 27.82%), with only a small number from consumers (n = 160, 6.22%). Among the reporting countries, the majority of ADR reports originated from China (n = 17,644, 55.24%), followed by France (n = 272, 10.57%) and Japan (n = 106, 4.12%). Serious consequences accounted for more than 90% of the AEs reported; among these other serious was most common (n = 1984, 60.14%), followed by hospitalization (n = 823, 24.95%), life threatening (n = 209, 6.34%), death (n = 207, 6.27%), disability (n = 62, 1.88%).

3.2 Time to onset and gender distribution analysis

To further investigate the association between ADR and time, we categorized the occurrence of ADR into intervals of less than 3 days, three to 7 days, one to 2 weeks, 2 weeks to 1 month, and more than 1 month. As depicted in the pyramid diagram (Figure 3A), it is evident that ADRs predominantly manifest within the initial 3 days following medication initiation, with a majority occurring within the first week. However, the prolonged time interval between the occurrence of certain ADRs and the initiation of initial medication also warrants careful attention and vigilance. Moreover, we conducted a stratified analysis of IMI/CIL-related AE signals based on gender and generated a volcano plot. Each point within the plot represents an AE signal, and statistically significant signals were labelled. In male individuals, the most salient signals were epilepsy, delirium, disorganized speech, and muscle twitching; whereas in female individuals, the most prominent signals were epilepsy, delirium, disorganized speech, and dysphoria (Figure 3B).

3.3 Signal mining at the SOC level

Figure 4; Supplementary Table S1 presents the mining results of AE signals associated with IMI/CIL in the FAERS database at the SOC level. A total of 24 SOCs were identified as being linked to the ADR. When ranked by number of cases, the top three SOCs are as follows: nervous system disorders (n = 1,259, ROR = 2.15, PRR = 2.15, IC = 1.1, EBGM = 2.14), psychiatric disorders (n = 927, ROR = 2.55, PRR = 2.33, IC = 1.22, EBGM = 2.33) and investigations (n = 637, ROR = 1.55, PRR = 1.5, IC = 0.58, EBGM = 1.5). While neurological/psychiatric disorders have been reported in drug instructions, our findings suggest that their severity may not be consistent with previous reports; it appears that IMI/CIL may exhibit greater neurotoxicity compared to other β-lactam antibiotics.

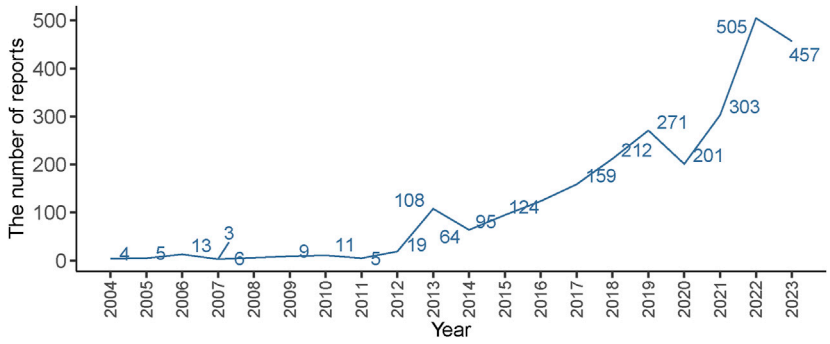


FIGURE 2
Distribution of AEs of IMI/CIL from 2004 Q1 to 2023 Q4.

3.4 Signal mining at the PT level

Supplementary Table S2 presents the PT detection results sorted by ROR value, identifying a total of 100 ADR terms across 16 SOCs in this study. In addition, the six systems with significant signals encompassed nervous system disorders, psychiatric disorders, hepatobiliary disorders, investigations, infections and infestations, as well as skin and subcutaneous tissue disorders. Results with significant signals were visualized based on the ROR and chi-square values of AE (Figure 5). The most significant AE signal was observed within the Infections and infestations level, such as superinfection fungal (n = 5, ROR = 631.02). Epilepsy (n = 544, ROR = 180.64) emerged as the predominant AE signal among nervous system disorders, which consistent with the drug instruction recorded. Notably, toxic encephalopathy (n = 18, ROR = 34.22), cerebral atrophy (n = 8, ROR = 17.11), language disorder (n = 8, ROR = 31.48) were not previously documented in drug inserts or clinical trials. Within psychiatric disorders, disorganised speech (n = 69, ROR = 421.54), dysphoria (n = 70, ROR = 116.9) and delirium (n = 263, ROR = 72.31) exhibited the highest signal intensities and quantity but were never recorded in drug inserts. At the level of Musculoskeletal and connective tissue disorders, muscle twitching (n = 84, ROR = 31.64, 95%CI = 25.5–39.26) emerged as a significant AE signal with a substantial number of occurrences, consistent with the information provided in the drug label and thereby enhancing the credibility of our study. Other findings also demonstrating high intensity AE signals include dysbiosis, uremic encephalopathy, irregular sleep wake rhythm disorder and halo vision; their potential association with IMI/CIL warrants further investigation through larger clinical trials and fundamental research.

4 Discussion

In this study, we conducted a pioneering and comprehensive analysis of AE signals associated with IMI/CIL using various data analysis methods based on real-world AE reports. We identified 2574 AE reports where IMI/CIL was the PS drug. Our study offers extensive insights into the AEs linked to IMI/CIL, confirming existing safety concerns while also uncovering previously unreported AEs. The findings of this research validate that the major AEs of IMI/CIL are concentrated in six systems: nervous system disorders, psychiatric disorders, hepatobiliary disorders, investigations, infections and infestations, and skin and subcutaneous tissue disorders. A considerable proportion of these AEs were not referred to in previous studies. Furthermore, the research results indicate that AEs primarily occur in men, mainly in the elderly population (Age ≥ 60), and the occurrence of AEs is concentrated within the first 3 days after medication administration. The subsequent content presents a detailed discussion of our research result.

The self-reported AE reporting system exhibits a partial amount of missing or unknown data due to the variations in reporting subjects, which can be attributed to the non-mandatory nature of reporting. Regarding gender distribution, there is a significantly higher number of male (57.89%) reports compared to female (39.86%) reports, potentially influenced by the larger proportion of male patients with severe infections. This observation is in accordance with the outcomes of the RESTORE-IMI 2 Study (Titov et al., 2021). However, considering the intricate etiology within the spectrum of infectious diseases, this may impede our ability to observe and establish a clear association between gender and IMI/CIL-related AEs. Indeed, when evaluating drug safety, the analysis of gender differences must be taken into consideration, which is conducive to more precise management of AE. Our analysis of gender differences reveals that, in IMI/CIL-related AEs, the prevalent AEs in both men and women are generally consistent, mainly manifested as nervous system and psychiatric disorders, such as epilepsy, delirium, and disorganized speech. Nevertheless, it is notable that men are more prone to muscle twitching, which might be ascribed to the lesser muscle mass in women, leading to less obvious or less frequent muscle twitching. The research conducted by Abraham et al. indicates that in the ultrasonic diagnosis of neuromuscular diseases, a lower muscle thickness is often associated with false-negative outcomes (Abraham et al., 2023). In terms of age, AE primarily affects individuals aged 60 and above (58.94%), which can be attributed to the diminished immunity in older adults and their heightened susceptibility to severe infections. This finding strongly emphasizes the need for enhanced vigilance towards treatment safety in elderly patients. Furthermore, attention should also be directed towards individuals under the age of 20 (3.81%) as a few numbers of AEs continue to be reported. The majority of AEs related to IMI/CIL were reported by

TABLE 1 Basic information on AEs related to IMI/CIL.

Characteristics	Counts (n)	Proportion (%)
Number of events	2,574	
Gender		
Female	1,026	39.86%
Male	1,490	57.89%
Unknown	58	2.25%
Age		
<20	98	3.81%
20–40	265	10.30%
40–60	527	20.47%
≥60	1,517	58.94%
Unknow	167	6.49%
Reporter		
Pharmacist	1,422	55.24%
Other health-professional	716	27.82%
Physician	268	10.41%
Consumer	160	6.22%
Unknown	7	0.27%
Lawyer	1	0.04%
Reported countries		
China	1764	68.53%
Other	432	16.78%
France	272	10.57%
Japan	106	4.12%
Route		
Intravenous drip	1,547	60.10%
Intravenous	541	21.02%
Other	460	17.87%
Parenteral	15	0.58%
Intraperitoneal	11	0.43%
Outcomes		
Other serious	1984	60.14%
Hospitalization	823	24.95%
Life threatening	209	6.34%
Death	207	6.27%
Disability	62	1.88%
Required intervention to Prevent Permanent Impairment/Damage	12	0.36%
Congenital anomaly	2	0.06%

pharmacist (55.24%), as well as other health-professional (27.82%) and physician (10.41%), who are considered more reliable sources of reports. There were relatively few AEs reported by consumers (6.22%), suggesting that healthcare workers may be more attentive to IMI/CIL-related AEs during treatment, leading to an increase in this proportion. It is worth noting that despite being among the first drugs to be approved globally by the FDA, the vast majority of reports originated from China (68.53%), indicating unexpected regional differences in reporting trends. This may be attributed to the rapid admission and anti-infection treatment of patients in medical institutions in China, and the large treatment base has led to a significant increase in the number of AE reports. Additionally, with regards to AE outcomes, the majority of cases involved serious events such as other serious (60.14%), hospitalization (24.95%), life threatening (6.34%), death (6.27%) and disability (1.88%). Analysis of the time to onset revealed that AEs predominantly occurred within the first 3 days of drug use, followed by 3 days to 1 week, 1 week to 2 weeks, and very few reported beyond 2 weeks. These findings align with those of Simon Portsmouth et al. (2018). However, it is important to note that there were still some AEs reported after 2 weeks of drug use, indicating potential unforeseen safety risks associated with long-term use of IMI/CIL. These results underscore the significance of early recognition and dynamic monitoring for IMI/CIL-related AEs.

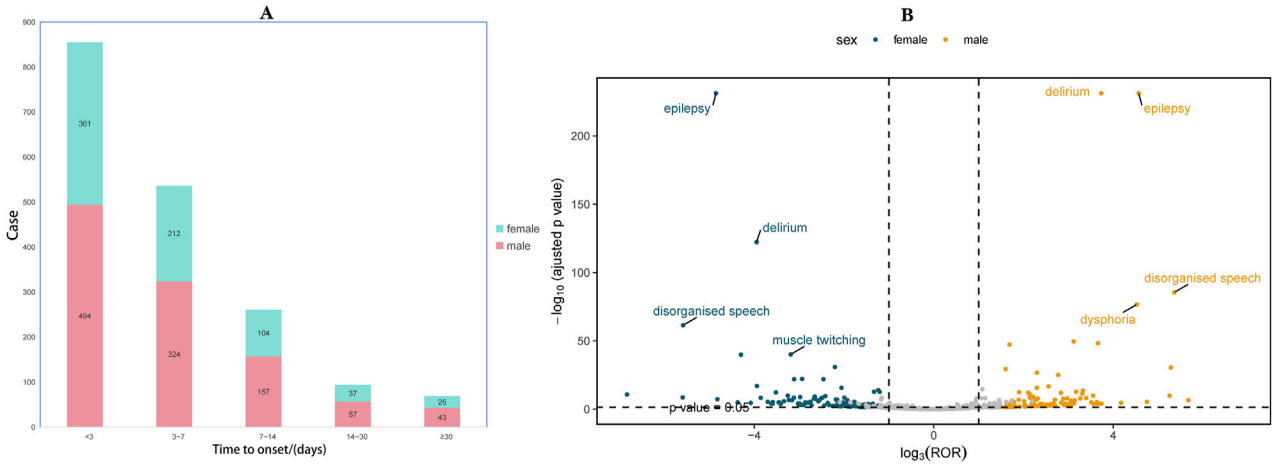


FIGURE 3
Time to onset and gender distribution of IMI/CIL-related AEs. **(A)** Result of time to onset; **(B)** Gender-differentiated risk signal volcano plot for IMI/CIL. The horizontal coordinate shows the log2 ROR value and the vertical coordinate indicates the adjusted p-value after -log10 conversion. Significant signals are highlighted and annotated in prominent colors. The p-value is adjusted with false discovery rate (FDR) method.

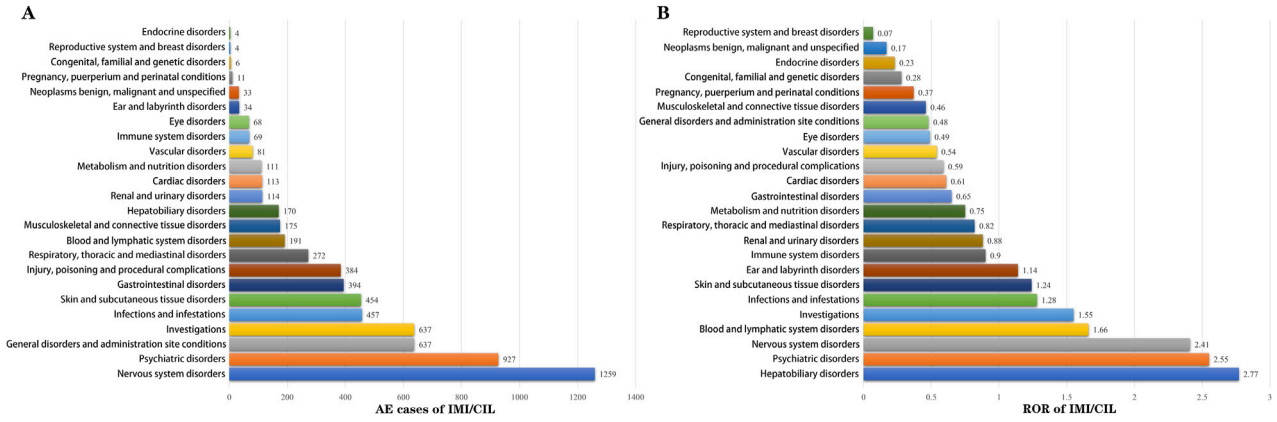


FIGURE 4
The bar chart displays the AEs at each SOC level. **(A)** Rank by AE cases; **(B)** Rank by ROR.

Furthermore, there has been an increasing trend in the number of reports on IMI/CIL-related AEs over the years, which may be attributed to either increased drug usage or heightened enthusiasm among medical professionals in reporting such AEs. The aforementioned findings highlight both widespread utilization and potentially severe consequences associated with IMI/CIL and emphasize the necessity for further comprehensive investigations aimed at identifying potential causal relationships in order to advance our understanding of IMI/CIL safety.

The IMI/CIL compound is generally well tolerated as a potent anti-infective agent. Employing the four signal detection methods, the top five SOC were nervous system disorders, psychiatric disorders, general disorders and administration site conditions, investigations and infections and infestations. At the nervous system/psychiatric disorders level, in addition to mental disorder, illusion, epilepsy and encephalopathy documented in the drug description, we have also identified novel signals including delirium, altered state of consciousness, language disorder, disorganized speech, irregular sleep wake rhythm disorder and delirium. Delirium and epilepsy accounted for the largest number of these. The occurrence of IMI/CIL related epilepsy has been widely reported, however, the incidence reported in clinical trials is notably low, ranging from 1.5% to 3% (Verwaest and Belgian Multicenter Study Group, 2000; Calandra et al., 1985; Calandra et al., 1986; Calandra et al., 1988b). In an observational study of 1,754 patients treated with IMI/CIL (Calandra et al., 1988b), seizures were observed in 52 patients (3%), out of which 16 cases (0.9%) were deemed by the investigators to have a strong association with the utilization of IMI/CIL (Calandra et al., 1988b). The study assessed risk factors for IMI/CIL-associated seizures, including underlying central nervous system disorders, renal insufficiency, overdose, and *Pseudomonas aeruginosa* infection (Calandra et al., 1988b). Another study has also suggested that pre-existing cerebral vascular disease may promote seizures prior to drug use, and the blood-brain

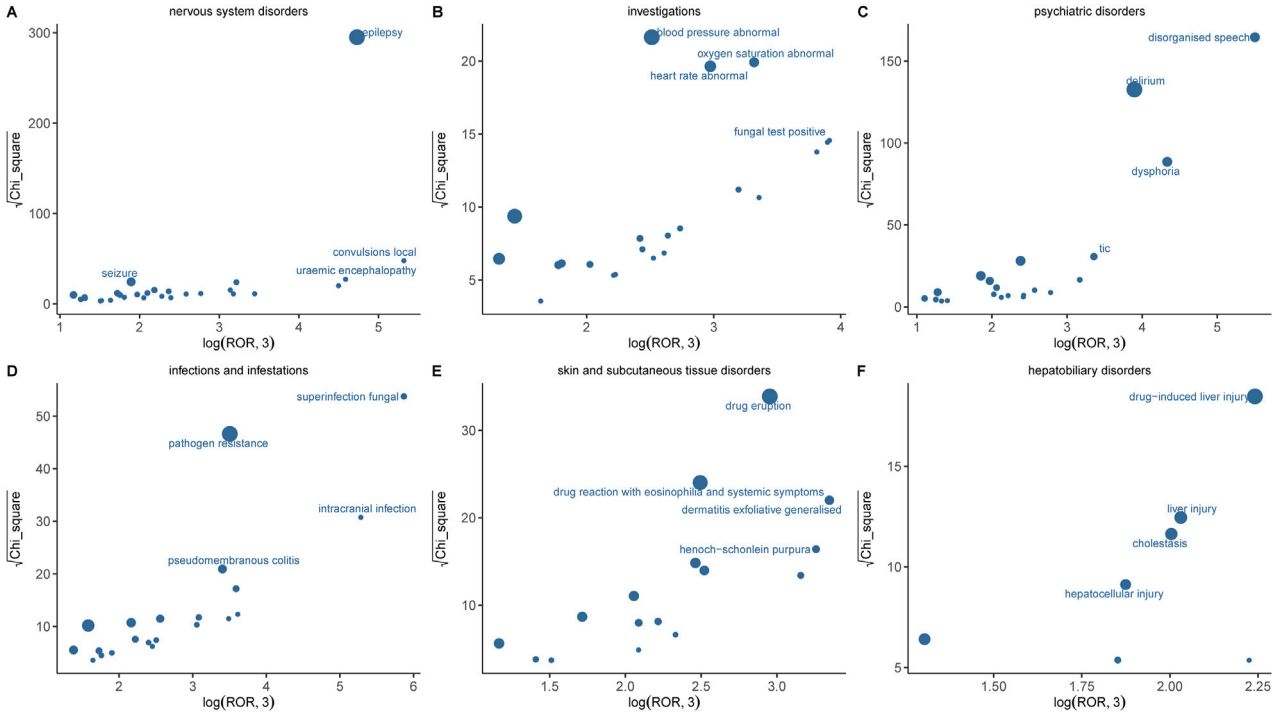


FIGURE 5
Comparison of six SOCs safety signals of IMI/CIL. **(A–F)** respectively presents the mining outcomes of adverse event signals of IMI/CIL in six system organ classes. The x-axis represents log2ROR, and the y-axis represents the square root of the $\chi 2$ value. In this graph, each point indicates a mined AE signal, with the size of the point corresponding to the quantity of reported AEs. The location of each AE in the graph is determined by the ROR (Reporting Odds Ratio) and PRR (Proportional Reporting Ratio) methods. If a point is located higher and further to the right in the graph, both algorithms suggest that the signal for that AE is strong.

barrier's increased vulnerability leads to higher imipenem concentrations in the brain, further exacerbating seizures (Lane et al., 1996). The occurrence of IMI/CIL related nervous system/psychiatric disorders may be attributed to the neurotoxic potential of carbapenem drugs, with an increased risk observed when the dosage is escalated. The toxicity observed is believed to be attributed to the interaction between gamma-aminobutyric acid (GABA) and the drug. Due to its structural similarity with the β-lactam ring, gamma-aminobutyric acid A GABA receptors are particularly susceptible to antagonism by this class of drugs, resulting in a reduction in GABA transmission. Consequently, a range of psychiatric symptoms such as delirium and hallucinations ensue (Norrby, 1996; Teng and Frei, 2022; Grill and Maganti, 2011; Chow et al., 2005). However, the exact cause of this toxicity, whether it is attributed to the drug itself or its metabolites, remains unclear and necessitates further investigation. The study conducted by Koppel et al. observed a higher prevalence of neurological reactions to IMI/CIL in comparison to other carbapenems, such as meropenem and ertapenem (Koppel et al., 2001). This could potentially be attributed to the stronger affinity of IMI/CIL for GABA-agonizing receptors (Miller et al., 2011; Kamei et al., 1983). The change in seizure incidence is attributed to the alkalinity of the side chain attached to the second carbon atom. The higher the alkalinity of the side chain, the greater its affinity for GABA agonist receptors and consequently, the stronger its neurotoxic effect (Chow et al., 2005; Koppel et al., 2001). However, IMI/CIL exhibits a more alkaline side chain compared to other drugs in the same class, which may explain its heightened neurotoxicity (Grill and Maganti, 2008; Snavely and Hodges, 1984). In conclusion, it is imperative for clinicians to conduct further research on the optimal therapeutic window of drug administration in order to mitigate potential neurotoxicity resulting from elevated intracranial drug concentrations. Physicians should refrain from blindly pursuing the desired therapeutic effects through high dosages, while disregarding the associated risks posed by escalating drug concentrations, particularly among patients with pre-existing central nervous system disorders, systemic vascular inflammation, and renal insufficiency.

Most AEs in infection and infestation may be attributed to disease progression in infected patients rather than being specific to the treatment with TZP. At the level of Infections and infestations, antibiotic resistance emerged as the most prevalent AE. Antibiotic resistance has always posed an insurmountable barrier in the treatment of infections. With the rise of drug-resistant bacteria, there is a continuous increase in carbapenem-resistant bacteria. The drug insert does not explicitly mention *acinetobacter* infection, *klebsiella* infection, abdominal infection, and enterococcal infection. However, these conditions should be considered as indications for IMI/CIL rather than being attributed to drug-induced AEs. Therefore, data mining can only serve as a process for discovering suspicious signals, and the causal relationship between drugs and AEs in the database needs to be rigorously evaluated through a signal evaluation process that includes medical assessment. The notable signals observed included pseudomembranous colitis and *Clostridium difficile* colitis. The incidence of *Clostridium difficile* colitis in our

study was comparable to that reported by Portsmouth et al. (2018). The occurrence of *clostridium difficile* infection associated with imipenem has been sporadically documented in case reports. In one instance, a geriatric patient with chronic kidney disease undergoing dialysis experienced diarrhea while receiving IMI/CIL treatment for 10 days. Subsequent stool culture confirmed the presence of *Clostridium difficile*, and symptoms resolved upon discontinuation of IMI/CIL therapy and initiation of vancomycin. Investigations also revealed positive signals for fungal test positive and *clostridium* test positive, indicating opportunistic infection. However, the specific mechanism of this infection remains unclear and may be associated with antibiotic-induced disruption of normal intestinal flora, overgrowth of *Clostridium difficile*, and bacterial toxin-mediated damage to enterocyte cytoskeleton integrity (Hassoun, 2018). Additionally, we have also identified several previously unreported AEs, including halo vision, ototoxicity, dysbiosis, foaming at mouth and irregular sleep-wake rhythm disorder. These could be attributed to a direct toxic or allergic reaction to the medication, or it may stem from the patient's underlying inherent disease or concurrent medication. Ocular toxicity and ototoxicity warrant careful monitoring by healthcare professionals. Considering their potential impact on vision and hearing, as well as the possible detrimental effect on patients' prognosis, no clinical trials or case reports have been documented thus far. The presence of eye disorders such as halo vision, gaze palsy, and pupillary reflex impairment may be attributed to GABA antagonism, as it has been postulated that a decrease in GABA transmission could lead to heightened excitability in the visual cortex (Kasteleijn-Nolst Trenité et al., 2001).

This study conducted a comprehensive assessment of the safety of IMI/CIL based on the FAERS database; however, the potential inherent limitations of the system itself should not be overlooked. Firstly, as an open-access spontaneous reporting system, FAERS lacks fixed standards and mandatory requirements for data completeness during submission, leading to a significant amount of missing data and confounding factors (Alatawi and Hansen, 2017). Secondly, the absence of a true total number of patients makes it challenging to calculate the true incidence. It is important to note that this study represents only preliminary speculation on drug-related AEs and their potential mechanisms; thus, establishing causal relationships between ADRs is not feasible. ADRs are influenced by various factors such as disease, internal environment, external influences, and individual differences. Therefore, further clinical and basic research is necessary to elucidate these causal relationships. Nonetheless, disproportion analysis serves as an effective method for signal strength mining and provides valuable insight into quantifying risk or causal role. Prospective studies are still required to determine the causality of ADRs with drugs in order to fully comprehend the risks associated with IMI/CIL use. At the same time, medical professionals should continue closely monitoring the occurrence of AEs in clinical practice and implementing timely intervention measures. Despite the constraints of realistic conditions, the analysis of IMI/CIL in this study can still offer favorable perspectives for enhancing drug safety and further research.

5 Conclusion

This study assessed the potential correlation between IMI/CIL and ADRs using real-world data from the FAERS database. Through a systematic analysis, previously unreported ADRs as well as known ADRs, including life-threatening serious AEs, were identified. Furthermore, their potential mechanisms were preliminarily explained. Therefore, it is imperative to remain vigilant towards AEs associated with IMI/CIL in clinical practice. However, meticulous attention is requisite to the inherent limitations of the FAERS database and the potential for bias and error. In conclusion, the findings of this study offer comprehensive evidence regarding the safety of IMI/CIL post-marketing, which is valuable for informing future research endeavors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

PJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing–original draft, Writing–review and editing. YZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing–original draft, Writing–review and editing. YG: Conceptualization, Formal Analysis, Investigation, Methodology, Software, Writing–review and editing. SW: Conceptualization, Data curation, Formal Analysis, Investigation, Software, Writing–review and editing. JY: Conceptualization, Data curation, Formal Analysis, Project administration, Resources, Writing–review and editing. YL: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing–review and editing. QL: Formal Analysis, Project administration, Resources, Supervision, Validation, Writing–original draft, Writing–review and editing, Visualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1524159/full#supplementary-material

References

Abraham, A., Fainmesser, Y., Drory, V. E., and Bril, V. (2023). Quantitative sonographic assessment of muscle thickness and fasciculations distribution is a sensitive tool for neuromuscular disorders. *PLoS One* 18 (9), e0292123. doi:10.1371/journal.pone.0292123

Alatawi, Y. M., and Hansen, R. A. (2017). Empirical estimation of under-reporting in the U.S. Food and drug administration adverse event reporting system (FAERS). *Expert Opin. Drug Saf.* 16 (7), 761–767. doi:10.1080/14740338.2017.1323867

Balfour, J. A., Bryson, H. M., and Brogden, R. N. (1996). Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 51 (1), 99–136. doi:10.2165/00003495-199651010-00008

Bradley, J. S., Garau, J., Lode, H., Rolston, K. V., Wilson, S. E., and Quinn, J. P. (1999). Carbapenems in clinical practice: a guide to their use in serious infection. *Int. J. Antimicrob. Agents* 11 (2), 93–100. doi:10.1016/s0924-8579(98)00094-6

Bush, K., and Bradford, P. A. (2020). Epidemiology of β-lactamase-producing pathogens. *Clin. Microbiol. Rev.* 33 (2), e00047. doi:10.1128/CMR.00047-19

Calandra, G., Lydick, E., Carrigan, J., Weiss, L., and Guess, H. (1988b). Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. *Am. J. Med.* 84 (5), 911–918. doi:10.1016/0002-9343(88)90071-x

Calandra, G. B., Brown, K. R., Grad, L. C., Ahonkhai, V. I., Wang, C., and Aziz, M. A. (1985). Review of adverse experiences and tolerability in the first 2,516 patients treated with imipenem/cilastatin. *Am. J. Med.* 78 (6A), 73–78. doi:10.1016/0002-9343(85)90104-4

Calandra, G. B., Ricci, F. M., Wang, C., and Brown, K. R. (1983). Safety and tolerance comparison of imipenem-cilastatin to cephalothin and cefazolin. *J. Antimicrob. Chemother.* 12 (Suppl. D), 125–131. doi:10.1093/jac/12.suppl_d.125

Calandra, G. B., Ricci, F. M., Wang, C., and Brown, K. R. (1988a). The efficacy results and safety profile of imipenem/cilastatin from the clinical research trials. *J. Clin. Pharmacol.* 28 (2), 120–127. doi:10.1002/j.1552-4604.1988.tb05735.x

Calandra, G. B., Wang, C., Aziz, M., and Brown, K. R. (1986). The safety profile of imipenem/cilastatin: worldwide clinical experience based on 3470 patients. *J. Antimicrob. Chemother.* 18 (Suppl. E), 193–202. doi:10.1093/jac/18.supplement_e.193

Cherif, B., Triki, H., Sahnoun, S., Hamden, K., Sallemi, A., Charfi, S., et al. (2019). Imipenem toxicity in male reproductive organs as a result of inflammatory microenvironment and oxidative stress in germinal cells. *Toxicology* 416, 44–53. doi:10.1016/j.tox.2019.02.001

Chow, K. M., Hui, A. C., and Szeto, C. C. (2005). Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. *Eur. J. Clin. Microbiol. Infect. Dis.* 24 (10), 649–653. doi:10.1007/s10096-005-0021-y

Drawz, S. M., and Bonomo, R. A. (2010). Three decades of beta-lactamase inhibitors. *Clin. Microbiol. Rev.* 23 (1), 160–201. doi:10.1128/CMR.00037-09

Fariñas, M. C., de Vega, T., Garmendia, J., and González-Macías, J. (1993). Severe neutropenia in a patient treated with imipenem/cilastatin. *Eur. J. Clin. Microbiol. Infect. Dis.* 12 (4), 303–304. doi:10.1007/BF01967266

Ge, W., Hu, H., Li, C., Wang, L., and Xia, J. (2021). Safety profile of carbapenems: data mining of the FDA adverse events reporting system. *Int. J. Clin. Pharmacol. Ther.* 59 (9), 594–602. doi:10.5414/CP203811

Grill, M. F., and Maganti, R. (2008). Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. *Ann. Pharmacother.* 42 (12), 1843–1850. doi:10.1345/aph.1L307

Grill, M. F., and Maganti, R. K. (2011). Neurotoxic effects associated with antibiotic use: management considerations. *Br. J. Clin. Pharmacol.* 72 (3), 381–393. doi:10.1111/j.1365-2125.2011.03991.x

Hassoun, A. (2018). *Clostridium difficile* associated disease. *BMJ* 363, k4369. doi:10.1136/bmj.k4369

Kamei, C., Sunami, A., and Tasaka, K. (1983). Epileptogenic activity of cephalosporins in rats and their structure-activity relationship. *Epilepsia* 24 (4), 431–439. doi:10.1111/j.1528-1157.1983.tb04913.x

Kasteleijn-Nolst Trenité, D. G., Guerrini, R., Binnie, C. D., and Genton, P. (2001). Visual sensitivity and epilepsy: a proposed terminology and classification for clinical and EEG phenomenology. *Epilepsia* 42 (5), 692–701. doi:10.1046/j.1528-1157.2001.30600.x

Koppel, B. S., Hauser, W. A., Politis, C., van Duin, D., and Daras, M. (2001). Seizures in the critically ill: the role of imipenem. *Epilepsia* 42 (12), 1590–1593. doi:10.1046/j.1528-1157.2001.34701.x

Lane, M., Kania, D., and Rapp, R. P. (1996). Seizures related to use of imipenem-cilastatin. *Am. J. Health Syst. Pharm.* 53 (13), 1605–1606. doi:10.1093/ajhp/53.13.1605

Lucena, M., Andrade, R., Cabello, M., Clavijo, E., and Queipo de Llano, E. (1992). Imipenem/cilastatin-associated hiccups. *Ann. Pharmacother.* 26 (11), 1459. doi:10.1177/106002809202601125

MacKenzie, F. M., Gould, I. M., Chapman, D. G., and Jason, D. (1994). Comparison of methodologies used in assessing the postantibiotic effect. *J. Antimicrob. Chemother.* 34 (2), 223–230. doi:10.1093/jac/34.2.223

Miller, A. D., Ball, A. M., Bookstaver, P. B., Dornblaser, E. K., and Bennett, C. L. (2011). Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. *Pharmacotherapy* 31 (4), 408–423. doi:10.1592/phco.31.4.408

Norrby, S. R. (1996). Neurotoxicity of carbapenem antibacterials. *Drug Saf.* 15 (2), 87–90. doi:10.2165/00002018-199615020-00001

O'Riordan, J., Javed, M., Doherty, C., and Hutchinson, M. (1994). Worsening of myasthenia gravis on treatment with imipenem/cilastatin. *J. Neurol. Neurosurg. Psychiatry* 57 (3), 383. doi:10.1136/jnnp.57.3.383

Paterson, D. L. (2000). Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). *Clin. Microbiol. Infect.* 6 (9), 460–463. doi:10.1046/j.1469-0691.2000.00107.x

Paterson, D. L., and Bonomo, R. A. (2005). Extended-spectrum beta-lactamases: a clinical update. *Clin. Microbiol. Rev.* 18 (4), 657–686. doi:10.1128/CMR.18.4.657-686.2005

Portsmouth, S., van Veenhuyzen, D., Echols, R., Machida, M., Ferreira, J. C. A., Ariyasu, M., et al. (2018). Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect. Dis.* 18 (12), 1319–1328. doi:10.1016/S1473-3099(18)30554-1

Qiao, W., Chang, C., Wang, Q., Cao, X., and Zhang, X. (2022). Imipenem cilastatin sodium-associated thrombocytopenia in an older patient: a case report and literature review. *Int. J. Clin. Pharmacol. Ther.* 60 (8), 358–363. doi:10.5414/CP204215

Snavely, S. R., and Hodges, G. R. (1984). The neurotoxicity of antibacterial agents. *Ann. Intern Med.* 101 (1), 92–104. doi:10.7326/0003-4819-101-1-92

Tahri, A., Ksouda, K., Kallel, R., Daoud, S., Boudawara, T., Zeghal, K. M., et al. (2017). A carbapenem antibiotic imipenem/cilastatin induces an oxidative stress-status and

gonadotoxic effects in « wistar » rats. *Biomed. Pharmacother.* 95, 308–316. doi:10.1016/j.biopha.2017.08.039

Tahri, A., Lahyani, A., Kallel, R., Ayadi, F., Boudawara, T., and Sahnoun, Z. (2018). Exposure to imipenem/cilastatin causes nephrotoxicity and even urolithiasis in Wistar rats. *Toxicology* 404-405, 59–67. doi:10.1016/j.tox.2018.05.011

Teng, C., and Frei, C. R. (2022). Delirium associations with antibiotics: a pharmacovigilance study of the FDA adverse event reporting system (FAERS). *Drugs Real World Outcomes* 9 (1), 23–29. doi:10.1007/s40801-021-00268-1

Titov, I., Wunderink, R. G., Roquilly, A., Rodríguez Gonzalez, D., David-Wang, A., Boucher, H. W., et al. (2021). A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 study). *Clin. Infect. Dis.* 73 (11), e4539–e4548. doi:10.1093/cid/ciaa803

Verwaest, C., and Belgian Multicenter Study Group (2000). Meropenem versus imipenem/cilastatin as empirical monotherapy for serious bacterial infections in the intensive care unit. *Clin. Microbiol. Infect.* 6 (6), 294–302. doi:10.1046/j.1469-0691.2000.00082.x

Zhanel, G. G., Wiebe, R., Dilay, L., Thomson, K., Rubinstein, E., Hoban, D. J., et al. (2007). Comparative review of the carbapenems. *Drugs* 67 (7), 1027–1052. doi:10.2165/00003495-200767070-00006

Zhang, X., Jiang, Y., Guo, Y., Zhou, W., Qiao, W., Zhu, H., et al. (2024). Safety evaluation of ceftazidime/avibactam based on FAERS database. *Infection* 52, 2195–2205. doi:10.1007/s15010-024-02248-3

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 18 February 2025
DOI 10.3389/fphar.2025.1459067

OPEN ACCESS

EDITED BY
Anick Bérard,
Montreal University, Canada

REVIEWED BY
Josef Yayan,
University of Witten/Herdecke, Germany
Moetaza M. Soliman,
Mansoura University, Egypt

*CORRESPONDENCE
Yonggong Yang,
yyg6807@126.com
Mengying Liu,
liumengying@njglyy.com
Jinping Zhang,
zjp16500@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 26 August 2024
ACCEPTED 27 January 2025
PUBLISHED 18 February 2025

CITATION
Wu F, Wang S, Xu X, Zhang W, Zhou J, Niu R, Cai W, Yang Y, Liu M and Zhang J (2025) Pharmacovigilance analysis of polatuzumab plus bendamustine and rituximab treatment protocol: identifying comprehensive safety signals using FDA database.
Front. Pharmacol. 16:1459067.
doi: 10.3389/fphar.2025.1459067

Pharmacovigilance analysis of polatuzumab plus bendamustine and rituximab treatment protocol: identifying comprehensive safety signals using FDA database

Fang Wu[1,2†], Siliang Wang[1,2†], Xihui Xu[3†], Weihui Zhang[1,2], Jie Zhou[1,2], Runyan Niu[1,2], Wenting Cai[1,2], Yonggong Yang[3*], Mengying Liu[1,2*] and Jinping Zhang[1,2*]

[1]Department of Pharmacy, Nanjing Drum Tower Hospital, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China, [2]Department of Pharmacy, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China, [3]Department of Hematology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Background: The combination of polatuzumab, bendamustine and rituximab (pola+BR) was authorized for the treatment of relapsed or refractory Diffuse large B cell lymphoma (DLBCL). This study used the FDA database to identify safety signals related to the treatment protocol.

Methods: The adverse events (AEs) from 2019Q1 to 2023Q3 were analyzed by calculating the reporting odds ratio. Severe and non-severe cases were compared using either an independent samples t-test or chi-squared (χ^2) test. Additionally, a score sheet was employed to prioritize the signals.

Results: In all database, 58 significant signals were detected within 1,597 patients accepting the treatment protocol. Common AEs like neutropenia, thrombocytopenia, and peripheral neuropathy, as well as other AEs like anaemia, sepsis, cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) were a major focus. In addtion, 51.7%, 45.6% and 1.7% were sorted into low, moderate and high priority in term of clinical importance, respectively. Unexpected significant signals included intestinal obstruction, epilepsy, deep vein thrombosis, haemorrhage, increased blood lactate dehydrogenase and hypercalcemia.

Conclusion: Our study identified significant AE signals for pola+BR through realworld disproportionality analysis data and analyzed the severity and clinical priority of these signals, which can assist clinicians in managing related AEs.

KEYWORDS

pharmacovigilance, polatuzumab vediton, drug safety, disproportionality analysis, FAERS

1 Introduction

Diffuse large B cell lymphoma (DLBCL) is the prevailing form of non-Hodgkin lymphoma (Vodicka et al., 2022). The classic initial treatment for DLBCL is R-CHOP, a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CHOP has the potential to cure the majority of patients. Nevertheless, approximately 40% of patients will experience treatment-resistant illness or recurrence (Tilly et al., 2022). Polatuzumab can provide patients with more effective treatment options for DLBCL. Polatuzumab specifically targets CD79b which is extensively expressed on cancerous B cells. The drug delivers monomethyl auristatin E to B cells to kill them (Deeks, 2019). Numerous global clinical trials are underway, which evaluate the efficacy of treatment protocol included polatuzumab for DLBCL (Palanca-Wessels et al., 2015; Diefenbach et al., 2021; Tilly et al., 2019).

Pola+BR was approved in 2019 for relapsed or refractory DLBCL, which was based on the pivotal trial GO29365 (Sehn et al., 2022). Pola+BR is one of the second-line treatment protocol for DLBCL in the 2023 National Comprehensive Cancer Network (NCCN) guidelines recommendations (Zelenetz et al., 2023). A few of clinical trials has evaluated the effectiveness and safety of Pola+BR, which demonstrated clinical benefit (Argnani et al., 2022; Dal et al., 2023; Wang et al., 2022). However, real-world study of the protocol has not been conducted globally by now. The FDA has developed the Food and Drug Administration Adverse Event Reporting System (FAERS) to enable people to submit reports on adverse events (AEs). Our objective was to characterize AEs of pola+BR by using the FAERS to perform large-scale post-marketing surveillance.

2 Patients and methods

2.1 The design of the study and data source

We analyzed the safety of pola+BR in B lymphoma through a comprehensive retrospective appraisement and downloaded data from DEMO, DRUG, REAC, OUTC, and INDI tables contained in the FAERS database covering the period from 2019Q1 to 2023Q3.

2.2 Data fetch and analysis

We cleaned and merged the datasets before statistical analysis because of the duplicate reports. Initially, reports with the most recent FDA acceptance date were chosen, and repeat records were subsequently eliminated. Secondly, the study only focused on role_cod

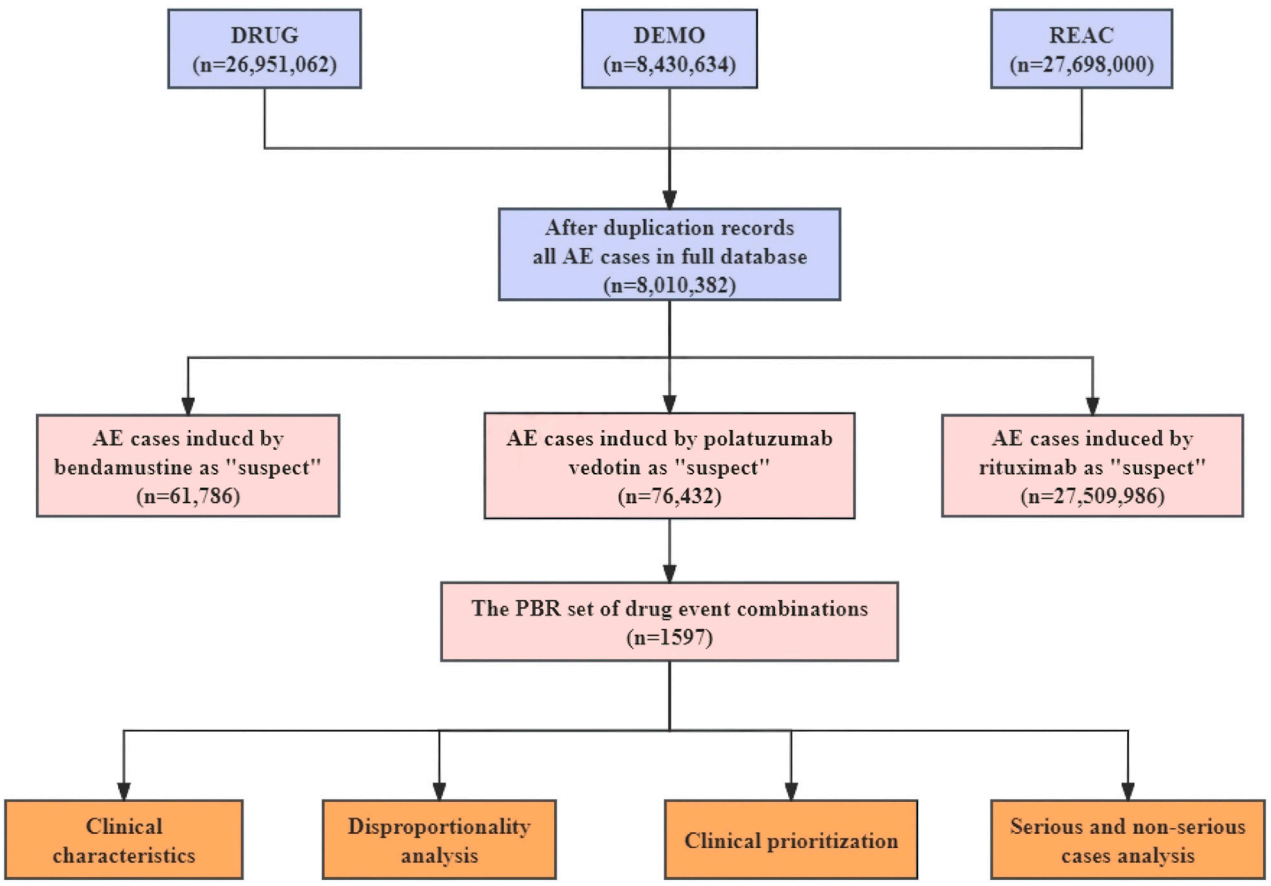


FIGURE 1
The process of extracting, processing, and analyzing data from food and drug administration adverse event reporting (FAERS) database. AE, Adverse events; Pola+BR, Polotuzumab combination Bendamustine and Rituximab.

TABLE 1 Characteristics of adverse events reports associated with the pola+BR treatment protocol. From 2019Q1 to 2023Q3.

Characteristics	Pola+BR (N = 1,597)
Gender, n (%)	
Female	496 (31.06%)
Male	698 (43.71%)
Unknown	385 (24.11%)
Age (years), n (%)	
<18	2 (0.13%)
18≤and≤65	414 (25.92%)
>65	354 (22.17%)
Unknown	809 (50.66%)
Reported countries, n (%)	
United States	33 (2.07%)
Italy	213 (13.34%)
Canada	6 (0.38%)
Great Britain	323 (20.23%)
Germany	262 (16.41%%)
Others	760 (47.59%)
Indications, n (%)	
DLBCL	1,249 (78.21%)
DLBCL refractory	59 (3.69%)
DLBCL recurrent	24 (1.50%)
Others	265 (16.59%)
Outcomes, n (%)	
Non-serious outcome	1,123 (70.32%)
Serious outcome	474 (29.68%)
Report year, n (%)	
2019	1 (0.06%)
2020	23 (1.44%)
2021	108 (6.76)
2022	476 (29.81%)
2023	971 (60.80%)

of drugs that were reported as 'primary suspects' or 'secondary suspects'. Ultimately, a total of 8,010,382 cases of AEs had been uploaded to the FAERS during the study period and contained pola+BR-related AEs in 1,597 patients. The preferred terms (PTs) were categorized into System Organ Classes (SOC) based on the Medical Dictionary for regulatory Activities (MedDRA) Version 24.0. The study, serious AEs were defined as outcomes leading to hospitalizations, life-threatening illnesses, disabilities, or death (Matsumoto et al., 2023). Reporting odd ratio (ROR) represents a widely used and reliable measure of disproportionality analysis for pharmacovigilance studies based on a two-by-two contingency table, which can identify potential correlations between reported drugs and AEs. Figure 1 illustrates the procedure of extracting, processing, and analyzing data.

2.3 Statistical analysis

The ROR algorithm was used to detect AEs signals (Supplementary Table S1). To reduce false positives, we only retained PTs with at least 10 reports (Shu et al., 2022). A signal would be deemed significant if the lower limit of the 95% confidence interval for the ROR was greater than 1. We compared AE types between severe and non-severe cases. Comparisons were made by either a Pearson's chi-squared ($\chi 2$) or Fisher's exact test used for comparing proportion, while an independent samples t-test was utilized for continuous variables. By conducting a sensitivity analysis of the trend of ROR values over time to verify the robustness of the top ten signals (Zhao et al., 2023). Reports were imported and extracted by MySQL 15.0 and Navicat Premium 15, and statistical analyses were conducted with Microsoft Excel 2021 and GraphPad prism 9.

2.4 Clinical prioritization of signals

The prioritization of significant signals utilized a semi-quantitative score which contained factors such as the quantity of reports, ROR_{025} values, the percentage of death, classification as designated medical events (DMEs) or important medical events (IMEs), and the appraisement of evidence (Gatti et al., 2021; Guo et al., 2022). Identifying AEs with low, moderate, or high clinical priority can be done by categorizing scores as 0–4, 5–7, or 8–10. Supplementary Table S2 provides detailed information on these categories.

3 Results

3.1 Descriptive analysis

Following the completion of data cleaning, a total of 1,597 case reports with the pola+BR treatment protocol were collected between January 2019 and September 2023. The comprehensive clinical characteristics can be displayed in Table 1 and Figure 2. The proportion of patients using pola+BR was higher among males (43.71%) than females (31.06%), and 29.68% patients exprienced serious outcomes. Notablely, 83% of the patients were diagnosed with DLBCL and the number of patients using this treatment regimen has increased year by year.

3.2 Disproportionality analysis

There were 58 significant PTs in 11 SOCs shown in Table 2 and Figure 3. In addition PTs with fewer than 10 reports were listed in Supplementary Table S3. COVID-19, neutropenia, pancytopenia, thrombocytopenia and anaemia were the most common AEs besides disease progress, death and blood lactate dehydrogenate. Unexpected adverse events (AEs) that were not identified in previous clinical studies and instructions were classified for 6 PTs, such as intestinal obstruction, epilepsy, deep vein thrombosis, haemorrhage, increased blood lactate dehydrogenase and hypercalcemia.

3.3 Clinical prioritization of significant signals

Clinical prioritization of AEs was summarized in Table 3. All together, 26 out of 58 PTs (40.63%) were categorized as IMEs. A

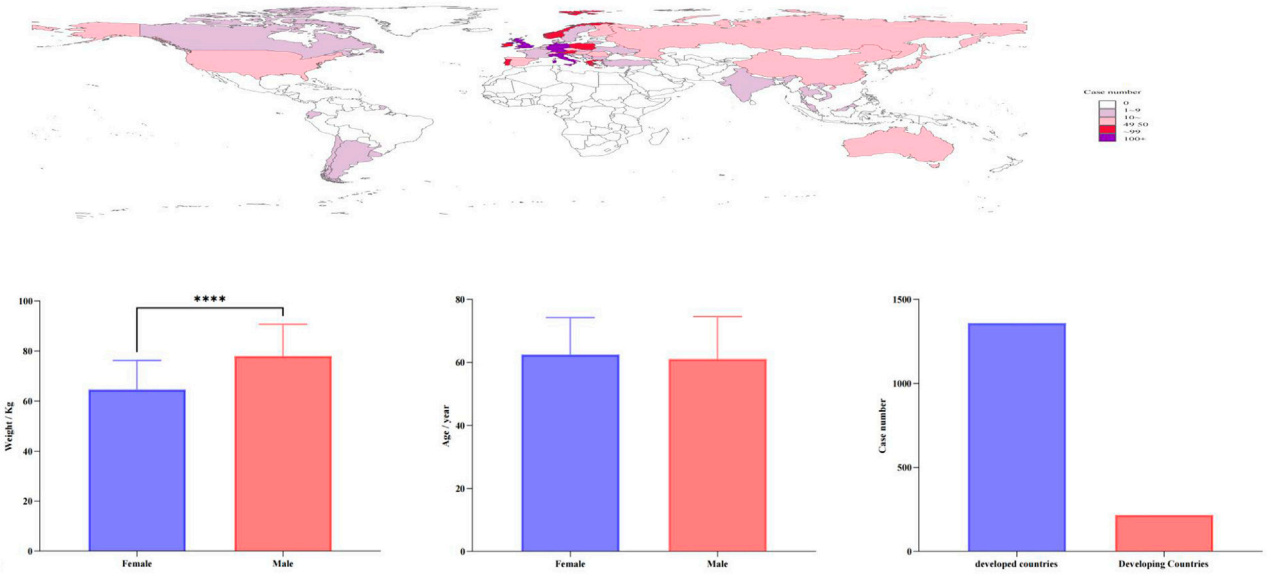


FIGURE 2
Case distribution and group characteristics of adverse event reports associated with the Pola+BR treatment protocol.

total of 5 PTs (7.81%) were identified as DMEs, including pancytopenia, febrile neutropenia, neutropenic infection, neutropenic sepsis, and renal failure. On the basis of clinical priority score, PTs were sorted into low, moderate, and high clinical priority, comprising 30 (51.7%), 27 (46.6%), and one (1.7%) respectively. Pancytopenia (score 8) emerged as high clinical priorities. Neutropenia, thrombocytopenia, anaemia, febrile neutropenia, intestinal obstruction, cytokine release syndrome (CRS), sepsis, cytomegalovirus infection reactivation, neurotoxicity and polyneuropathy were graded as moderate clinical prioporities. Among the 27 adverse events identified as moderate clinical priorities were conditions like neutropenia, thrombocytopenia, anaemia, febrile neutropenia, intestinal obstruction, CRS, sepsis, cytomegalovirus infection reactivation, neurotoxicity, polyneuropathy, and so on. With the evidence evaluated, it was determined that 22 AEs showed high clinical evidence with a rating of "++."

3.4 Contrasting severe and non-severe cases

The study included 1,597 patients of whom 474 had serious outcomes. Table 4 displays a statistically significant difference in gender (p = 0.02) between severe and non-severe cases. Males (32.23%) had a higher rate of serious AEs compared to females (26.01%). By contrast, age (p = 0.922) and weight (p = 0.608) did not differ between the two groups. With a p-value of less than 0.05, 42 PTs were more prone to be identified as serious AEs, including anaemia, febrile neutropenia, thrombocytopenia, intestinal obstruction, pyrexia, CRS, COVID-19, sepsis, neuropathy peripheral, epilepsy, renal failure and deep vein thrombosis. Additionally, other PTs showed a tendency to be classified into non-severe AEs with a p-value greater than 0.05, such as pancytopenia, oedema, aspartate aminotransferase increased and alanine aminotransferase increased.

3.5 Sensitivity analysis

To reduce the risk of false positives in AEs detection and confirm the stability of the signals, this study conducted a sensitivity analysis on the top ten positive signals by case report number. By calculating the reporting ROR and its 95% confidence interval corresponding to the annual cumulative case volume of disease progression, blood lactate dehydrogenase increased, COVID-19, death, neutropenia, pancytopenia, thrombocytopenia, anaemia, pyrexia and sepsis, we assessed the trend of the signals over time, as detailed in Figure 4. As the number of cases continues to accumulate, the 95% confidence intervals for the ROR values of these 10 positive signals gradually narrow and stabilize, further validating the robustness of the signals.

4 Discussion

The most recent safety profiles of the pola+BR treatment protocol were examined in this study through post-marketing analysis by using data from the FAERS. We found that the number of patients taking pola+BR has increased year by year and more patients will possibly choose the pola+BR regimen in the future. Therefore, it is important to comprehensively monitor AEs in this regimen. As shown in Figure 2, the reports of related AEs of Pola + BR were mainly concentrated in developed countries, and the reasons may involve two main aspects: First, the FAERS database is a system relying on spontaneous reporting. In addition to FAERS, there are other databases such as Vigibase and Japanese Adverse Drug Event Reporting System, which may lead to the FAERS

10.3389/fphar.2025.1459067

TABLE 2 Disproportionate distribution of positive signals of the pola+BR treatment protocol.

SOC	PT	N	ROR (95%CI)
Blood and lymphatic system disorders	Neutropenia	102	8.78 (7.19–10.74)
	Pancytopenia	54	14.59 (11.12–19.15)
	Thrombocytopenia	53	6.45 (4.90–8.48)
	Anaemia	52	3.68 (2.79–4.85)
	Febrile neutropenia	45	8.29 (6.16–11.15)
	Cytopenia	31	24.21 (16.95–34.57)
	Blood disorder	22	35.22 (23.09–53.72)
	Leukopenia	17	4.32 (2.68–6.97)
	Haematotoxicity	16	21.67 (13.23–35.50)
	Myelosuppression	15	5.24 (3.15–8.17)
Gastrointestinal disorders	**Intestinal obstruction**	16	5.00 (3.06–8.19)
General disorders and administration site conditions	Disease progression	864	213.94 (193.80–236.17)
	Death	109	1.83 (1.51–2.23)
	Pyrexia	49	1.71 (1.29–2.27)
	Ill-defined disorder	35	5.13 (3.67–7.17)
	General physical health deterioration	30	3.16 (2.20–4.53)
	Mucosal inflammation	17	8.71 (5.40–14.05)
	Oedema	10	2.72 (1.46–5.06)
Immune system disorders	Cytokine release syndrome	20	10.80 (6.94–16.79)
	Immunosuppression	13	15.94 (9.23–27.54)
Infections and infestations	COVID-19	158	5.40 (4.59–6.37)
	Sepsis	47	5.70 (4.26–7.62)
	Cytomegalovirus infection reactivation	39	81.32 (59.04–112.01)
	Infection	36	2.78 (2.00–3.87)
	Septic shock	30	9.42 (6.56–13.52)
	Bacterial infection	20	12.85 (8.26–19.99)
	Fungal infection	20	7.29 (4.69–11.33)
	Urosepsis	20	26.37 (16.94–41.03)
	Cytomegalovirus infection	17	12.06 (7.47–19.45)
	Neutropenic sepsis	15	25.91 (15.56–43.14)
	Neutropenic infection	14	258.54 (150.77–443.35)
	Candida infection	12	7.09 (4.01–12.51)
	Bacteraemia	11	11.34 (6.26–20.53)
	Tooth abscess	11	12.06 (6.66–21.84)
	Candida pneumonia	10	427.75 (223.88–817.25)
	COVID-19 pneumonia	10	4.50 (2.42–8.39)
	Infected skin ulcer	10	67.75 (36.23–126.68)
	Varicella zoster virus infection	10	46.30 (24.79–86.47)

(Continued on following page)

TABLE 2 (*Continued*) Disproportionate distribution of positive signals of the pola+BR treatment protocol.

SOC	PT	N	ROR (95%CI)
Investigations	**Blood lactate dehydrogenase increased**	172	193.76 (165.00–227.52)
	C-reactive protein increased	29	7.11 (4.92–10.26)
	Haemoglobin decreased	24	2.96 (1.98–4.43)
	Aspartate aminotransferase increased	22	6.32 (4.15–9.63)
	Blood bilirubin increased	22	13.42 (8.81–20.46)
	Alanine aminotransferase increased	19	4.46 (2.84–7.02)
	Glomerular filtration rate decreased	13	11.42 (6.61–19.72)
	Inflammatory marker increased	11	19.48 (10.75–35.29)
Metabolism and nutrition disorders	**Hypercalcaemia**	21	20.59 (13.38–31.70)
Nervous system disorders	Neuropathy peripheral	27	3.23 (2.21–4.73)
	Confusional state	19	1.69 (1.07–2.65)
	Neurotoxicity	17	10.80 (6.69–17.43)
	Polyneuropathy	12	10.78 (6.11–19.04)
	Epilepsy	11	5.04 (2.78–9.12)
	Immune effector cell-associated neurotoxicity syndrome	11	25.43 (14.03–46.08)
	Disturbance in attention	10	2.78 (1.49–5.18)
Renal and urinary disorders	Renal failure	32	2.30 (1.62–3.27)
Respiratory.thoracic and mediastinal disorders	Respiratory failure	15	3.16 (1.90–5.25)
Vascular disorders	**Deep vein thrombosis**	20	6.32 (4.07–9.83)
	Haemorrhage	14	1.73 (1.02–2.93)

Unexpected signals are in bold.
SOC, system organ classes; PTs, preferred terms; N, number of cases; ROR, reporting odds ration; CI, confidence interval.

collected reports mainly from European and American countries. Second, UGT1A1 gene polymorphisms closely related to the drug metabolism of antibody-conjugated drugs were associated with the occurrence of treatment-related AEs, while UGT1A1 expression varied across ethnic groups (Tarantino et al., 2023). Together, these factors may contribute to the geographical imbalance in the reporting of Pola + BR-related AEs. According to our research, males (32.23%) were prone to exhibit serious AEs. In accordance with epidemiologic studies of DLBCL, pola+BR-associated AEs were more common in males (43.71%) than females (31.06%). This phenomenon may also be associated with body weight, as illustrated in Figure 2, which demonstrates a significant difference in body weight between male and female patient groups experiencing AEs related to pola+BR. Additionally, studies (Gibiansky et al., 2022; Yin et al., 2021) have shown that changes in body weight affect the pharmacokinetics of certain antibody-drug conjugates. Our findings indicated that there was no disparity in body weight between severe and non-severe instances. However, a time-to-event analysis study (Lu et al., 2017) on polatizumab discovered that body weight served as a prognostic indicator for secondary peripheral neuropathy in patients treated with polatizumab.

Polatuzumab received approval in June 2019, which was due to the outcomes of the clinical trial GO29365 (3). The most reported AEs in patients accepting pola+BR were neutropenia, diarrhea, nausea, thrombocytopenia and peripheral neuropathy (>30%). In the clinical trial GO29365, 41.7% of pola+BR patients reported serious AEs, and the most serious AEs were febrile neutropenia, sepsis, infectious pneumonia and pyrexia occurring in more than 5% of cases. In our study, neutropenia and thrombocytopenia were involved in the most reported AEs. In the pola+BR group, 29.68% of patients experienced serious adverse events (AEs), including febrile neutropenia, sepsis, and COVID-19 pneumonia. This consistency further substantiates the reliability of our research findings. Myelosuppression, periphral neuropathy, and infusion-related reactions led to dose reductions or discontinuation according to the polatuzumab vedotin labeling. In the pivotal clinical trial GO29365, treatment was terminated on account of thrombocytopenia (>5%), neutropenia (>4%), periphral neuropathy (2.6%) and infection (2.6%) among patients treated with pola+BR. In our study, thrombocytopenia, anaemia, febrile neutropenia, cytomegalovirus infection reactivation and immunosuppression were rated as moderate clinical priority and all of these were reported as serious AEs more possibly. It manifests that patients accepting pola+BR need adequate supportive care, such as transfusion support, growth factors infusion, appropriate antimicrobial prophylaxis and monitoring for infections (Smith et al., 2021).

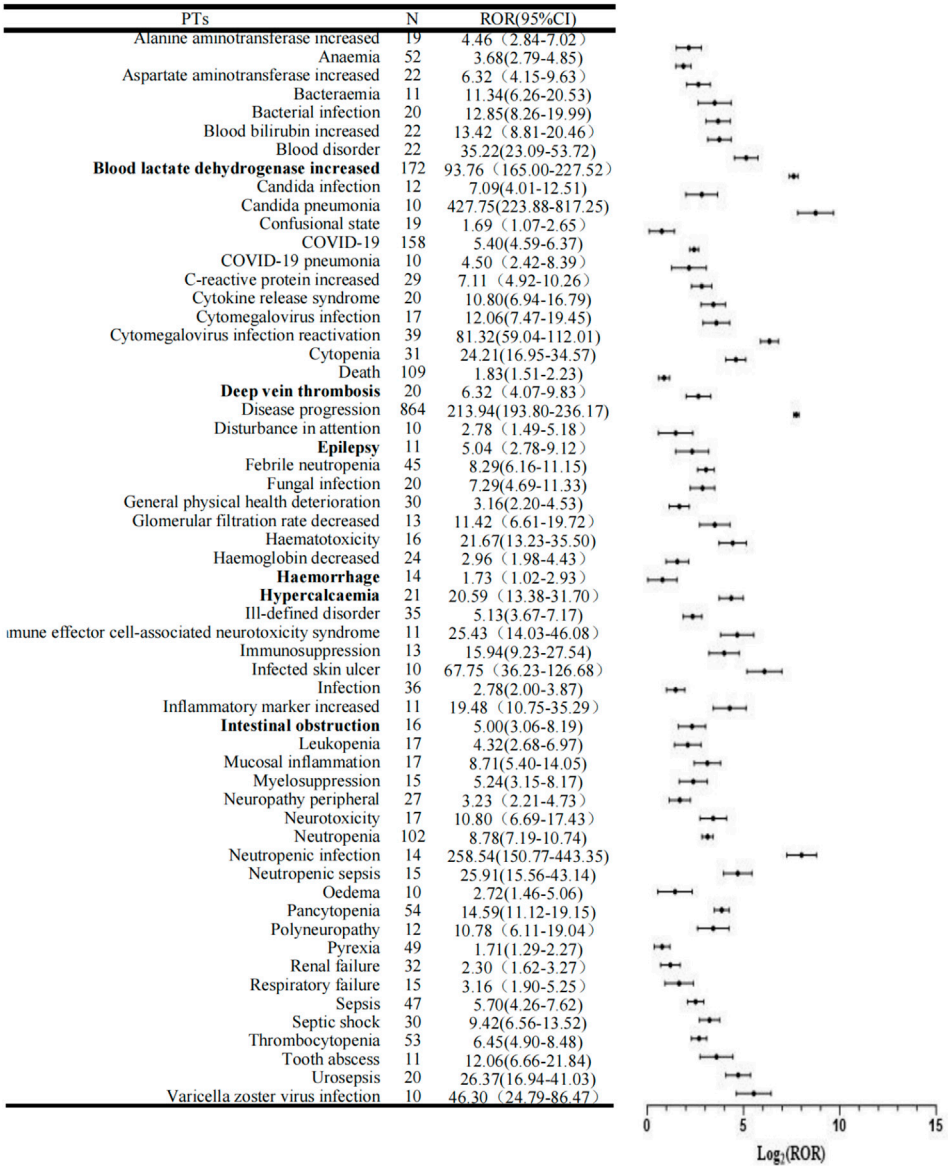


FIGURE 3
Forest plots of disproportionality of the Pola+BR treatment protocol. PTs, preferred terms; N, number of cases; ROR, Reporting Odds Ration; CI, Confidence Interval.

At present, sepsis and the septic shock are confronting important clinical problems in the field of acute critical care medicine. A new extension cohort study (Sehn et al., 2022) of pola+BR in relapsed/refractory DLBCL, 9.9% patients discontinued treatment due to serious sepsis in the pooled pola+BR cohort. In our study, sepsis, sepsis shock and neutropenic sepsis were rated as moderate clinical priority and prone to be listed in serious AEs. An analysis (Xia et al., 2022) of drug safety using the FAERS database revealed 35 cases of sepsis, 21 cases of sepsis shock and 8 cases of neutropenic sepsis associated with polatuzumab vedotin from the first quarter of 2004 to the third quarter of 2021. The ROR of polatuzumab inducing sepsis-related AEs is 8.30, which suggests that polatuzumab increases the risk of sepsis-related AEs. Clinicians should be alert to sepsis-related AEs when pola+BR is applied to patients. Initiatives such as early recognition, severity assessment and early therapy (antimicrobials and hemodynamic optimization) are beneficial to reduce both morbidity and mortality of sepsis (Jouffroy et al., 2024). In clinical practice, dynamic monitoring of early warning scoring systems such as the National Early Warning Score (NEWS), Sequential Organ Failure Assessment (SOFA) score, and Multisystem Organ Dysfunction Syndrome (MODS) severity score are crucial for the early identification and intervention of sepsis. Studies have shown that the NEWS score performs well in identifying high-risk patients, particularly in non-critical care units, with both high sensitivity and specificity (Pullyblank et al., 2020). Additionally, the SOFA score is widely used to assess the organ function status of sepsis patients, effectively predicting mortality

10.3389/fphar.2025.1459067

TABLE 3 Clinical priority assessing results of positive signals.

SOC	PT	n	ROR025	Death (n)	IME/ DME	Relevant evidence evation	Priority level (score)
Blood and lymphatic system disorders	Neutropenia	102	7.19	20	IME	++	Moderate (7)
	Pancytopenia	54	11.12	17	DEM	++	High (8)
	Thrombocytopenia	53	4.90	10	IME	++	Moderate (6)
	Anaemia	52	2.79	14	NA	++	Moderate (5)
	Febrile neutropenia	45	6.16	12	DEM	++	Moderate (7)
	Cytopenia	31	16.95	2	IME	+	Moderate (5)
	Blood disorder	22	23.09	3	NA	++	Moderate (5)
	Leukopenia	17	2.68	3	IME	+	Low (4)
	Haematotoxicity	16	13.23	0	NA	++	Moderate (5)
	Myelosuppression	15	3.15	0	IME	++	Moderate (5)
Gastrointestinal disorders	Intestinal obstruction	16	3.06	0	IME	+	Low (4)
General disorders and administration site conditions	Disease progression	864	193.80	120	NA	—	Moderate (5)
	Death	109	1.51	109	IME	—	Low (4)
	Pyrexia	49	1.29	8	NA	++	Low (3)
	Ill-defined disorder	35	3.67	7	NA	–	Low (2)
	General physical health deterioration	30	2.20	8	NA	+	Low (3)
	Mucosal inflammation	17	5.40	0	NA	+	Low (4)
	Oedema	10	1.46	3	NA	++	Low (3)
Immune system disorders	Cytokine release syndrome	20	6.94	0	IME	+	Moderate (5)
	Immunosuppression	13	9.23	1	IME	+	Moderate (5)
Infections and infestations	COVID-19	158	4.59	47	NA	+	Low (4)
	Sepsis	47	4.26	16	IME	++	Moderate (5)
	Cytomegalovirus infection reactivation	39	59.04	2	IME	+	Moderate (5)
	Infection	36	2.00	12	NA	++	Low (4)
	Septic shock	30	6.56	15	IME	++	Moderate (6)
	Urosepsis	20	16.94	11	IME	+	Moderate (5)
	Bacterial infection	20	8.26	14	NA	+	Low (4)
	Fungal infection	20	4.69	2	NA	+	Low (3)
	Cytomegalovirus infection	17	7.47	2	IME	+	Moderate (5)
	Neutropenic sepsis	15	15.56	0	DEM	++	Moderate (7)
	Neutropenic infection	14	150.77	0	DEM	++	Moderate (7)
	Candida infection	12	4.01	8	NA	+	Low (3)
	Bacteraemia	11	6.26	11	IME	+	Moderate (5)
	Tooth abscess	11	6.66	0	IME	+	Moderate (5)
	COVID-19 pneumonia	10	2.42	7	IME	++	Moderate (5)
	Candida pneumonia	10	223.88	0	IME	+	Moderate (5)

(Continued on following page)

TABLE 3 (*Continued*) Clinical priority assessing results of positive signals.

SOC	PT	n	ROR025	Death (n)	IME/ DME	Relevant evidence evation	Priority level (score)
	Infected skin ulcer	10	36.23	0	NA	+	Low (4)
	Varicella zoster virus infection	10	24.79	1	NA	+	Low (4)
Investigations	Blood lactate dehydrogenase increased	172	165.00	36	NA	+	Moderate (5)
	C-reactive protein increased	29	4.92	8	NA	+	Low (3)
	Haemoglobin decreased	24	1.98	0	NA	++	Low (3)
	Aspartate aminotransferase increased	22	4.15	5	NA	++	Low (4)
	Blood bilirubin increased	22	8.81	0	NA	—	Low (3)
	Alanine aminotransferase increased	19	2.84	5	NA	++	Low (4)
	Glomerular filtration rate decreased	13	6.61	1	NA	+	Low (4)
	Inflammatory marker increased	11	10.75	0	NA	+	Low (4)
Metabolism and nutrition disorders	Hypercalcaemia	21	13.38	5	NA	+	Low (4)
Nervous system disorders	Neuropathy peripheral	27	2.21	7	IME	++	Moderate (5)
	Confusional state	19	1.07	8	NA	+	Low (2)
	Neurotoxicity	17	6.69	0	IME	++	Moderate (6)
	Polyneuropathy	12	6.11	0	IME	+	Moderate (5)
	Immune effector cell-associated neurotoxicity syndrome	11	14.03	1	IME	+	Moderate (5)
	Epilepsy	11	2.78	0	IME	+	Low (4)
	Disturbance in attention	10	1.49	5	NA	+	Low (2)
Renal and urinary disorders	Renal failure	32	1.62	12	DEM	+	Low (4)
respiratory.thoracic and mediastinal disorders	Respiratory failure	15	1.90	2	IME	+	Low (3)
Vascular disorders	Deep vein thrombosis	20	4.07	1	IME	+	Low (4)
	Haemorrhage	14	1.02	5	IME	++	low (4)

A priority score between 8 and 10, 5–7 or 0–4 represents the signal with high, moderate or low clinical priority, respectively. NA, Not Applicable (for relevant criterias); n, number of cases; SOC, System Organ Classes; PTs, Preferred Terms; ROR_{025}, the lower limit of 95% confidence interval of ROR; IME, important medical events; DME, designated medical events.

rates during hospitalization (Lambden et al., 2019). This multidimensional evaluation method provides clinicians with more precise decision-making support, contributing to better patient outcomes in sepsis management.

Over the past decades, numerous innovative medications have received approval in the fields of oncology and hematology. Cancer immunotherapy has progressed rapidly in recent years. Efficient immunotherapies such as anti-CD20 monoclonal antibody (rituximab) and antibodies against CD79b (polatuzumab) have already been approved for DLBCL (Roth et al., 2021). However, these powerful immunotherapeutic drugs are also linked to potentially deadly side effects—particularly disorders of the immune system, which are drawing attention alongside clinical application experience. CRS and ICANS (Freyer and Porter, 2020) are the most frequent immune-related toxicites. CRS presents typically as pyrexia, fatigue, loss of appetite and so on, but in severe cases, it can also lead to low blood pressure, oxygen deficiency, and/or organ dysfunction (Shimabukuro-Vornhagen et al., 2018). ICANS usually manifests toxic brain disorder, difficulties in speech, confusion, and in more severe cases, seizures, amyosthenia, and brain swelling have been observed (Gu et al., 2022). Patients with ICANS almost always have a history of CRS before developing ICANS, and ICANS usually occurs after CRS remission (Morris et al., 2022). Eleven patients who presented ICANS in our study had also experienced CRS. While CRS and ICANS are serious AEs, most symptoms that do not cause permanent harm can be resolved. Therefore, it is of great importance to identify and manage CRS and ICANS. In the early identification of neurotoxicity, it is crucial to promptly monitor for neurological symptoms in patients during the treatment process. These symptoms may include pain, numbness, dizziness, and so on. Medical professionals should remain vigilant about the potential

10.3389/fphar.2025.1459067

TABLE 4 Differences in clinical characteristics of severe and non-severe reports.

	Serious cases	Non-serious cases	Statistic	p-value
Age, years (Mean ± SD)	61.05 ± 14.02	58 ± 13.04	0.10[c]	0.922
weight, kg (Mean ± SD)	73.72 ± 16.4	73.62 ± 13.32	0.51[c]	0.608
Sex distribution, n				
Male	**225**	**473**	**5.39**[d]	**0.020**[a]
Female	129	367		
Types of AEs, n				
Anaemia	**26**	**26**	**10.633**[d]	**0.001**[a]
Febrile neutropenia	**26**	**19**	**33.710**[d]	**<0.001**[a]
Thrombocytopenia	**26**	**27**	**9.861**[d]	**0.002**[a]
Haematotoxicity	**15**	**1**	**31.787**[d]	**<0.001**[a]
Leukopenia	**12**	**5**	**13.777**[d]	**<0.001**[a]
Neutropenia	37	65	2.270[d]	0.131[a]
Pancytopenia	31	23	3.706[d]	0.054[a]
Cytopenia	14	17	3.630[d]	0.057[a]
Myelosuppression	6	9	0.773[d]	0.379[a]
Blood disorder	3	19	2.751[d]	0.097[a]
Intestinal obstruction	**0**	**16**	**—**	**0.005**[b]
Disease progression	**202**	**662**	**35.809**[d]	**<0.001**[a]
Death	**109**	**0**	**277.160**[d]	**<0.001**[a]
Pyrexia	**40**	**9**	**65.371**[d]	**<0.001**[a]
General physical health deterioration	**17**	**13**	**10.668**[d]	**0.001**[a]
Mucosal inflammation	**14**	**3**	**22.841**[d]	**<0.001**[a]
Ill-defined disorder	7	28	1.607[d]	0.205[a]
Oedema	3	7	—	0.982[b]
Cytokine release syndrome	**17**	**3**	**29.697**[d]	**<0.001**[a]
Immunosuppression	**13**	**0**	**—**	**<0.001**[b]
COVID-19	**79**	**79**	**34.687**[d]	**<0.001**[a]
Sepsis	**32**	**15**	**34.220**[d]	**<0.001**[a]
Septic shock	**28**	**2**	**59.353**[d]	**<0.001**[a]
Infection	**17**	**19**	**5.430**[d]	**0.020**[a]
Bacterial infection	**14**	**6**	**15.775**[d]	**<0.001**[a]
Fungal infection	**12**	**8**	**8.921**[d]	**0.003**[a]
Urosepsis	**11**	**9**	**6.221**[d]	**0.013**[a]
Candida infection	**11**	**1**	**—**	**<0.001**[b]
Bacteraemia	**11**	**0**	**—**	**<0.001**[b]
Tooth abscess	**11**	**0**	**—**	**<0.001**[b]
Infected skin ulcer	**10**	**0**	**—**	**<0.001**[b]
Cytomegalovirus infection	**9**	**8**	**4.454**[d]	**0.035**[a]
COVID-19 pneumonia	**7**	**3**	**—**	**0.010**[b]

(Continued on following page)

TABLE 4 (*Continued*) Differences in clinical characteristics of severe and non-severe reports.

	Serious cases	Non-serious cases	Statistic	p-value
Cytomegalovirus infection reactivation	**2**	**37**	**11.546**[d]	**<0.001**[a]
Neutropenic sepsis	**0**	**15**	**—**	**0.008**[b]
Neutropenic infection	**0**	**14**	**—**	**0.014**[b]
Candida pneumonia	4	6	—	0.495[b]
Varicella zoster virus infection	2	8	—	0.732[b]
C-reactive protein increased	**15**	**14**	**6.877**[d]	**0.009**[a]
Inflammatory marker increased	**11**	**0**	**—**	**<0.001**[b]
Haemoglobin decreased	**2**	**22**	**5.320**[d]	**0.021**[a]
Blood bilirubin increased	**0**	**22**	**9.416**[d]	**0.002**[a]
Blood lactate dehydrogenase increased	48	124	0.291[d]	0.590[a]
Aspartate aminotransferase increased	5	17	0.517[d]	0.472[a]
Alanine aminotransferase increased	5	14	0.104[d]	0.747[a]
Glomerular filtration rate decreased	1	12	—	0.124[b]
Hypercalcaemia	**11**	**10**	**5.254**[d]	**0.022**[a]
Neuropathy peripheral	**14**	**13**	**6.468**[d]	**0.011**[a]
Confusional state	**13**	**6**	**13.827**[d]	**0.002**[a]
Epilepsy	**11**	**0**	**—**	**<0.001**[b]
Immune effector cell-associated neurotoxicity syndrome	**11**	**0**	**—**	**<0.001**[b]
Polyneuropathy	**0**	**12**	**—**	**0.023**[b]
Disturbance in attention	5	5	—	0.173[b]
Neurotoxicity	2	15	2.643[d]	0.104[a]
Renal failure	**20**	**12**	**16.852**[d]	**<0.001**[a]
Respiratory failure	6	9	—	0.399[b]
Deep vein thrombosis	**1**	**19**	**5.911**[d]	**0.015**[a]
Haemorrhage	**9**	**5**	**—**	**0.007**[b]

Results that are statistically significant are in bold.
[a]Proportions were compared using Pearson $\chi 2$ test.
[b]Fisher's exact test.
[c]The t-statistic of the independent samples t-test.
[d]The $\chi 2$ value of the Pearson chi-square test.
AEs, Adverse Events; n, number of cases.

risk of neurotoxicity associated with Pola+BR and stop treatment in a timely manner upon detection of relevant symptoms to prevent further neurological damage.

Unexpected safety signals included epilepsy, intestinal obstruction, deep vein thrombosis, haemorrhage, blood lactate dehydrogenase increased and hypercalcaemia. In three case reports (Haefner et al., 2007; Hosoi et al., 2010; Jennane et al., 2022), the patients treated with a rituximab-containing regimen presented generalized seizures. All of them developed posterior reversible encephalopathy syndrome following MRI examination. This suggests that when epilepsy occurs in patients with pola+BR, a rare reversible encephalopathy syndrome caused by rituximab in this regimen may emerge. Recent studies have indicated that Polatuzumab Vedotin may elicit immune responses which can affect the stability of the nervous system and potentially lead to neurological complications such as seizures. The mechanisms underlying these immune responses are not yet fully understood, but research (Broekaart et al., 2018) suggests that activation of the immune system may be associated with seizures and disease progression, particularly in cases of where there is a disruption in the blood-brain barrier function. In addition, the use of Polatuzumab Vedotin may be associated with the onset of other autoimmune diseases. For example, some patients treated with this drug have developed symptoms similar to those of autoimmune myositis, which may further burden the nervous system (Kamo et al., 2019). These observations suggest that when using Polatuzumab Vedotin clinically, doctors should closely monitor neurological symptoms in patients, especially those with a history

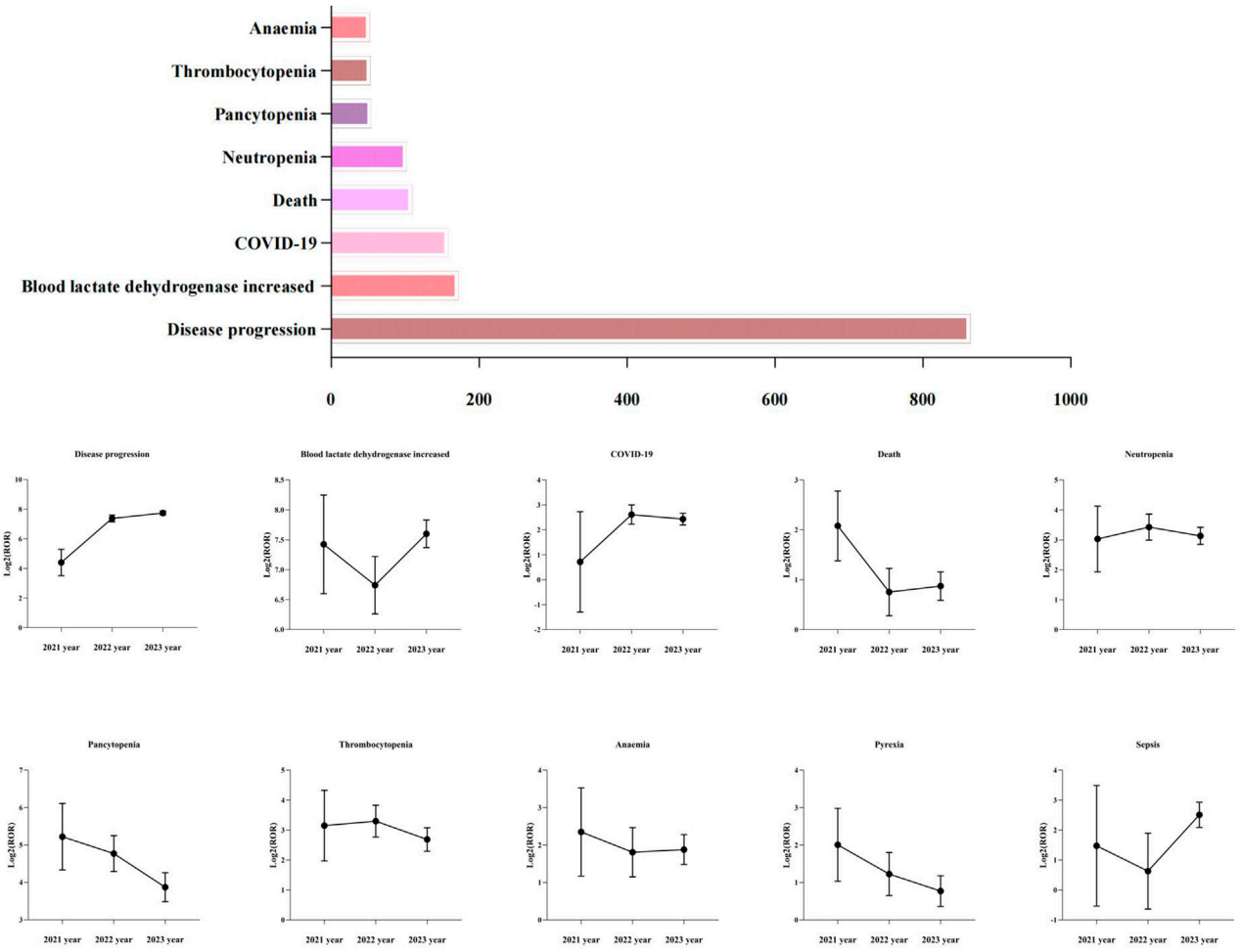


FIGURE 4
The top ten positive signals of case number and their sensitivity analysis. ROR, Reporting Odds Ration.

of epilepsy or other neurological disorders. In a clinical analysis (Kasi et al., 2012) of rituximab, the most widespread gastrointestinal symptoms were bowel obstruction and perforations, typically occurring 6 days after treatment. Studies have shown that damage to the intestinal mucosa is associated with multiple factors, including the direct effects of the drug, dysbiosis of the gut microbiota, and abnormal immune system responses. For example, certain chemotherapeutic agents have been shown to cause dysbiosis of the gut microbiota, leading to intestinal inflammation and dysfunction, which may share similarities with the mechanism of action of Polatuzumab Vedotin (Huang et al., 2022). In another clinical trial of polatuzumab (Lynch et al., 2023), two patients experienced deep vein thrombosis. In another clinical trial of polatuzumab (Wang et al., 2022), one patient experienced intracranial hemorrhage. Blood lactate dehydrogenase increased and hypercalcaemia are likely to be relative to the disease itself or the disease progression.

In this study, there were several limitations. Initially, data submitted to FAERS were incomplete, and not all adverse reports were uploaded to FAERS. Therefore, the incidence of identified risks could not be quantified accurately (Noguchi et al., 2021). Before conducting AEs retrieval, we standardized the drug names using MedDRA terminology, covering the brand names, trade names, and generic names of the drugs, among others. This step ensured that the data we collected was as comprehensive as possible, thereby mitigating the impact of missing data. Additionally, reporting biases can exist, because people prefer to reporting relatively serious AEs. Although the FAERS database compiles global data, the reports are primarily concentrated in European and American countries, with relatively fewer reports from other regions. It is noteworthy that different racial groups may have varying sensitivities to the Pola+BR regimen, which could lead to different AE manifestations. Ultimately, the study considered the pola+BR treatment regimen as a unified entity, which makes it difficult to ascertain the impact of individual drug on the identified signals. Therefore, it is necessary to conduct large-scale prospective clinical studies to address questions that the FAERS database cannot answer, thereby optimizing the rational use of clinical medication.

5 Conclusion

Our pharmacovigilance study analyzes real-world large-sample safety data to determine the correlation between the pola+BR

treatment protocol and AEs. From 2019Q1 to 2023Q3, reports regarding the pola+BR treatment protocol increase by years. Out of the 58 identified significant signals, thrombocytopenia, anaemia, febrile neutropenia, sepsis, neuropathy peripheral, CRS and ICANS should be highly concerned. Of note, 6 PTs--epilepsy, intestinal obstruction, deep vein thrombosis, haemorrhage, blood lactate dehydrogenase increased and hypercalcaemia were new unexpect signals. In addition, 1, 27, and 30 AEs were sorted into high, moderate, and low clinical priorities. Our study enhances comprehension of the safety characteristics of pola+BR, which will assist medical practitioners in handling associated AEs during clinical practice.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

FW: Conceptualization, Methodology, Writing–original draft. SW: Formal Analysis, Investigation, Writing–original draft. XX: Conceptualization, Methodology, Writing–review and editing. WZ: Formal Analysis, Writing–original draft. JZ: Data curation, Software, Writing–review and editing. RN: Data curation, Software, Writing–review and editing. WC: Data curation, Software, Writing–review and editing. YY: Supervision, Validation, Writing–review and editing. ML: Conceptualization, Supervision, Writing–review and editing. JPZ: Conceptualization, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by fundings for (Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University. NO. 2022-LCYJ-PY-48); (Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University. NO. 2023-LCYJ-MS-32); and (Research Project established by Chinese Pharmaceutical Association Hospital Pharmacy department. NO. CPA-Z05-ZC-2023002).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1459067/full#supplementary-material

References

Argnani, L., Broccoli, A., Pellegrini, C., Fabbri, A., Puccini, B., Bruna, R., et al. (2022). Real-world outcomes of relapsed/refractory diffuse large B-cell lymphoma treated with polatuzumab vedotin-based therapy. *Hemasphere* 6 (12), e798. doi:10.1097/hs9.0000000000000798

Broekaart, D. W. M., Anink, J. J., Baayen, J. C., Idema, S., de Vries, H. E., Aronica, E., et al. (2018). Activation of the innate immune system is evident throughout epileptogenesis and is associated with blood-brain barrier dysfunction and seizure progression. *Epilepsia* 59 (10), 1931–1944. doi:10.1111/epi.14550

Dal, M. S., Ulu, B. U., Uzay, A., Akay, O. M., Beşışık, S., Yenerel, M. N., et al. (2023). Polatuzumab vedotin, rituximab, and bendamustine combination in relapsed or refractory diffuse large B-cell lymphoma: a real-world data from Turkey. *Ann. Hematol.* 102 (1), 133–140. doi:10.1007/s00277-022-05052-x

Deeks, E. D. (2019). Polatuzumab vedotin: first global approval. *Drugs* 79 (13), 1467–1475. doi:10.1007/s40265-019-01175-0

Diefenbach, C., Kahl, B. S., McMillan, A., Briones, J., Banerjee, L., Cordoba, R., et al. (2021). Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed or refractory follicular lymphoma: a cohort of a multicentre, single-arm, phase 1b/2 study. *Lancet Haematol.* 8 (12), e891–e901. doi:10.1016/s2352-3026(21)00311-2

Freyer, C. W., and Porter, D. L. (2020). Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies. *J. Allergy Clin. Immunol.* 146 (5), 940–948. doi:10.1016/j.jaci.2020.07.025

Gatti, M., Antonazzo, I. C., Diemberger, I., De Ponti, F., and Raschi, E. (2021). Adverse events with sacubitril/valsartan in the real world: emerging signals to target preventive strategies from the FDA adverse event reporting system. *Eur. J. Prev. Cardiol.* 28 (9), 983–989. doi:10.1177/2047487320915663

Gibiansky, L., Passey, C., Voellinger, J., Gunawan, R., Hanley, W. D., Gupta, M., et al. (2022). Population pharmacokinetic analysis for tisotumab vedotin in patients with locally advanced and/or metastatic solid tumors. *CPT Pharmacometrics Syst. Pharmacol.* 11 (10), 1358–1370. doi:10.1002/psp4.12850

Gu, T., Hu, K., Si, X., Hu, Y., and Huang, H. (2022). Mechanisms of immune effector cell-associated neurotoxicity syndrome after CAR-T treatment. *WIREs Mech. Dis.* 14 (6), e1576. doi:10.1002/wsbm.1576

Guo, H., Wang, B., Yuan, S., Wu, S., Liu, J., He, M., et al. (2022). Neurological adverse events associated with esketamine: a disproportionality analysis for signal detection leveraging the FDA adverse event reporting system. *Front. Pharmacol.* 13, 849758. doi:10.3389/fphar.2022.849758

Haefner, M. D., Siciliano, R. D., Widmer, L. A., Vogel Wigger, B. M., and Frick, S. (2007). Reversible posterior leukoencephalopathy syndrome after treatment of diffuse large B-cell lymphoma. *Onkologie* 30 (3), 138–140. doi:10.1159/000098706

Hosoi, M., Yamamoto, G., Imai, Y., and Kurokawa, M. (2010). Reversible posterior leukoencephalopathy syndrome following R-CHOP therapy for diffuse large B-cell lymphoma. *Ann. Hematol.* 89 (2), 207–208. doi:10.1007/s00277-009-0783-x

Huang, B., Gui, M., Ni, Z., He, Y., Zhao, J., Peng, J., et al. (2022). Chemotherapeutic drugs induce different gut microbiota disorder pattern and NOD/RIP2/NF-κB signaling pathway activation that lead to different degrees of intestinal injury. *Microbiol. Spectr.* 10 (6), e0167722. doi:10.1128/spectrum.01677-22

Jennane, S., Mahtat, E. M., Ababou, M., El Maaroufi, H., and Doghmi, K. (2022). Posterior reversible encephalopathy syndrome secondary to R-CHOP chemotherapy regimen. *Cureus* 14 (5), e24988. doi:10.7759/cureus.24988

Jouffroy, R., Djossou, F., Neviere, R., Jaber, S., Vivien, B., Heming, N., et al. (2024). The chain of survival and rehabilitation for sepsis: concepts and proposals for healthcare trajectory optimization. *Ann. Intensive Care* 14 (1), 58. doi:10.1186/s13613-024-01282-6

Kamo, H., Hatano, T., Kanai, K., Aoki, N., Kamiyama, D., Yokoyama, K., et al. (2019). Pembrolizumab-related systemic myositis involving ocular and hindneck muscles resembling myasthenic gravis: a case report. *BMC Neurol.* 19 (1), 184. doi:10.1186/s12883-019-1416-1

Kasi, P. M., Tawbi, H. A., Oddis, C. V., and Kulkarni, H. S. (2012). Clinical review: serious adverse events associated with the use of rituximab - a critical care perspective. *Crit. Care* 16 (4), 231. doi:10.1186/cc11304

Lambden, S., Laterre, P. F., Levy, M. M., and Francois, B. (2019). The SOFA score-development, utility and challenges of accurate assessment in clinical trials. *Crit. Care* 23 (1), 374. doi:10.1186/s13054-019-2663-7

Lu, D., Gillespie, W. R., Girish, S., Agarwal, P., Li, C., Hirata, J., et al. (2017). Time-to-Event analysis of polatuzumab vedotin-induced peripheral neuropathy to assist in the comparison of clinical dosing regimens. *CPT Pharmacometrics Syst. Pharmacol.* 6 (6), 401–408. doi:10.1002/psp4.12192

Lynch, R. C., Poh, C., Ujjani, C. S., Warren, E. H., Smith, S. D., Shadman, M., et al. (2023). Polatuzumab vedotin with infusional chemotherapy for untreated aggressive B-cell non-Hodgkin lymphomas. *Blood Adv.* 7 (11), 2449–2458. doi:10.1182/bloodadvances.2022009145

Matsumoto, J., Iwata, N., Watari, S., Ushio, S., Shiromizu, S., Takeda, T., et al. (2023). Adverse events of axitinib plus pembrolizumab versus lenvatinib plus pembrolizumab: a pharmacovigilance study in Food and drug administration adverse event reporting system. *Eur. Urol. Focus* 9 (1), 141–144. doi:10.1016/j.euf.2022.07.003

Morris, E. C., Neelapu, S. S., Giavridis, T., and Sadelain, M. (2022). Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat. Rev. Immunol.* 22 (2), 85–96. doi:10.1038/s41577-021-00547-6

Noguchi, Y., Tachi, T., and Teramachi, H. (2021). Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief. Bioinform* 22 (6), bbab347. doi:10.1093/bib/bbab347

Palanca-Wessels, M. C., Czuczman, M., Salles, G., Assouline, S., Sehn, L. H., Flinn, I., et al. (2015). Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. *Lancet Oncol.* 16 (6), 704–715. doi:10.1016/s1470-2045(15)70128-2

Pullyblank, A., Tavaré, A., Little, H., Redfern, E., le Roux, H., Inada-Kim, M., et al. (2020). Implementation of the National Early Warning Score in patients with suspicion of sepsis: evaluation of a system-wide quality improvement project. *Br. J. Gen. Pract.* 70 (695), e381–e388. doi:10.3399/bjgp20X709349

Roth, P., Winklhofer, S., Müller, A. M. S., Dummer, R., Mair, M. J., Gramatzki, D., et al. (2021). Neurological complications of cancer immunotherapy. *Cancer Treat. Rev.* 97, 102189. doi:10.1016/j.ctrv.2021.102189

Sehn, L. H., Hertzberg, M., Opat, S., Herrera, A. F., Assouline, S., Flowers, C. R., et al. (2022). Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood Adv.* 6 (2), 533–543. doi:10.1182/bloodadvances.2021005794

Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M., Stemmler, H. J., Schlößer, H. A., Schlaak, M., et al. (2018). Cytokine release syndrome. *J. Immunother. Cancer* 6 (1), 56. doi:10.1186/s40425-018-0343-9

Shu, Y., He, X., Wu, P., Liu, Y., Ding, Y., and Zhang, Q. (2022). Gastrointestinal adverse events associated with semaglutide: a pharmacovigilance study based on FDA adverse event reporting system. *Front. Public Health* 10, 996179. doi:10.3389/fpubh.2022.996179

Smith, S. D., Lopedote, P., Samara, Y., Mei, M., Herrera, A. F., Winter, A. M., et al. (2021). Polatuzumab vedotin for relapsed/refractory aggressive B-cell lymphoma: a multicenter post-marketing analysis. *Clin. Lymphoma Myeloma Leuk.* 21 (3), 170–175. doi:10.1016/j.clml.2020.12.013

Tarantino, P., Ricciuti, B., Pradhan, S. M., and Tolaney, S. M. (2023). Optimizing the safety of antibody-drug conjugates for patients with solid tumours. *Nat. Rev. Clin. Oncol.* 20 (8), 558–576. doi:10.1038/s41571-023-00783-w

Tilly, H., Morschhauser, F., Bartlett, N. L., Mehta, A., Salles, G., Haioun, C., et al. (2019). Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. *Lancet Oncol.* 20 (7), 998–1010. doi:10.1016/s1470-2045(19)30091-9

Tilly, H., Morschhauser, F., Sehn, L. H., Friedberg, J. W., Trněný, M., Sharman, J. P., et al. (2022). Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N. Engl. J. Med.* 386 (4), 351–363. doi:10.1056/NEJMoa2115304

Vodicka, P., Klener, P., and Trneny, M. (2022). Diffuse large B-cell lymphoma (DLBCL): early patient management and emerging treatment options. *Onco Targets Ther.* 15, 1481–1501. doi:10.2147/ott.S326632

Wang, Y. W., Tsai, X. C., Hou, H. A., Tien, F. M., Liu, J. H., Chou, W. C., et al. (2022). Polatuzumab vedotin-based salvage immunochemotherapy as third-line or beyond treatment for patients with diffuse large B-cell lymphoma: a real-world experience. *Ann. Hematol.* 101 (2), 349–358. doi:10.1007/s00277-021-04711-9

Xia, S., Zhao, Y. C., Guo, L., Gong, H., Wang, Y. K., Ma, R., et al. (2022). Do antibody-drug conjugates increase the risk of sepsis in cancer patients? A pharmacovigilance study. *Front. Pharmacol.* 13, 967017. doi:10.3389/fphar.2022.967017

Yin, O., Xiong, Y., Endo, S., Yoshihara, K., Garimella, T., AbuTarif, M., et al. (2021). Population pharmacokinetics of trastuzumab deruxtecan in patients with HER2-positive breast cancer and other solid tumors. *Clin. Pharmacol. Ther.* 109 (5), 1314–1325. doi:10.1002/cpt.2096

Zelenetz, A. D., Gordon, L. I., Abramson, J. S., Advani, R. H., Andreadis, B., Bartlett, N. L., et al. (2023). NCCN Guidelines® insights: B-cell lymphomas, version 6.2023. *J. Natl. Compr. Canc Netw.* 21 (11), 1118–1131. doi:10.6004/jnccn.2023.0057

Zhao, X., Wu, J., and Zhu, S. (2023). Ocular disorders associated with PCSK9 inhibitors: a pharmacovigilance disproportionality analysis. *Br. J. Clin. Pharmacol.* 89 (2), 458–469. doi:10.1111/bcp.15494

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 10 March 2025
DOI 10.3389/fphar.2025.1538881

OPEN ACCESS

EDITED BY
Yao Liu,
Daping Hospital, China

REVIEWED BY
Bin Zhao,
Peking Union Medical College Hospital (CAMS), China
Silvia Belloni,
University of Pavia, Italy

*CORRESPONDENCE
Chengliang Wang,
wangcl_kd@outlook.com
Li Chen,
chenl_hxey@scu.edu.cn

RECEIVED 03 December 2024
ACCEPTED 13 February 2025
PUBLISHED 10 March 2025

CITATION
Tang X, Wang C, Li Y, Tang J, Zhang G and Chen L (2025) Signal detection and safety analysis of three tyrosine kinase inhibitors for HER-2 positive breast cancer: a retrospective study based on the FAERS database. *Front. Pharmacol.* 16:1538881. doi: 10.3389/fphar.2025.1538881

Signal detection and safety analysis of three tyrosine kinase inhibitors for HER-2 positive breast cancer: a retrospective study based on the FAERS database

Xiting Tang[1], Chengliang Wang[1]*, Yanwei Li[1], Jing Tang[1], Guoping Zhang[1] and Li Chen[2,3,4]*

[1]Department of Pharmacy, People's Hospital of Ganzi Tibetan Autonomous Prefecture, Kangding, China, [2]Department of Pharmacy, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China, [3]Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [4]Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country, Leioa, Spain

Objective: To identify adverse event (ADE) signals of three tyrosine kinase inhibitors (TKIs) (Tucatinib, Lapatinib, and Neratinib) used for HER-2 positive breast cancer by utilizing the FAERS database, and to analyze their safety profiles to provide references for clinical risk management.

Methods: Data from the FAERS database spanning Q1 2015 to Q3 2024 were retrieved, including reports where Tucatinib, Lapatinib, or Neratinib was identified as the primary suspect drug. Disproportionality analysis (ROR, PRR) and the Comprehensive Standard method were employed to detect potential ADE signals. The distribution of ADEs across different System Organ Classifications (SOCs) was also analyzed.

Results: A total of 7,848 ADE reports were analyzed, identifying 557 significant signals. The primary ADEs were concentrated in gastrointestinal disorders, general conditions, administration site reactions, and skin and subcutaneous tissue disorders. Neratinib exhibited higher gastrointestinal toxicity, Lapatinib was associated with notable skin toxicities, and Tucatinib showed specific adverse reactions linked to combination therapies.

Conclusion: The three TKIs demonstrated distinct ADE signal profiles, with gastrointestinal, systemic, and skin toxicities being the major areas of concern. Future research should validate these findings and develop effective management strategies to enhance treatment safety and improve the quality of life for HER-2 positive breast cancer patients.

KEYWORDS

FAERS database, tyrosine kinase inhibitors (TKIs), HER-2 positive breast cancer, adverse event signals, safety analysis, disproportionality analysis (ROR, PRR)

1 Introduction

HER-2 positive breast cancer is a subtype defined by the overexpression of the HER-2 gene, accounting for about 15%–20% of all breast cancer cases (Slamon et al., 1987). This subtype is associated with rapid tumor growth and a high metastatic potential, which has made it a primary focus in clinical research. In the past decade, targeted therapies, including tyrosine kinase inhibitors (TKIs), have significantly improved the treatment of HER-2 positive breast cancer. These drugs inhibit the kinase activity of the HER-2 receptor, thereby preventing tumor cell proliferation and metastasis, which leads to improved survival rates and treatment outcomes (Swain et al., 2015).

Despite these advancements, TKI therapies are associated with significant side effects that can reduce patients' quality of life and increase the likelihood of treatment interruptions, potentially resulting in higher mortality rates (Saura et al., 2020; Murthy et al., 2020). Each drug is associated with distinct side effects: Neratinib is commonly linked to gastrointestinal issues, such as diarrhea and nausea; Lapatinib is associated with skin toxicities, including rashes and dryness; and Tucatinib combination therapies may lead to more widespread systemic effects, such as cardiac damage and liver dysfunction (Cameron et al., 2010; Xu et al., 2021).

While these findings are valuable, they are primarily derived from clinical trial data, which often have limitations, such as small sample sizes and strict inclusion criteria. These limitations hinder the generalization of the results to real-world clinical settings. Therefore, research using real-world data is crucial for gaining a more comprehensive understanding of the safety profiles of these drugs and for more accurately assessing their potential risks in diverse populations (Yazdani et al., 2020).

The FDA Adverse Event Reporting System (FAERS) is a global database that collects adverse drug event reports from across the globe. FAERS is a crucial tool for identifying potential safety risks of marketed drugs (Sakaeda et al., 2011). FAERS is particularly valuable because it includes data from diverse populations and clinical contexts, allowing for the identification of adverse reactions in real-world use. However, retrospective analyses of adverse event signals for HER-2 positive breast cancer TKIs remain scarce, particularly regarding their impact on different physiological systems and specific adverse event profiles (Harbeck et al., 2020).

This study aims to utilize the FAERS database to analyze adverse event signals for Tucatinib, Lapatinib, and Neratinib, focusing on gastrointestinal disorders, systemic effects, and skin toxicities (Sharma et al., 2022). By conducting a comprehensive analysis of the adverse events associated with these drugs, this study seeks to identify the primary safety profiles of each drug. This will provide valuable insights for clinical drug risk management and contribute to the development of personalized treatment strategies for HER-2 positive breast cancer (Modi et al., 2020).

2 Materials and methods

2.1 Data source

This study analyzed data from the FAERS database, which is updated quarterly and serves as a comprehensive repository of detailed post-marketing adverse event reports. However, as outlined by the FDA in their FAERS public dashboard description (FDA, 2024), the database has limitations related to data validity, including underreporting, voluntary reporting bias, and the potential for incomplete or inaccurate reports. These limitations should be considered when interpreting the findings of this study. The database provides detailed information on report counts, patient demographics (e.g., age and gender), and the severity of adverse drug events (ADEs). The FAERS database consists of seven key tables: patient demographics and administrative details (DEMO), drug information (DRUG), adverse reaction records (REAC), patient outcomes (OUTC), report sources (RPSR), therapy timelines (THER), indications for use or diagnoses (INDI), and deleted case records (DELETED).

2.2 Data processing

Data were retrieved from the FAERS database by querying the generic names "Tucatinib," "Lapatinib," and "Neratinib," covering 39 quarters from Q1 2015 to Q3 2024. However, the FAERS database has certain limitations, including the possibility of underreporting and biases due to voluntary reporting, which may impact the generalizability and completeness of the data. Only reports where the target drug was identified as the primary suspect were included. Potential duplicates were removed using a deduplication process, necessitated by the quarterly updates of the database. In accordance with FDA guidelines (Hu et al., 2020), duplicates with identical CASEID values were resolved by retaining the most recent FDA_DT. If both CASEID and FDA_DT were identical, the record with the higher PRIMARYID was prioritized. Reports listed in the DELETED table were excluded from analysis. Data were imported and analyzed using MySQL 8.0.

2.3 Data standardization

The FAERS database uses the Medical Dictionary for Regulatory Activities (MedDRA) coding system to classify and standardize adverse event data. In this study, MedDRA version 27.0 preferred terms (PT) and system organ classifications (SOC) were utilized to standardize the descriptions of adverse drug events (ADEs) (Sakaeda et al., 2013; Omar et al., 2021).

2.4 Data analysis

The number of ADE reports identifying the target drug as the primary suspect was compiled. Potential ADE signals were identified using disproportionality analysis (Table 1) (Sakaeda et al., 2013; Luo et al., 2021). The Reporting Odds Ratio (ROR) and Comprehensive Standard (MHRA) methods were applied to calculate ROR, proportional reporting ratio (PRR), and chi-square (X^2) values. To minimize false-positive signals, only values exceeding predefined thresholds were recognized as valid signals for PTs (Table 2) (Chen et al., 2022; Sakaeda et al., 2011; Jin et al., 2021). Higher values represent stronger signals, reflecting an increased likelihood of an association between the target drug and the ADE, although causality cannot be confirmed (Zhou et al., 2022). All

TABLE 1 Fourfold table of disproportional method.

Drug category	Number of target ADE reports	Number of other ADE reports	Total
Target Drug	a	b	a+b
Other Drugs	c	d	c + d
Total	a+c	b + d	N = a+b + c + d

TABLE 2 Formulas and thresholds of ROR and PRR methods.

Method	Formula	Threshold
ROR Method	$ROR = \frac{a/c}{b/d}$ $95\%CI = e^{\ln(ROR)\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	a≥3,Lower bound of 95% CI forROR > 1Considered a valid signal
MHRA Method	$PRR = \frac{a/(a+b)}{c/(c+d)}$ $X^2 = \frac{(ad-bc)^2(a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}$	a≥3,PRR≥2,X2≥4Indicative of a valid signal

TABLE 3 Summary of Basic Information on TKI-Related ADE Reports

Information	Category	Reported Cases [n (%)]		
		Tucatinib	Lapatinib	Neratinib
Cases		2713	3503	1632
Gender	Male	94 (3.46%)	160 (4.57%)	2 (0.12%)
	Female	2441 (89.97%)	2927 (83.56%)	54 (3.31%)
	Unknown	178 (6.56%)	416 (11.88%)	1576 (96.57%)
Age Group	≤18	1 (0.04%)	3 (0.09%)	0 (0.00%)
	18~60	562 (20.72%)	1060 (30.26%)	34 (2.08%)
	≥60	523 (19.28%)	795 (22.69%)	14 (0.86%)
	Unknown	1627 (59.97%)	1645 (46.96%)	1584 (97.06%)
Reporter	Healthcare Providers	1782 (65.68%)	1775 (50.67%)	1412 (86.52%)
	Non-Healthcare	929 (34.24%)	1626(46.42%)	214(13.11%)
	Unknown	2 (0.07%)	102 (2.91%)	6 (0.37%)
Top5 Reported Countries		US [2234 (82.34%)]	US [2229 (63.63%)]	US [1377 (84.38%)]
		FR [120 (4.42%)]	IN [106 (3.03%)]	CA [57 (3.49%)]
		GR [53 (1.95%)]	CN [93 (2.65%)]	AR [52 (3.19%)]
		DE [44 (1.62%)]	JP [91 (2.60%)]	GB [34 (2.08%)]
		ES [34 (1.25%)]	IT [73 (2.08%)]	DE [33 (2.02%)]

statistical analyses and visualizations were conducted using Microsoft Excel and GraphPad Prism 8.

3 Results

3.1 Basic information on ADE reports

This study analyzed 7,848 adverse event reports for Tucatinib, Lapatinib, and Neratinib obtained from the FAERS database, spanning Q1 2015 to Q3 2024. The findings indicated that the majority of adverse event reports involved female patients, while Neratinib had a notably higher proportion of cases with unspecified gender. Reports involving male patients were also observed. Most cases with available age information involved patients aged 18–60 years, although some reports included patients under 18. A substantial proportion of cases lacked age data. Most reports were submitted by healthcare professionals; however, Tucatinib and Lapatinib had a relatively higher proportion of non-professional submissions. Geographically, the United States accounted for the

TABLE 4 Top 20 PTs of TKI-Related ADEs by Report Count and ROR.

Tucatinib				Lapatinib				Neratinib			
PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)	PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)	PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)
Gamma radiation therapy	5	1775.84 (639.19)	1772.57 (6523.15)	HER2 positive breast cancer	5	89.93 (37.03)	89.81 (429.06)	Drug titration	40	4451.91 (3026.26)	4342.82 (113760.31)
Congenital pulmonary airway malformation	3	496.87 (151.55)	496.32 (1348.15)	Nail bed bleeding	7	58.49 (31.30)	58.33 (555.03)	Breast reconstruction	5	209.00 (85.93)	208.37 (1006.46)
Congenital pulmonary airway malformation	3	496.87 (151.55)	496.32 (1348.15)	Onychalgia	10	38.01 (30.30)	37.20 (2688.06)	Breast cellulitis	3	154.03 (49.11)	153.75 (446.95)
Nail discomfort	3	186.32 (58.81)	186.12 (532.41)	Nail bed disorder	4	29.87 (22.09)	29.52 (1176.24)	Metastases to abdominal cavity	3	85.51 (27.39)	85.36 (247.56)
Brain tumour operation	4	164.31 (60.64)	164.07 (627.57)	Metastases to central nervous system	77	28.09 (10.50)	28.06 (103.61)	Breast cancer metastatic	35	52.61 (37.60)	51.51 (1723.38)
Hypertelorism	3	158.57 (50.20)	158.40 (454.71)	Colorectal cancer metastatic	9	25.84 (16.44)	25.71 (448.24)	Diarrhoea	1016	49.30 (44.61)	19.23 (18107.56)
Eating disorder symptom	9	152.96 (78.71)	152.45 (1313.81)	Breast cancer metastatic	43	24.50 (10.97)	24.46 (134.14)	Early satiety	4	41.88 (15.66)	41.78 (158.42)
Fingerprint loss	3	131.91 (41.89)	131.77 (379.26)	Metastases to skin	5	22.63 (16.13)	22.42 (692.05)	Emergency care	11	38.60 (21.30)	38.35 (398.31)
Tumour marker abnormal	7	116.88 (55.19)	116.58 (783.76)	Pleural thickening	4	19.91 (13.62)	19.76 (478.61)	Mastectomy	4	34.21 (12.80)	34.13 (128.12)
Radiotherapy	24	103.68 (69.09)	102.78 (2369.97)	Malignant ascites	3	18.64 (5.99)	18.63 (49.81)	Metastases to central nervous system	25	26.14 (17.60)	25.76 (593.47)
Craniotomy	5	97.50 (40.20)	97.32 (467.48)	Paronychia	19	25.00 (8.04)	24.95 (68.78)	Bladder spasm	3	25.00 (8.04)	24.95 (68.78)
Fluid replacement	5	97.50 (40.20)	97.32 (467.48)	Palmar-plantar erythrodysaesthesia syndrome	97	24.50 (10.98)	24.41 (134.34)	Drug titration error	6	24.50 (10.98)	24.41 (134.34)
Tumour marker decreased	3	96.17 (30.66)	96.06 (276.86)	Nail infection	6	23.31 (7.50)	23.27 (63.75)	Onycholysis	3	23.31 (7.50)	23.27 (63.75)
Ear malformation	3	73.43 (23.47)	73.35 (210.97)	Brain cancer metastatic	3	22.10 (10.51)	22.01 (140.06)	Breast cancer stage IV	7	22.10 (10.51)	22.01 (140.06)
Brain operation	21	69.93 (45.38)	69.39 (1396.18)	Brain neoplasm	34	21.42 (12.40)	21.26 (250.41)	Onychoclasis	13	21.42 (12.40)	21.26 (250.41)
Intracranial tumour haemorrhage	3	64.53 (20.65)	64.46 (185.02)	Breast cancer recurrent	10	19.20 (9.13)	19.12 (119.95)	Gastrointestinal sounds abnormal	7	19.20 (9.13)	19.12 (119.95)

(Continued on following page)

10.3389/fphar.2025.1538881

TABLE 4 (*Continued*) Top 20 PTs of TKI-Related ADEs by Report Count and ROR.

Tucatinib				Lapatinib				Neratinib			
PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)	PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)	PT	Case (n)	ROR (95% CI lower limit)	PRR (X^2)
Nose deformity	3	61.85 (19.80)	61.78 (177.19)	Nail disorder	27	19.13 (6.16)	19.10 (51.34)	Faeces pale	3	19.13 (6.16)	19.10 (51.34)
Blood bilirubin abnormal	9	59.36 (30.73)	59.16 (508.59)	Noninfective encephalitis	3	17.57 (8.76)	17.49 (124.12)	Dermatitis acneiform	8	17.57 (8.76)	17.49 (124.12)
Tumour excision	6	59.33 (26.51)	59.20 (339.29)	Breast neoplasm	3	17.50 (12.46)	17.16 (516.9)	Prescribed underdose	34	17.500 (12.46)	17.16 (516.90)
Product temperature excursion issue	34	57.01 (40.57)	56.31 (1826.69)	Oncologic complication	3	15.79 (11.18)	15.49 (446.95)	Blood potassium decreased	33	15.79 (11.18)	15.49 (446.95)

largest number of reports, followed by France, India, and China (see Table 3).

3.2 ADE signal detection results

This study identified 557 significant signals from the adverse event reports of 7,848 patients, with the top 20 preferred terms (PTs) ranked by descending Reporting Odds Ratio (ROR) (see Table 4). The identified adverse events varied substantially across the drugs. For Tucatinib, notable high-signal events included "Gamma ray therapy" (ROR: 1775.84) and "Congenital malformation of the lung and airway" (ROR: 496.87). Lapatinib showed significant associations with "HER2-positive breast cancer" (ROR: 89.93) and "Nail bed bleeding" (ROR: 72.67). For Neratinib, high signal intensities were observed for "Drug titration" (ROR: 4451.91) and "Breast reconstruction" (ROR: 209.00).

3.3 System organ class involvement in ADE signals

The three TKIs exhibited distinct distribution patterns across System Organ Classification (SOC) categories of adverse events. Tucatinib was associated with 23 SOCs, Lapatinib with 18 SOCs, and Neratinib with 20 SOCs. Adverse events were primarily concentrated in gastrointestinal disorders and general disorders, including administration site conditions. Gastrointestinal disorders accounted for 28.27% and 28.79% of adverse events for Tucatinib and Lapatinib, respectively, whereas Neratinib demonstrated a significantly higher proportion at 50.21%. Additionally, Lapatinib exhibited the highest percentage of adverse events related to skin and subcutaneous tissue disorders (17.58%), while Neratinib showed the highest proportion in injury, poisoning, and procedural complications (8.33%). Overall, adverse events predominantly concentrated in gastrointestinal disorders, general disorders (including administration site conditions), and skin and subcutaneous tissue disorders (see Figure 1).

3.3.1 PT distribution in gastrointestinal disorders

For gastrointestinal disorders, Tucatinib was most strongly associated with diarrhea (ROR: 6207.48), followed by nausea (ROR: 1249.54) and vomiting (ROR: 496.59). Lapatinib showed significant associations with diarrhea (ROR: 4449.35), stomatitis (ROR: 179.04), and vomiting (ROR: 155.14). Neratinib exhibited a high prevalence of gastrointestinal events, particularly diarrhea (ROR: 18107.56), nausea (ROR: 2593.08), constipation (ROR: 2585.67), and vomiting (ROR: 1169.06) (see Figure 2).

3.3.2 PT distribution in general disorders and administration site conditions

For general disorders and administration site conditions, Tucatinib was most strongly associated with "Events not assessable" (ROR: 1499.58), followed by fatigue (ROR: 1092.52) and disease progression (ROR: 897.36). Lapatinib was significantly associated with death (ROR: 1415.46), disease progression (ROR: 345.34), and mucosal inflammation (ROR: 14.97). Neratinib exhibited a high prevalence of fatigue (ROR: 1543.41), disease progression (ROR: 173.52), and early satiety (ROR: 158.42) (see Figure 3).

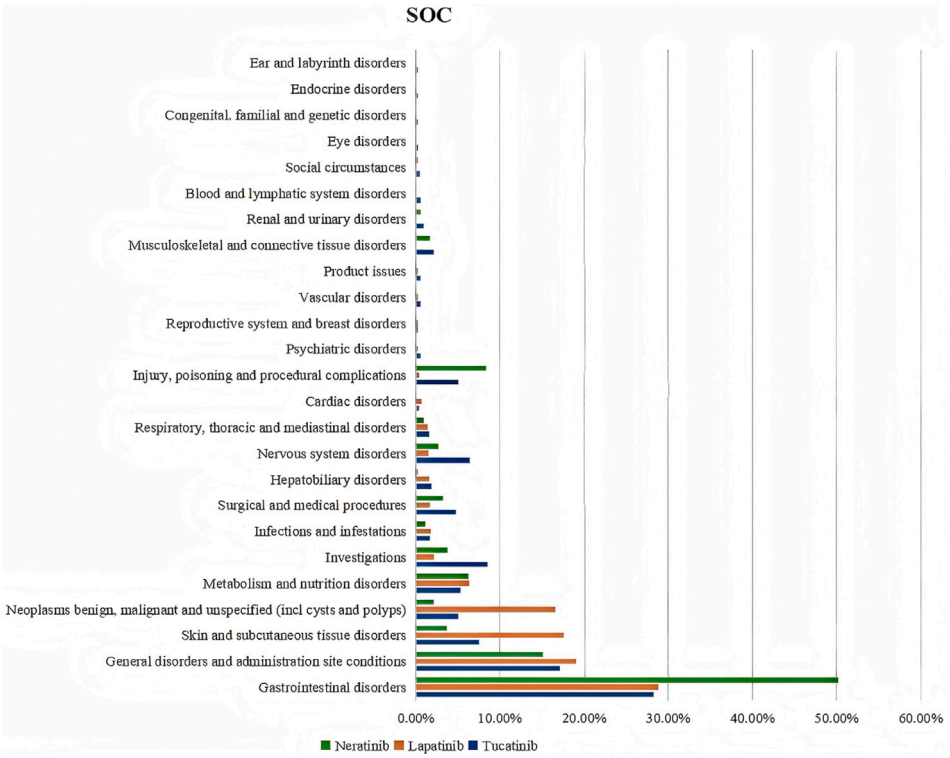


FIGURE 1
SOC occurrence of TKIs ADEs.

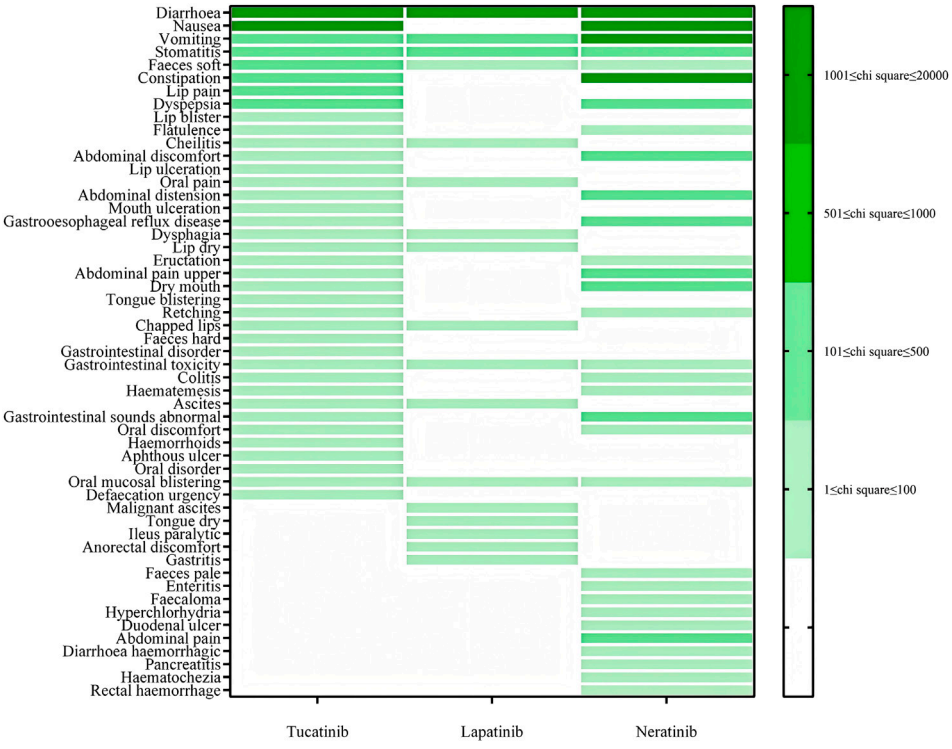


FIGURE 2
PT distribution for gastrointestinal disorders.

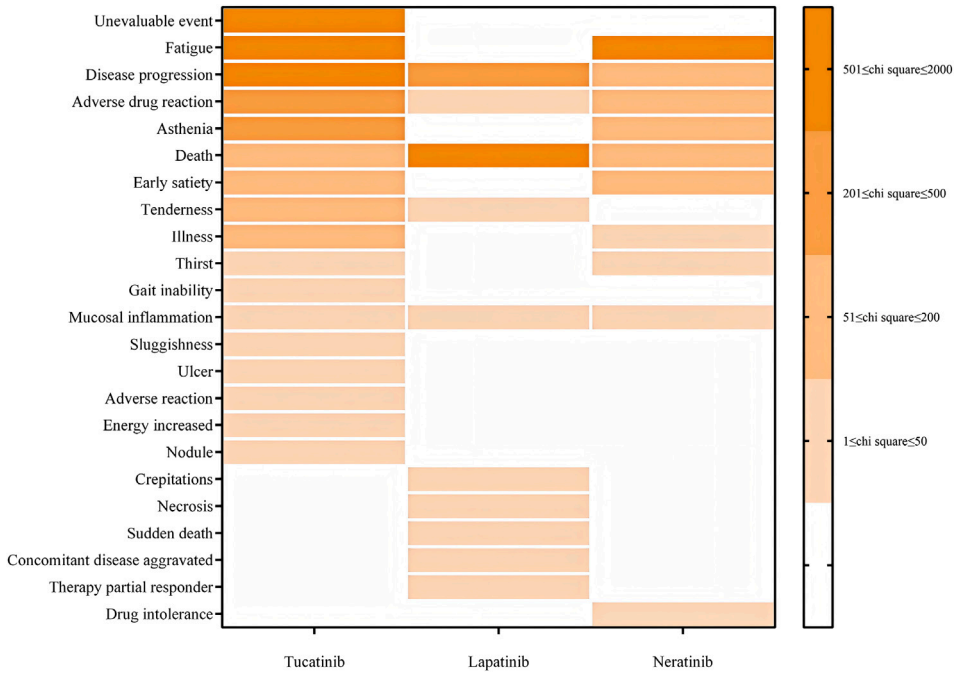


FIGURE 3
PT distribution for general disorders and administration site reactions.

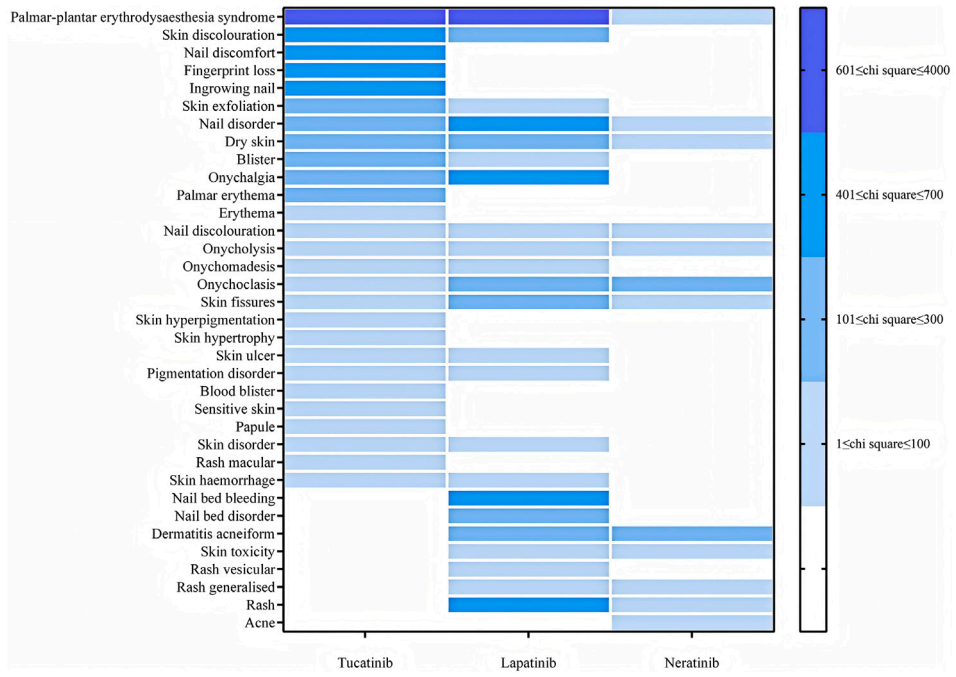


FIGURE 4
PT distribution for skin and subcutaneous tissue disorders.

3.3.3 PT distribution in skin and subcutaneous tissue disorders

For skin and subcutaneous tissue disorders, Tucatinib was most strongly associated with palmar-plantar erythrodysesthesia syndrome (ROR: 3394.03), followed by skin discoloration (ROR: 621.17) and nail discomfort (ROR: 532.41). Lapatinib was significantly associated with palmar-plantar erythrodysesthesia syndrome (ROR: 2146.74), nail pain (ROR: 555.03), and nail bed

bleeding (ROR: 484.62). Neratinib exhibited a high prevalence of nail breakage (ROR: 250.41), acneiform dermatitis (ROR: 124.12), and skin fissures (ROR: 84.47) (see Figure 4).

4 Discussion

4.1 Analysis of basic information on ADE reports

This study presents a detailed analysis of adverse event (ADE) reports for Tucatinib, Lapatinib, and Neratinib based on data from the FAERS database. The analysis examines gender distribution, age distribution, report sources, and geographic trends. Results indicated that most patients were female, consistent with the primary use of these drugs in female-related cancers. The higher proportion of cases with unspecified gender in Neratinib reports, where 96.57% of the gender data was unknown, may result from incomplete reporting. This could be attributed to the reporting preferences of the submitters, who might prioritize patient privacy, leading to the omission of gender information. A small number of male cases were reported, likely associated with rare instances of HER-2 positive breast cancer in men or the use of these drugs in other solid tumors, such as gastric cancer, which is more prevalent in males. Special attention may be required for male patients to monitor potential differences in adverse reactions associated with hormonal variations (Zhou et al., 2021). Regarding age distribution, the majority of patients were aged 18–60 years, though some reports involved children and adolescents. This finding may suggest experimental or personalized use in rare pediatric HER-2-related cancers. Reports involving pediatric patients underscore the need for rigorous safety monitoring, as children exhibit distinct metabolic and drug response mechanisms compared to adults, particularly during long-term TKI therapy. Future studies should collect prospective data and emphasize personalized treatment strategies to more accurately evaluate safety in young patients (Gao et al., 2020). Regarding report sources, most ADEs for Tucatinib and Neratinib were submitted by healthcare professionals, whereas Lapatinib had a higher proportion of reports from non-professionals. This may indicate broader use of Lapatinib among the general population, possibly due to self-medication or self-management in resource-limited areas where patients self-report adverse events (Liu et al., 2021). Geographically, the majority of reports originated from the United States, followed by France, India, and China. This distribution reflects differences in the adoption of these drugs across countries and variations in drug safety monitoring systems. The prevalence of reports from the United States may be attributed to its robust safety monitoring infrastructure and the larger population using these drugs. Reports from France, India, and China highlight a more global adoption of these therapies, with significant contributions from China indicating growing usage and improved drug safety monitoring. Variations across regions underscore the importance of considering factors such as race, healthcare resources, and drug availability, which may influence adverse event incidence (Fan et al., 2024; Chen et al., 2021).

Overall, the gender, age, report sources, and geographic distributions underscore the importance of individualized risk assessments and tailored safety monitoring for diverse patient groups in clinical practice. The broader use of Lapatinib and the instances of self-management highlight the need for personalized decision-making and vigilant monitoring, particularly in areas with limited healthcare resources (Harbeck et al., 2020).

4.2 Signal strength and key safety analysis

This study identified high Reporting Odds Ratio (ROR) values for specific adverse event signals, offering valuable insights into clinical risk management. For example, the strong signal for "Gamma ray therapy" associated with Tucatinib may suggest a synergistic effect when combined with other treatments. Meanwhile, the signal for "Nail bed bleeding" associated with Lapatinib highlights a significant risk of skin toxicity. High signals for "Drug titration" and "Breast reconstruction" with Neratinib underscore the need for individualized dose adjustments and highlight the challenges of managing patients undergoing reconstructive surgery (Krop et al., 2021).

Further analysis suggests that the high signal for "Gamma ray therapy" associated with Tucatinib could reflect its specific use alongside radiotherapy. However, the association may simply be due to a synergistic effect with combination therapies, and it currently lacks sufficient validation and in-depth analysis. Therefore, future research should further investigate this synergistic effect and assess its clinical relevance in various treatment combinations. Additionally, the signal for "Congenital malformation of the lung and airway" may point to rare side effects that require attention in specific patient populations (Jones et al., 2022).

The "Nail bed bleeding" signal for Lapatinib underscores severe skin toxicity, potentially associated with its effects on fast-growing cells (Harbeck et al., 2020). Furthermore, the high signals for "Drug titration" and "Breast reconstruction" with Neratinib suggest the need for complex dose adjustments and emphasize challenges faced by patients undergoing long-term treatment after surgery (Chan et al., 2020).

4.3 System organ class analysis of ADE signals

As illustrated in Figure 1, the majority of adverse events associated with the three TKIs are categorized under gastrointestinal disorders, general disorders, administration site reactions, and skin and subcutaneous tissue disorders. The subsequent sections provide a detailed analysis of these adverse events and discuss their clinical significance.

4.3.1 Gastrointestinal disorders

Gastrointestinal adverse events represent a significant challenge in the treatment of HER2-positive breast cancer with tyrosine kinase inhibitors (TKIs). Notably, Neratinib exhibits a significantly higher signal for diarrhea compared to other TKIs, indicating a substantial impact on gastrointestinal function that necessitates close monitoring. This effect may result from Neratinib's nonspecific inhibition of the epidermal growth

factor receptor (EGFR), which irritates the gastrointestinal lining, increasing the frequency of diarrhea, nausea, and constipation (Hinnerichs et al., 2022). Effective management strategies for these adverse events include proactive monitoring, preventive use of antidiarrheal medications, dietary guidance, and dose adjustments to alleviate symptoms and improve patient comfort (Saura et al., 2020; Crown et al., 2021). Tucatinib and Lapatinib are also associated with gastrointestinal side effects, though these tend to be less severe than those observed with Neratinib. For these drugs, early intervention and personalized management are crucial to reducing the risk of adverse effects and maintaining treatment adherence (Murthy et al., 2020; Cameron et al., 2010).

4.3.2 General disorders and administration site reactions

General disorders and administration site reactions, including fatigue and indicators of disease progression, were prevalent across all three drugs. These findings underscore the importance of vigilant health monitoring, particularly for patients receiving long-term treatment. Fatigue, a common consequence of cancer therapy, is influenced by multiple factors, including drug toxicity, the cancer itself, and the patient's physical and psychological state (Abrahams et al., 2016). In clinical practice, fatigue management includes supportive care, psychological counseling, and personalized treatment adjustments (Bower, 2014). Reports of disease progression suggest that these drugs may be insufficiently effective for certain patients, highlighting the need for regular evaluations and treatment adjustments (Diéras et al., 2017). The higher mortality rate reported, particularly in the Lapatinib group, indicates a substantial burden of adverse effects among high-risk patients, necessitating thorough patient selection and vigilant monitoring to mitigate risks and optimize outcomes (Cameron et al., 2010).

4.3.3 Skin and subcutaneous tissue disorders

Adverse events affecting the skin and subcutaneous tissues represent significant concerns for all three TKIs. Palmar-plantar erythrodysesthesia syndrome (PPES) is particularly prevalent among patients receiving Tucatinib or Lapatinib (Montemurro et al., 2019). This reaction is believed to result from the inhibition of epidermal keratinocytes by these drugs (Sadeghi et al., 2020) To alleviate symptoms, patients are advised to use topical moisturizers, minimize excessive friction, and adjust doses as necessary (Duvic et al., 2018). Early identification and supportive care are essential for effectively managing hand-foot syndrome and preventing treatment interruptions (Razonable and Aithal, 2018). Other adverse events, such as skin discoloration and nail-related issues, are also frequent and may adversely impact patients' quality of life or cause emotional distress (Dirks et al., 2021). Healthcare providers should reassure patients that these side effects are typically reversible and manageable, which can help sustain adherence to treatment (Fischer et al., 2020). Furthermore, the high incidence of acneiform dermatitis observed in Neratinib-treated patients suggests an inflammatory response. Managing this condition may involve topical anti-inflammatory agents and meticulous skin care (Sun et al., 2021).

4.4 Future research directions

Building upon the findings from this study, future research should focus on further enhancing our understanding of the safety profiles of Tucatinib, Lapatinib, and Neratinib. The potential synergistic effect of Tucatinib when used in combination with radiotherapy is particularly worth exploring. Although a strong signal was observed for "Gamma ray therapy," this association needs to be validated in clinical settings to assess whether this potential interaction significantly impacts treatment outcomes. Additionally, further investigations should address the rare side effects observed with Tucatinib, such as "Congenital malformation of the lung and airway." These effects should be studied in targeted patient populations to better understand the underlying mechanisms and predisposing factors, which could lead to more tailored risk management strategies. The complexity of managing dose adjustments and long-term therapy in patients undergoing reconstructive surgery highlights the importance of personalized treatment protocols, particularly for Neratinib. Future studies could include detailed assessments of the pharmacokinetics and pharmacodynamics of Neratinib in different patient groups, providing insights to optimize treatment regimens. Finally, expanding this research to include a more diverse global population, as well as additional HER-2 positive cancer types, would further validate these findings and contribute to a broader clinical application. This would not only improve patient safety but also enhance treatment outcomes.

5 Research limitations

This study has several limitations. The FAERS database, while a valuable resource for pharmacovigilance, is subject to underreporting and voluntary reporting biases. Such biases can lead to an incomplete representation of adverse events and affect the reliability of the findings. Additionally, since the data are collected from various sources, including healthcare providers and patients, there is a risk of data inconsistency or inaccuracies. Moreover, the exclusion of duplicate reports was based on a deduplication process, which may not entirely eliminate errors. Finally, the results of this study should be interpreted with caution due to the inherent limitations of retrospective data analysis and the absence of a direct causal relationship between the drugs and adverse events.

6 Conclusion

This study presents a systematic analysis of adverse events associated with Tucatinib, Lapatinib, and Neratinib in the treatment of HER-2 positive breast cancer, utilizing FAERS database data to elucidate the key safety characteristics and toxicity profiles of these drugs. Gastrointestinal disorders, general conditions, and skin and subcutaneous tissue disorders were identified as the primary areas of concern across the three TKIs. The gastrointestinal side effects of Neratinib warrant special attention, while the skin and systemic reactions associated with Lapatinib represent distinct risks. Future research should focus on

further validating these findings, identifying specific risk factors in diverse patient subgroups, and evaluating the effectiveness of various management strategies. This approach aims to optimize therapeutic benefits for patients while minimizing adverse effects, ultimately enhancing overall quality of life and treatment adherence.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: FDA Adverse Event Reporting System (FAERS) (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html).

Author contributions

XT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–original draft. CW: Conceptualization, Data curation, Project administration, Software, Validation, Writing–review and editing, Formal Analysis, Methodology. YL: Formal Analysis, Validation, Visualization, Writing–original draft. JT: Investigation, Supervision, Visualization, Writing–original draft. GZ: Data curation, Methodology, Software, Writing–original draft. LC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that Gen AI was used in the creation of this manuscript. Generative AI (ChatGPT) was used during the preparation of this manuscript to provide language editing and grammar improvement suggestions.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Abrahams, H. J. G., Gielissen, M. F. M., Schmits, I. C., Verhagen, C. A. H. H. V. M., Rovers, M. M., and Knoop, H. (2016). Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann. Oncol.* 27 (6), 965–974. doi:10.1093/annonc/mdw099

Bower, J. E. (2014). Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat. Rev. Clin. Oncol.* 11 (10), 597–609. doi:10.1038/nrclinonc.2014.127

Cameron, D., Casey, M., Oliva, C., Newstat, B., Imwalle, B., and Geyer, C. E. (2010). Lapatinib plus capecitabine in women with HER2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 15 (9), 924–934. doi:10.1634/theoncologist.2009-0181

Chan, A., Delaloge, S., and Holmes, F. A. (2020). A phase II randomized study evaluating dose escalation for Neratinib: safety and adherence in HER2-positive breast cancer. *Ann. Oncol.* 31 (9), 1239–1245. doi:10.1016/j.annonc.2020.06.012

Chen, J. J., Huo, X. C., Wang, S. X., Wang, F., and Zhao, Q. (2022). Data mining for adverse drug reaction signals of daptomycin based on real-world data: a disproportionality analysis of the US Food and Drug Administration adverse event reporting system. *Int. J. Clin. Pharm.* 44 (6), 1351–1360. doi:10.1007/s11096-022-01472-x

Chen, Y., Xie, F., Chen, L., Rujirachata, P., Ba, L., Zhang, X., et al. (2021). Comparative safety analysis of HER2-targeted therapies: evidence from the FAERS database. *Breast Cancer Res. Treat.* 188 (2), 463–473. doi:10.1007/s10549-021-06098-0

Crown, J., Dieras, V., Staroslawska, E., Burns, H. A., Rouzier, R., Shtivelband, M., et al. (2021). Updated guidelines for managing gastrointestinal adverse effects of Neratinib in HER2-positive breast cancer patients. *Breast Cancer Res. Treat.* 185 (3), 679–687. doi:10.1007/s10549-021-06103-8

Diéras, V., Harbeck, N., Budd, G. T., LoRusso, P. M., Ferrero, J. M., Badovinac-Crnjevic, T., et al. (2017). Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol.* 18 (6), 743–754. doi:10.1016/S1470-2045(17)30313-3

Dirks, D. L., Wu, K., and Upton, M. P. (2021). Quality of life and psychosocial impacts of chemotherapy-induced skin toxicities. *Support Care Cancer* 29 (9), 5343–5350. doi:10.1007/s00520-021-06185-8

Duvic, M., Vu, M., and Bichakjian, C. K. (2018). Managing hand-foot syndrome associated with anticancer therapies. *J. Clin. Oncol.* 36 (5), 586–589. doi:10.1200/JCO.2017.75.8485

Fan, Y., Wu, T., Xu, P., and Yang, C. (2024). Gastrointestinal toxicity in patients with breast cancer receiving targeted therapy. *Front. Pharmacol.* 14, 1425171. doi:10.3389/fphar.2024.1425171

FDA. (2024). *FDA Adverse Event Reporting System (FAERS) public dashboard*. Rockville, MD: U.S. Food and Drug Administration. Available at: https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

Fischer, A., Khosravi, A., Kelley, E., Zagadailov, E., Hess, L. M., Lowe, B., et al. (2020). The role of patient communication in enhancing adherence to anticancer therapies. *Patient Educ. Couns.* 103 (1), 42–48. doi:10.1016/j.pec.2019.08.031

Gao, Y., Wu, J., Chen, Y., Gao, Q., Wang, X., Yang, D., et al. (2020). Analysis of adverse event reports for HER2-targeted therapies in breast cancer from the FAERS database. *Cancer Chemother. Pharmacol.* 85 (5), 999–1007. doi:10.1007/s00280-020-04124-6

Harbeck, N., Eggemann, H., Jackisch, C., Conrad, B., Marten, A., Moebus, V., et al. (2020). Managing adverse events associated with HER2-targeted therapies in metastatic breast cancer. *Oncologist* 25 (4), e593–e603. doi:10.1634/theoncologist.2019-0656

Hinnerichs, K., Friedrich, M., and Waller, C. F. (2022). Mechanisms of Neratinib-induced diarrhea and management strategies in HER2-positive breast cancer treatment. *Cancer Treat. Rev.* 104, 102366. doi:10.1016/j.ctrv.2022.102366

Hu, Y., Gong, J., Zhang, L., Li, X., Li, X., Zhao, B., et al. (2020). Colitis following the use of immune checkpoint inhibitors: a real-world analysis of spontaneous reports submitted to the FDA adverse event reporting system. *Int. Immunopharmacol.* 84, 106601. doi:10.1016/j.intimp.2020.106601

Jin, Z., Chen, C., Du, Y., Li, K., Fang, X., An, Q., et al. (2021). Mining of dementia event signals related to benzodiazepines based on FAERS. *Her. Med.* 40 (10), 1356–1360. doi:10.3876/j.cnki.1674-6376.2021.10.002

Jones, T., Yan, Q., Chen, F., Smith, P., Wu, R., Patel, D., et al. (2022). Dermatologic adverse events associated with tyrosine kinase inhibitors: a review of clinical implications. *Cancer Treat. Rev.* 102, 102324. doi:10.1016/j.ctrv.2022.102324

Krop, I. E., Kim, S. B., and Martin, A. G. (2021). Impact of Tucatinib combined with trastuzumab and capecitabine in HER2-positive breast cancer: a subgroup analysis of radiation outcomes. *Clin. Cancer Res.* 27 (5), 1231–1239. doi:10.1158/1078-0432.CCR-20-2631

Liu, Y., Zhang, L., Xu, L., Li, Z., Wang, L., Chen, C., et al. (2021). Global safety of HER2-targeted therapies: a pharmacovigilance study using the FAERS database. *Cancer Med.* 10 (8), 2899–2907. doi:10.1002/cam4.4089

Luo, L., Zhang, J., Chen, L., Sun, C., Wang, H., Liu, Q., et al. (2021). Mining of adverse event signals for tocilizumab based on the US FAERS database. *China Pharm.* 32 (15), 1874–1879. doi:10.13523/j.cnki.cp.2021.15.16

Modi, S., Park, H., Murthy, R. K., Iwata, H., Tamura, K., Tsurutani, J., et al. (2020). Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low–expressing advanced breast cancer: results from a phase Ib study. *J. Clin. Oncol.* 38 (17), 1887–1896. doi:10.1200/JCO.19.02318

Montemurro, F., Di Maio, M., Mazzoni, F., Adamoli, L., Ezzalfani, M., Scaltriti, M., et al. (2019). Palmar-plantar erythrodysesthesia in breast cancer patients receiving Lapatinib: a review of the literature. *Breast Cancer Res. Treat.* 174 (3), 563–572. doi:10.1007/s10549-019-05160-0

Murthy, R. K., Loi, S., Okines, A., Paplomata, E., Hamilton, E., Hurvitz, S. A., et al. (2020). Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N. Engl. J. Med.* 382 (7), 597–609. doi:10.1056/NEJMoa1914609

Omar, N. E., Fahmy Soliman, A. I., Eshra, M., Saeed, T., Hamad, A., and Abou-Ali, A. (2021). Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS). *ESMO Open* 6 (6), 100315. doi:10.1016/j.esmoop.2021.100315

Razonable, R. R., and Aithal, G. P. (2018). Management of hand-foot syndrome in oncology patients. *Cancer Treat. Rev.* 70, 13–22. doi:10.1016/j.ctrv.2018.07.001

Sadeghi, N., Zhuang, L., Huang, L., Li, J., Zhang, M., Lang, L., et al. (2020). Successful treatment of refractory genital warts using 0.5% podophyllotoxin-loaded nanostructured lipid carriers. *Dermatol Ther.* 33 (2), e13245. doi:10.1111/dth.13245

Sakaeda, T., Kadoyama, K., and Okuno, Y. (2011). Adverse event profiles of platinum agents: data mining of the public version of the FDA adverse event reporting system, AERS, and reproducibility of clinical observations. *Int. J. Med. Sci.* 8 (6), 487–491. doi:10.7150/ijms.8.487

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10 (7), 796–803. doi:10.7150/ijms.6048

Saura, C., Oliveira, M., Feng, Y. H., Dai, M. S., Chen, S. W., Hurvitz, S. A., et al. (2020). Neratinib plus capecitabine versus Lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: phase III NALA trial. *J. Clin. Oncol.* 38 (27), 3138–3149. doi:10.1200/JCO.20.00147

Sharma, P., Rothermel, L. D., Kadiyala, R. S., Freedman, R. A., Feinberg, B. A., Tolaney, S. M., et al. (2022). Adverse events associated with tyrosine kinase inhibitors in HER2-positive breast cancer: insights from real-world data. *Cancer Treat. Rev.* 108, 102378. doi:10.1016/j.ctrv.2022.102378

Slamon, D. J., Clark, G. M., Wong, S. G., Levin, W. J., Ullrich, A., and McGuire, W. L. (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235 (4785), 177–182. doi:10.1126/science.3798106

Sun, Y., Li, X., Li, Y., Liu, H., Wang, G., Chen, Y., et al. (2021). Management of acneiform dermatitis in HER2-positive breast cancer patients treated with Neratinib. *Cancer Chemother. Pharmacol.* 88 (4), 517–528. doi:10.1007/s00280-021-04300-5

Swain, S. M., Baselga, J., Kim, S. B., Ro, J., Semiglazov, V., Campone, M., et al. (2015). Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N. Engl. J. Med.* 372 (8), 724–734. doi:10.1056/NEJMoa1413513

Xu, B., Yan, M., Ma, F., Hu, X., Feng, J., Ouyang, Q., et al. (2021). Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* 22 (3), 351–360. doi:10.1016/S1470-2045(20)30702-6

Yazdani, S., Gerretsen, J., Proskorovsky, I., Freedman O, Shecter D, Shepshelovich D, O., Shecter, D., Shepshelovich, D., et al. (2020). Comparing adverse event profiles of HER2-targeted therapies: a systematic review and meta-analysis. *Eur. J. Cancer* 133, 120–130. doi:10.1016/j.ejca.2020.04.013

Zhou, Y., Chen, M., Liu, L., and Chen, Z. (2022). Difference in gastrointestinal risk associated with use of GLP-1 receptor agonists: a real-world pharmacovigilance study. *Diabetes Metab. Syndr. Obes.* 15, 155–163. doi:10.2147/DMSO.S348025

Zhou, Y., Zhang, L., Sun, Q., Zhang, X., Li, P., Chen, M., et al. (2021). Pharmacovigilance analysis of adverse events related to the use of trastuzumab in HER2-positive breast cancer. *Front. Oncol.* 11, 724. doi:10.3389/fonc.2021.725273

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 19 March 2025
DOI 10.3389/fphar.2025.1426847

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Luis Alberto Vallejo-Castillo,
National Polytechnic Institute (IPN), Mexico
Rishat Ruzi,
First Affiliated Hospital of Xinjiang Medical University, China

*CORRESPONDENCE
Yang Gao,
gaoyangxueshu@163.com
Huanping Wang,
fangw139@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 02 May 2024
ACCEPTED 25 February 2025
PUBLISHED 19 March 2025

CITATION
Fang W, Wang H, Zhang X, Zhu H, Yan W and Gao Y (2025) Immune checkpoint inhibitors-induced pancreatitis: a systematic review and real-world pharmacovigilance analysis. *Front. Pharmacol.* 16:1426847. doi: 10.3389/fphar.2025.1426847

Immune checkpoint inhibitors-induced pancreatitis: a systematic review and real-world pharmacovigilance analysis

Wei Fang[1†], Huanping Wang[1*†], Xiaoran Zhang[2], Hongxia Zhu[1], Wei Yan[1] and Yang Gao[3*]

[1]Department of Endocrinology, Chengdu Shuangliu Hospital of Traditional Chinese Medicine, Chengdu, China, [2]Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China, [3]Laboratory of Ultrasound Medicine, West China Hospital, Sichuan University, Chengdu, China

Purpose: Immune checkpoint inhibitors-induced pancreatitis (ICIs-P) is an uncommon immune-related adverse event. The available evidence consists mostly of case reports, case series, and narrative reviews. This research focuses on the clinical characteristics and management options for ICIs-P to provide a practice-based global perspective on this disease.

Methods: Five electronic databases were systematically reviewed to identify the relevant studies. Furthermore, we performed a disproportionality analysis utilizing OpenVigil 2.1 to interrogate the United States Food and Drug Administration's Adverse Event Reporting System (FAERS) database.

Results: A total of 61 patients from 58 studies were included in this study. Most patients with ICIs-P were males (60.7%). Most patients received anti-PD-1/PD-L1 monotherapy (78.7%) or anti-PD-1/PD-L1 monotherapy in conjunction with CTLA-4 blockade (19.7%). The median time from the initiation of immune checkpoint inhibitors treatment to pancreatitis was 108 days (range 52–278). Most cases were severe or life-threatening (G3–G4; 64.0%). Corticosteroids were administered to 73.8% of the patients during the treatment of pancreatitis. Regarding treatment outcomes, ICIs-P was reversible in most cases (83.6%), despite the 8.2% relapse and 8.2% deaths. We identified 606 reports of pancreatitis associated with ICIs in the FAERS database, with the greatest proportion of males (50.7%), 62.0% of PD-1 inhibitors, and 22.1% of all reports of death or life-threatening outcomes. Signals indicating pancreatitis were observed across all ICIs, with particular emphasis on Cemiplimab, Pembrolizumab and Nivolumab.

Conclusion: By using a pharmacovigilance database, we discovered an elevated risk of pancreatitis following ICIs therapy, especially with PD-1 inhibitors. Meanwhile, risk factors for ICIs-P remain poorly understood, and diagnosis is challenging. Which may manifest as asymptomatic elevated pancreatic enzyme levels or clinical pancreatitis. Patients with pancreatitis symptoms should have

their lipase and amylase levels and radiology evaluated. Diagnosis should be made by excluding other causes. Steroids are the cornerstone of ICIs-P treatment and slow dose reduction is recommended to reduce recurrence.

KEYWORDS

immune checkpoint inhibitors, pancreatitis, immune-related adverse event, immunotherapy, pharmacovigilance analysis

1 Introduction

Recently, immune checkpoint inhibitors (ICIs) have attracted considerable attention because of their remarkable efficacy. Immune checkpoints are the trigger points of immune system suppressive pathways and are mostly expressed on the surface of activated T lymphocytes, which can inhibit the killing effect of the immune system on target cells. Tumor cells evade the killing effects of the immune system by activating these inhibitory pathways. ICIs primarily include three types of cytotoxic T lymphocyte-associated antigen (CTLA-4) and programmed death receptor/ligand1 (PD-1/PD-L1) inhibitors (Postow et al., 2018). Patients may present with different clinical manifestations of related gland involvement, as ICIs may lead to excessive activation of T lymphocytes with serious side effects on the pituitary gland, thyroid gland, pancreas, and adrenal glands (Sznol et al., 2017). ICIs-P is a rare immune-related adverse event (irAEs) that causes a low quality of life and affects patient security (Jiang et al., 2018; Bai et al., 2021).

Although the incidence of ICIs-P is relatively low, its clinical manifestations exhibit considerable heterogeneity, ranging from asymptomatic biochemical abnormalities to severe acute pancreatitis (Nwankwo et al., 2024). The pathophysiological mechanisms underlying ICIs-P remain incompletely understood, with current evidence suggesting potential involvement of T cell-mediated autoimmune responses or dysregulation of immune tolerance (Fang et al., 2023). Furthermore, significant controversies persist regarding risk factors, diagnostic criteria, therapeutic strategies, and prognosis, due to the paucity of large-scale prospective studies (Brahmer et al., 2018; Thompson et al., 2019; Sayed et al., 2022). The existing literature predominantly consists of case reports and small retrospective studies (Kramer et al., 2023; Tanabe et al., 2024), with a notable scarcity of systematic reviews and real-world data analyses. In light of these limitations, this study aims to comprehensively evaluate the clinical characteristics, risk factors, and therapeutic strategies of ICIs-P through systematic review of case reports and analysis of real-world pharmacovigilance data. By integrating existing evidence with real-world data, we anticipate providing clinicians with more comprehensive diagnostic and therapeutic references, thereby optimizing the management of ICIs-P.

2 Materials and methods

2.1 Systematic review

2.1.1 Search strategy

This review was designed in accordance with the PRISMA guidelines. PubMed, Web of Science, Cochrane Library, and EMBASE databases were retrieved from the inception date to February 2025 using the literature search strategy reported in Supplementary Table S1 (Supplementary Information 1). The references of the included studies were manually searched to retrieve additional eligible studies. Only English and Chinese publications were included in this analysis.

2.1.2 Selection criteria

The following study types were included: case reports, case series, observational studies, randomized controlled trials (RCTs), review articles, letters, and correspondence involving relevant cases. Meta-analyses, duplicate cases, review articles lacking patient information, conference abstracts, and animal studies were also excluded. The inclusion criteria were as follows:1) studies containing individual case reports or case series and 2) patients with confirmed ICIs-P association. The diagnosis of ICIs-P was based on the National Comprehensive Cancer Network (NCCN) classification criteria or the physician's opinion. If the authors did not specify the NCCN classification, we inferred it based on the clinical information (Thompson et al., 2019). The specific diagnostic criteria are listed in Table 1.

2.1.3 Data extraction

Reference identification and data collection were performed individually by two reviewers (Y.G. and W.F.) following the established criteria and data collection forms. Any disagreements were resolved through joint negotiations, and if a consensus could not be reached, an adjudication was performed by a third researcher (W.Y.). The titles and abstracts of the retrieved publications were screened to identify potential articles, and full texts were screened. The purpose of this review was to compare variables between studies. To obtain maximum information, we did not use quality assessment as an article inclusion criterion. Information from the included studies was extracted as follows: first author; publication year; age; sex; race; tumor type; checkpoint inhibitors treatment; number of cycles or days of treatment; symptoms at onset; IgG4 antibody; relevant prior medical history; presence of diabetes; glucose, glycated hemoglobin, lipase, and amylase levels; imaging; ICIs management; other irAEs; and outcomes.

2.2 Pharmacovigilance analysis

2.2.1 Data sources and collection

FAERS is a database used for post-marketing monitoring of all drugs and therapeutic biological products approved by Food and Drug Administration (FDA). OpenVigil 2.1 is a publicly available tool for extracting FAERS-related data (http://openvigil.sourceforge.net/). In this study, OpenVigil 2.1 was used to obtain adverse events data in FAERS from the time of initial FDA approval to

TABLE 1 Diagnostic criteria for immune checkpoint inhibitors-induced pancreatitis.

① A clear history of use of immune checkpoint inhibitors
② At least two of the following three criteria were met
(1) Persistent pain in the upper abdomen; (2) elevated serum lipase/amylase levels (at least three times the upper normal limit); and (3) characteristic findings of acute pancreatitis on abdominal imaging
③ Other causes of acute pancreatitis were excluded

TABLE 2 List of ICIs marketed in the United States and dates of FDA approval.

Effect target	Drug name	Brand names	FDA Approval time
PD-1			
	Pembrolizumab	*Keytruda*	September 2014
	Nivolumab	*Opdivo, Opdualag*	December 2014
	Cemiplimab	*Libtayo*	September 2018
	Dostarlimab	*Jemperli*	April 2021
	Toripalimab	*Loqtorzi*	October 2023
	Retifanlimab	*Zynyz*	March 2023
PD-L1			
	Atezolizumab	*Tecentriq,Tecentriq,Hybreza*	May 2016
	Durvalumab	*Imfinzi*	May 2017
	Avelumab	*Bavencio*	March 2017
CTLA-4			
	Ipilimumab	*Yervoy*	March 2011
	Tremelimumab	*Imjudo*	October 2022

30 September 2024, and drug names were standardized according to Drugbank and Drugs@FDA.

The search for ICIs included its generic name and brand names (Table 2). Utilizing MedDRA version 26.0, we identified 25 preferred terms (PTs) listed in Supplementary Table F1 (Supplementary Information 2) to systematically collect cases associated with "acute pancreatitis" (Standardized MedDRA Queries (SMQ): 20000022) and closely related clinical conditions (Guo et al., 2024). We gathered detailed clinical information for each adverse event report, encompassing data such as outcomes, medication names, role codes, dosages, indications, events, genders, reporter countries, and ages. For the collected data, first, we selected only the reports listed as the primary suspected drug and excluded the remaining reports. Second, in adherence to the guidelines of FDA, our study implemented a rigorous process to identify and eliminate duplicate reports. The data filtering procedure employed in this study is detailed in Supplementary Figure F1 (Supplementary Information 2).

2.2.2 Signal mining

In this research, four widely utilized disproportionality analysis techniques were implemented: reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) (Wang et al., 2024). ROR and PRR quantify the relationship between actual and anticipated reporting frequencies, where elevated values suggest a more pronounced drug-adverse event (AE) correlation. Both BCPNN and MGPS use Bayesian statistical approaches in their computations. Notably, MGPS yields more consistent results than ROR, effectively decreasing the likelihood of false positive outcomes. Simultaneously, BCPNN's Information Component (IC) serves as an indicator of the intensity of drug-AE signal associations (Wu et al., 2024; Noguchi et al., 2021). The integration of these four methodologies in our investigation significantly enhances the reliability of drug-AE signal detection while substantially reducing the occurrence of false positive results. The equations and criteria for these algorithms are detailed in Supplementary Table F2 (Supplementary Information 2). If any of the four algorithms met the predefined criteria, a positive signal of pancreatitis was identified (Guo et al., 2024).

2.3 Statistical analysis

SPSS v.22.0 (SPSS Inc., Chicago, IL, USA) was used for all the statistical analyses. Categorical variables are expressed as numbers

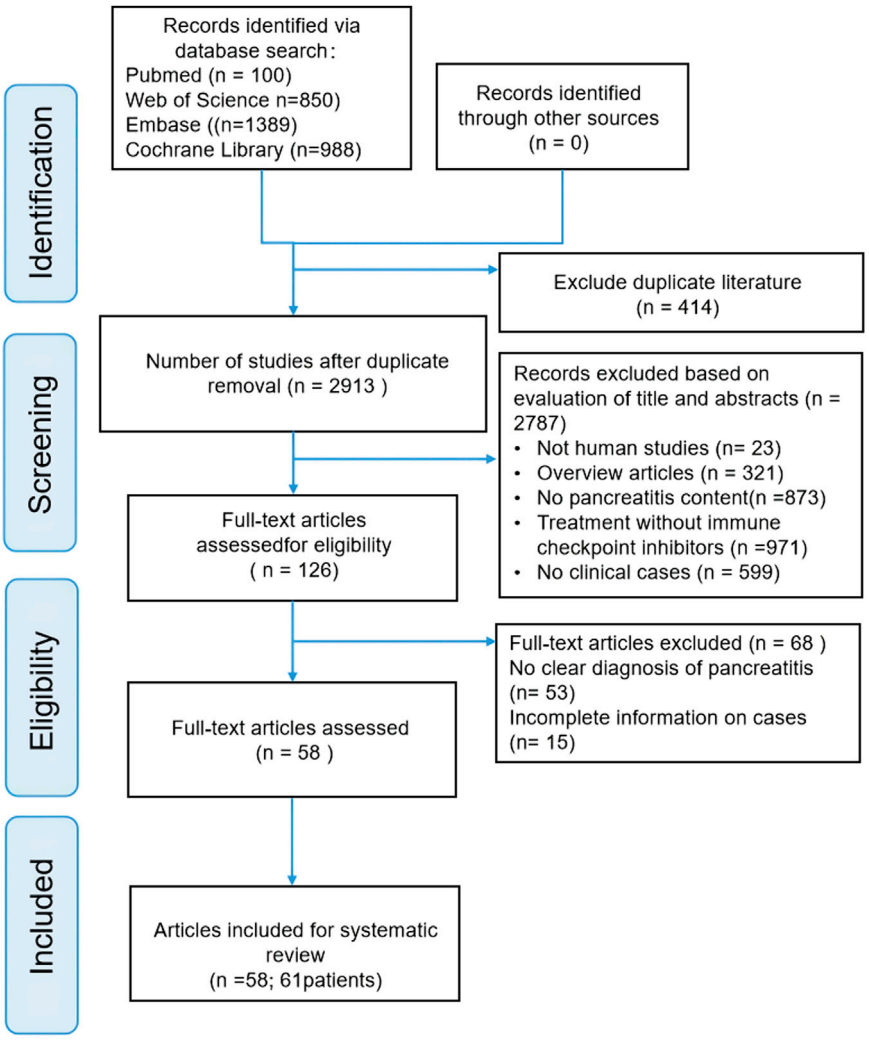


FIGURE 1
Flow chart of study selection.

and percentages, and continuous variables are expressed as medians and interquartile ranges (IQR).

3 Results

3.1 Literature search results

Our literature search found 3,327 articles in the selected databases, and no article was found in gray literature. First, 414 duplicate articles were excluded from analysis. Then of 2,787 references were excluded by browsing titles and abstracts for meta-analyses, reviews, absence of clinical cases, and irrelevant literature. Of the remaining 126 records, 68 were further excluded after reading the complete text for the following reasons: no precise diagnosis of pancreatitis (n = 53) and incomplete cases (n = 15). Ultimately, 58 articles involving 61 patients were included in this review. The screening process is illustrated in Figure 1. Supplementary Table S2 (Supplementary Information 1) shows basic information on the 58 publications.

3.2 Patient characteristics

A summary of the main characteristics of the 61 patients is presented in Table 3. Most patients were male (37/61, 60.7%), and the median age at ICIs-P diagnosis was 58 years (range, 23–82 years). The predominant tumor types were melanoma (18/61, 29.5%) and NSCLC (16/61, 26.2%). The most commonly used immune checkpoint drugs for monotherapy were pembrolizumab (23/61, 37.7%) and nivolumab (17/61, 27.9%), while nivolumab and ipilimumab were the most commonly used combination drugs (7/61, 11.5%). Blocking the PD-1/PD-L pathway was observed in 78.7% (48/61) of the cases. The median time to onset of pancreatitis after the start of ICIs was 108 (range, 52–278) days, but there were some cases of early toxicity occurring on day 1 of treatment (Jiang et al., 2018)or late toxicity occurring after 1 year of therapy with ICIs (Bachiller et al., 2020; Kakuwa et al., 2020; Yilmaz and Baran, 2022)

TABLE 3 Summary results on the characteristics of patients with ICIs-P.

Characteristic	All cases (N = 61)
Age, years	
Median (range)	58 (23–82)
Gender	N (%)
Male/Female, N (%)	37(60.7)/24(39.3)
Tumor type	N (%)
Melanoma	18 (29.5)
NSCLC	16 (26.2)
RCC	6 (9.8)
UC	2 (3.3)
metrocarcinoma	2 (3.3)
Other Tumor	17 (27.9)
Agent(ICIs)	N (%)
Pembrolizumab	23 (37.7)
Nivolumab	17 (27.9)
Toripalimab	3 (4.9)
Atezolizumab	2 (3.3)
Nivolumab + Ipilimumab	7 (11.5)
Ipilimumab + Pembrolizumab	4 (6.5)
Pembrolizumab + bevacizumab	1 (1.6)
Other ICIs (Frequency only 1 time)	4 (6.5)
ICIs type	N (%)
Anti-PD-1/L1	48 (78.7)
Anti-CTLA-4	1 (1.6)
Combination	12 (19.7)
The median time of onset, day (min-max) [IQR]	108 (1–1,020) [52–278]
Symptoms	N (%)#
Typical symptoms of pancreatitis	46 (78.0)
Asymptomatic	9 (15.2)
Nonspecific symptoms	4 (6.8)
Elevation of serum amylase or lipase	N (%)
Yes/No	55(90.2)/6(9.8)
Imaging findings of pancreatitis	N (%)#
Yes/No	53(91.4)/5(8.6)
Grading of pancreatitis	N (%)
G3-G4	39 (64.0)
G2	15 (24.5)
G1	7 (11.5)
Other immune-related adverse events	N (%)*
Colitis	8 (12.3)
Hepatobiliary injury	12 (18.5)
Dysthyroidism (hyper/hypo)	5 (7.6)
Gastritis	2 (3.1)
Hyperlipemia	3 (4.6)
Other irAEs	6 (9.2)
None	29 (44.6)
Treatment of pancreatitis	N (%)
Intravenous fluids	6 (9.8)
Steroids/Steroids and other treatments	
For pancreatitis only	27 (44.3)
For other reasons also	18 (29.5)
Discontinuation of ICIs therapy only	2 (3.3)
Other	8 (13.1)
Management of ICIs	N (%)#
Permanently discontinued	30 (58.8)
Temporarily discontinued, then restarted	7 (13.7)
Continued	3 (5.9)
Treatment already completed at the onset	11 (21.6)
Outcome	N (%)
Improvement	51 (83.6)
Death	5 (8.2)
Recurrence	5 (8.2)

(Continued in next column)

TABLE 3 (*Continued*) Summary results on the characteristics of patients with ICIs-P.

Abbreviations: #Some articles are not available; *Some cases had multiple adverse reactions; ICIs-P, Immune checkpoint inhibitors-induced pancreatitis; N,number; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; UC, urothelial carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; CTLA-4, cytotoxic T lymphocyte antigen 4; IQR, interquartile range.

or even after the end of treatment (Capurso et al., 2018; Dehghani et al., 2018; Wright et al., 2021).

At the onset of pancreatitis,78.0% (46/59) of the patients presented with typical pancreatitis symptoms, such as abdominal pain and vomiting. Additionally, 6.8% (4/59) presented with atypical pancreatitis symptoms, such as weakness and thirst, and 15.2% (9/59) had no symptoms. Regarding ancillary tests, 90.2% (55/61) of the patients showed varying degrees of lipase or amylase elevation, and 91.4% (53/58) exhibited typical imaging manifestations of pancreatitis. Most patients with ICIs-P (39/61, 64.0%) had severe (G3) or life-threatening (G4) disease. The most common irAEs were colitis (8/65, 12.3%), hepatobiliary injury (12/65, 18.5%), and dysthyroidism (5/65, 7.6%).

Overall, corticosteroids were used in 73.8% (45/61) of the cases during the treatment of pancreatitis. Common corticosteroids include prednisone, prednisolone, and methylprednisolone. In a few mild cases, only rehydration therapy was used (6/61, 9.8%), and ICIs were discontinued (2/61, 3.3%). Regarding ICIs management, 72.5% (37/51) of patients discontinued ICIs during the treatment of pancreatitis, 58.8% (30/51) Permanently discontinued ICIs, and 13.7% (7/51) continued ICIs. In terms of treatment outcomes, although ICIs-P was largely reversible, with an improvement rate of 83.6% (51/61), 8.2% (5/61) of patients had a relapse, and 8.2% (5/61) of patients had an associated death. Notably, seven patients who were reintroduced to ICIs did not experience pancreatitis recurrence, and five recurrences occurred during steroid tapering.

Additionally, among the 61 patients, we identified four patients with pancreatitis and diabetes mellitus (Supplementary Table S3, Supplementary Information 1). All patients had a history of nivolumab treatment except one who was treated with Toripalimab, and elevated pancreatic enzyme levels and imaging changes were typically observed during all episodes of pancreatitis. One patient with a concurrent onset of pancreatitis and diabetes mellitus had improved outcomes without steroid treatment (Fang et al., 2023).

3.3 Descriptive analysis from FAERS

The FAERS database documented a total of 606 cases of ICIs-P between March 2011 and September 2024. Among the reported cases, PD-1 inhibitors accounted for 62.0% (376/606), PD-L1 inhibitors for 23.3% (141/606), and CTLA-4 inhibitors for 14.7% (89/606). The demographic and clinical characteristics of all ICIs-associated pancreatitis cases are detailed in Supplementary Table F3 (Supplementary Information 2). Specifically, 179 cases were associated with Nivolumab (179/606, 29.5%), 189 with Pembrolizumab (189/606, 31.2%), 106 with Atezolizumab (106/606, 17.5%), and 88 with Ipilimumab (88/606, 14.5%). Males (307/606, 50.7%) were more frequently affected than females (217/606, 35.8%), with the majority of cases occurring in the 61–80 age group (260/606, 42.9%). Notably, only two cases involving Pembrolizumab were reported in children or adolescents (2/606, 1.1%). Hospitalization was the most common outcome (231/606, 38.1%), while death or life-threatening outcomes accounted for 22.1% (134/606) of all reports. The top three reporting countries were Japan (38.9%, 236/606), the United States (30.7%, 186/606), and France (6.6%, 40/606).

3.4 Signal values associated with different ICIs

The identification of pancreatitis event signals associated with all ICIs was conducted following the criteria set by the four algorithms, and the corresponding results are detailed in Table 4. Apart from Dostarlimab (2/606), Toripalimab (2/606), Retifanlimab (0/606), and Tremelimumab (1/606), where the small number of cases may introduce uncertainty in the results and further research is needed for validation, the remaining ICIs satisfied all four criteria. Notably, among all ICIs, Cemiplimab demonstrated the strongest association with ICIs-P, as evidenced by an information component (IC) of 7.20 (IC025 3.54), a reporting odds ratio (ROR) of 151.20 (95% CI 74.39–307.36), a proportional reporting ratio (PRR) of 150.63 (χ^2 581.12), and an empirical Bayes geometric mean (EBGM) of 147.25 (EBGM05 76.96). Following Cemiplimab, Atezolizumab, Avelumab, Ipilimumab, Pembrolizumab, Nivolumab, and Durvalumab exhibited progressively lower values.

4 Discussion

4.1 Clinical features

From March 2011 to September 2024, the FAERS database documented 606 cases of immune checkpoint inhibitor-associated pancreatitis. Both pharmacovigilance analyses and retrospective case series revealed a male predominance, with a peak incidence in the 61–80 age group, consistent with the typical cancer onset age range and prior studies (Hori et al., 2024). Notably, only two cases involved children or adolescents, suggesting a lower incidence of ICIs-P in younger populations, which may be attributed to the infrequent use of immune checkpoint inhibitors in pediatric patients. PD-1 inhibitors were identified as the primary causative agents of ICIs-P, with pembrolizumab and nivolumab accounting for the highest proportions. A similar phenomenon was observed in case reviews. This distribution likely reflects the widespread clinical application of PD-1 inhibitors, particularly as first-line treatment options for various cancers (Kramer et al., 2023; Nwankwo et al., 2024). It is noteworthy that all immune checkpoint inhibitors exhibited positive signals for pancreatitis adverse events in the disproportionality analysis, although results for some drugs may be uncertain owing to limited case numbers. Statistically significant associations with pancreatitis were observed for pembrolizumab, nivolumab, atezolizumab, ipilimumab, cemiplimab, and tremelimumab. Retrospective case series indicated that melanoma and non-small cell lung cancer were the predominant tumor types, with a median time to pancreatitis onset of 108 days following ICIs treatment, consistent with previous findings (Sakaguchi et al., 2024). Typical pancreatitis symptoms were present in 78.0% of patients, while 15.2% were asymptomatic. Nearly all patients exhibited elevated lipase or amylase levels, and 64.0% experienced severe (Grade 3) or life-threatening (Grade 4) ICIs-P. Pharmacovigilance analyses also revealed that death or life-threatening outcomes accounted for 22.1% of cases. These findings suggest that ICIs-P represents a potentially life-threatening immune-related adverse event, warranting heightened vigilance among clinicians using immune checkpoint inhibitors, particularly in high-risk patients.

4.2 Controversial risk factors

The exact prevalence of ICIs-P remains unclear, with reported rates ranging from 0.3% to 14% (Michot et al., 2018; Su et al., 2018; George et al., 2019). This wide range may be due to the heterogeneity generated by the different severities of the cases and potential risk factors in these studies. Regarding patient characteristics, our study showed that male sex and melanoma appeared to increase the risk of developing ICIs-P. This finding agrees with the results of previous publications (Zhang et al., 2022). In clinical practice, ICIs should be used more cautiously in female patients because they are more likely to develop autoimmune disorders than male patients (Quintero et al., 2012; Conforti et al., 2018). Several researchers have analyzed the correlation between sex and pancreatic AEs and concluded that there is no noticeable discrepancy in irAEs between male and female patients (Jing et al., 2021; Ma et al., 2021; Zhang et al., 2022). In addition, our review indicated that ICIs-P patients aged <65 years were reported more frequently than those aged ≥65 yrs. Meanwhile, pharmacovigilance analysis also indicates that the age distribution of ICIs-P mainly concentrates in the range of 61–80 years old. However, the effect of age on ICIs-P is controversial, as some studies have reported a slightly higher prevalence of irAEs in older patients (Baldini et al., 2020), across the spectrum of irAEs (Paderi et al., 2021). Other studies have shown that age was not associated with irAEs (Gomes et al., 2021; Noseda et al., 2021). Therefore, future studies should focus on the sex and age disparities in patients with irAEs.

Notably, the strongest association between anti-PD-1 and ICIs-P among all the monotherapies was observed in our analysis, which is consistent with the results of two previous studies (Reese et al., 2020; Zhang et al., 2022). However, the association between ICIs and pancreatitis remains unclear. Several studies have shown that the

TABLE 4 Associations of immune checkpoint inhibitors with pancreatitis.

ICIs	N	ROR (95% CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
PD-1					
Pembrolizumab	189	2.30 (2.08.2.55)	2.30 (139.97)	1.20 (1.08)	2.29 (2.09)
Nivolumab	179	1.91 (1.73.2.12)	1.91 (79.83)	0.93 (0.84)	1.91 (1.74)
Cemiplimab	4	151.20 (74.39,307.36)	150.63 (581.12)	7.20 (3.54)	147.25 (76.96)
Dostarlimab	2	2.11 (0.78.5.68)	2.11 (1.16)	1.07 (0.40)	2.11 (0.85)
Toripalimab	2	1.64 (0.61.4.43)	1.64 (0.50)	0.71 (0.26)	1.64 (0.66)
Retifanlimab*	-	-	-	-	-
PD-L1					
Atezolizumab	106	3.05 (2.67.3.49)	3.05 (150.87)	1.60 (1.40)	3.04 (2.69)
Durvalumab	27	1.86 (1.44.2.42)	1.86 (11.59)	0.90 (0.69)	1.86 (1.47)
Avelumab	8	3.04 (1.79.5.17)	3.04 (9.58)	1.60 (0.94)	3.04 (1.87)
CTLA-4					
Ipilimumab	88	2.49 (2.15.2.89)	2.49 (78.37)	1.31 (1.13)	2.48 (2.17)
Tremelimumab	1	220.86 (53.76,907.30)	218.75 (214.86)	7.76 (1.89)	216.84 (59.54)

Abbreviations: *No target incident reported; N,number; ICIs, Immune checkpoint inhibitors; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayes geometric mean;PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte antigen 4.

prevalence of pancreatitis in ICIs therapy using anti-CTLA4 alone or in conjunction with nivolumab and ipilimumab is higher than that using PD-1/PD-L1 alone (Su et al., 2018; George et al., 2019; Bai et al., 2021). Therefore, prospective studies are required to investigate the exact association between pancreatitis and various ICIs therapies.

4.3 Challenging diagnoses

Accurate diagnosis of ICIs-P remains challenging because its clinical presentation can be insidious. The determination of acute pancreatitis requires at least two of the following characteristics: clinical symptoms in the abdomen, elevated pancreatic enzymes (serum lipase/amylase levels at least three times the normal value), and imaging findings of pancreatitis (Liu et al., 2021), such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography/Computed Tomography (PET/CT), demonstrating any of the following: (1) new focal or diffuse pancreatic enlargement; (2) diminished attenuation, surrounding fat stranding, and no suspicious metastases; and (3) diffuse enhanced F-deoxyglucose uptake (Alessandrino et al., 2019; Das et al., 2020). Currently, the CTCAE 5.0 (Freites-Martinez et al., 2021) and the NCCN (Thompson et al., 2019) provide insignificantly different grading criteria for ICIs-related pancreatic injury severity according to asymptomatic elevated pancreatic enzymes and pancreatitis.

However, this rare ICIs-P event can be observed as a common clinical symptom of acute pancreatitis or as an asymptomatic incidental finding (Chandler et al., 2021; Tanaka et al., 2021). Increased serum amylase and/or lipase levels in ICIs-P can also indicate asymptomatic or radiological abnormalities, and elevated pancreatic enzymes are confounding factors (Abu-Sbeih et al., 2019). Therefore, the NCCN guidelines do not recommend routine testing of pancreatic enzymes at baseline or during ICIs treatment. It follows that a ruled-out diagnosis establishes an ICIs-P diagnosis. The initial examination includes a comprehensive assessment of other causes, such as alcohol, gallstones, hypertriglyceridemia, drugs, viruses, genetic susceptibility, tumors, and anatomical variants (Grover et al., 2018).

In addition, Abu-Sbeih et al. reported that ICIs-Ps occurred frequently in patients who presented with additional irAEs (Abu-Sbeih et al., 2019). Thus, we suggest measuring lipase levels in patients with adverse events unrelated to the pancreas. Our findings showed that 55.4% of the patients treated with ICIs-P had other irAEs. Furthermore, some patients with elevated pancreatic enzyme levels can have pancreatitis detectable on abdominal imaging despite the absence of symptoms (Saito et al., 2019; Chandler et al., 2021; Yazaki et al., 2022). Our data showed that most patients with ICIs-P presented with the typical symptoms of pancreatitis (78.0%), abnormal laboratory findings (90.2%), and imaging abnormalities (91.4%). This could be because we excluded patients with elevated pancreatic enzyme levels who did not meet the diagnostic criteria for pancreatitis. Accordingly, imaging is recommended for patients treated with ICIs-P when elevated pancreatic enzymes are found to avoid delaying diagnosis. However, differential diagnosis remains challenging because the imaging features of ICIs-P are similar to those of autoimmune pancreatitis (AIP). Some scholars have defined ICIs-P as a type 3 AIP and have suggested that its diagnosis could be based on the AIP criteria (Shimosegawa et al., 2011; Okazaki et al., 2014). We summarized the available research evidence on Table 5 (Das et al., 2019; Ofuji et al., 2021; Yamamoto et al., 2021; Sayed et al., 2022; Zen, 2022).

4.4 Treatment and management

Owing to the rarity and insufficient evidence of ICIs-P, only the NCCN has proposed management guidelines for ICIs-P based on its severity (Thompson et al., 2019). Other guidelines provide no opinion or

TABLE 5 Comparison between three types of autoimmune pancreatitis.

Subtype of AIP	Type 1	Type 2	Type 3
Other nomenclatures	AIP without GEL IgG4-related LPSP	AIP with GEL IgG4-unrelated IDCP	Immune checkpoint inhibitors-induced pancreatitis
Prevalence	Asia > USA > EU	EU > USA > Asia	Unclear
Age	Old (60, typically >40)	Young (30, including children)	Aged (60, typically <65)
Gender	male >> female	male = female (NS)	male = female (NS)
Symptoms			
Obstructive jaundice	Often	Often	Rare
Abdominal pain	Rare	Common	Common
Pancreas swelling	Common	Common	Common
Serum levels of IgG4	Elevated (80%–90%)	Normal (10%)	Normal
Histology	Lymphoplasmacytic periductal infiltration	Granulocytic duct wall infiltration	T-lymphocyte and neutrophil infiltration
		Granulocyte epithelial lesions (GEL)	Increased $CD8^+/CD4^+$ T-cell ratio
			Acinar-ductal metaplasia
			Fibrosis
IgG4 + cells	++	- or +	- or +
Other organ Involvement (OOI)	Sclerosing cholangitis	Unrelated with OOI	Unrelated with OOI
	Sclerosing sialadenitis		
	Retroperitoneal fibrosis		
	others		
Ulcerative Colitis	Rare	Often	Common
Steroid	Responsive	Responsive	Partially responsive
Recurrence	High rate	Rare	Rare

Abbreviations: AIP, autoimmune pancreatitis; GEL, granulocyte epithelial lesions; IgG4, serum immunoglobulin G subtype 4; LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, lidiopathic duct centric pancreatitis; EU, european union; USA, united states of america.

limited advice regarding the treatment of this irAEs (Brahmer et al., 2018; Haanen et al., 2018; Brahmer et al., 2021). The NCCN guidelines do not recommend intervention for grade G1 pancreatitis (mild or asymptomatic lipase/amylase elevation), allow ICIs to be maintained for grade 2 pancreatitis (moderate), or suggest prednisone/methylprednisolone (0.5–1 mg/kg/d). For G3–G4 grade pancreatitis (severe and life-threatening), it is recommended to permanently discontinue immunotherapy and start therapy with 1–2 mg/kg/day of glucocorticoids. When the symptoms of ICIs-P improve to grade 1, steroids can be gradually reduced over 4–6 weeks; However, the NCCN guidelines are based on traditional acute pancreatitis rather than ICIs-P evidence; therefore, the current treatment options suggested may not be optimal.

However, the effect of steroids on patients with ICIs-P remains unclear. It has been suggested that there is no clear benefit of steroids in ICIs-P, either in terms of short- or long-term adverse outcomes or improved overall survival (Abu-Sbeih et al., 2019). Notably, Almost all patients in our study had recurrent ICIs-P during steroid reduction. The NCCN guidelines do not provide recommendations for treating steroid-refractory ICIs-P or ICIs-P that recurs during steroid tapering. However, guidelines recommend infliximab for other irAEs if no improvement is observed within 48 h of steroid administration (Thompson et al., 2019). Our report identified two cases of steroid-refractory ICIs-P and four cases of ICIs-P whose prognosis improved after treatment with infliximab and had an inadequate reaction to steroids, suggesting that infliximab may be a potentially feasible therapy for ICIs-P (Cinnor et al., 2017; Townsend et al., 2021). In addition, some authors (Ikeuchi et al., 2016) have stated that patients with severe pancreatitis may require prednisone doses of up to 4 mg/kg/day, arguing that ICIs-P therapy requires not only a high initial dose of systemic glucocorticoids, but also a very slow tapering of the dose. These are the key factors preventing ICIs-P recurrence (Kohlmann et al., 2019).

In addition, after the resolution of irAEs, the decision on whether ICIs should be reinstated should be made cautiously. Guidelines recommend rebooting immunotherapy when harmfulness returns to grade 1 or lower, whereas severe G3–G4 events should discontinue ICIs therapy permanently (Thompson et al., 2019). Some studies have found that survival and tumor remission rates were similar between patients who discontinued ICIs during the introductory phase due to irAEs and those who did not discontinue therapy among patients receiving combination immunotherapy or monotherapy (Schadendorf et al., 2017; Santini et al., 2018). Thus, it is reasonable to administer checkpoint inhibitors treatment to patients with positive reactions but with high-grade irAEs. However, recovery from ICIs treatment is not related to an enhanced risk of long-term adverse consequences with ICIs-P, and patients who resume ICIs therapy have a marginally longer overall

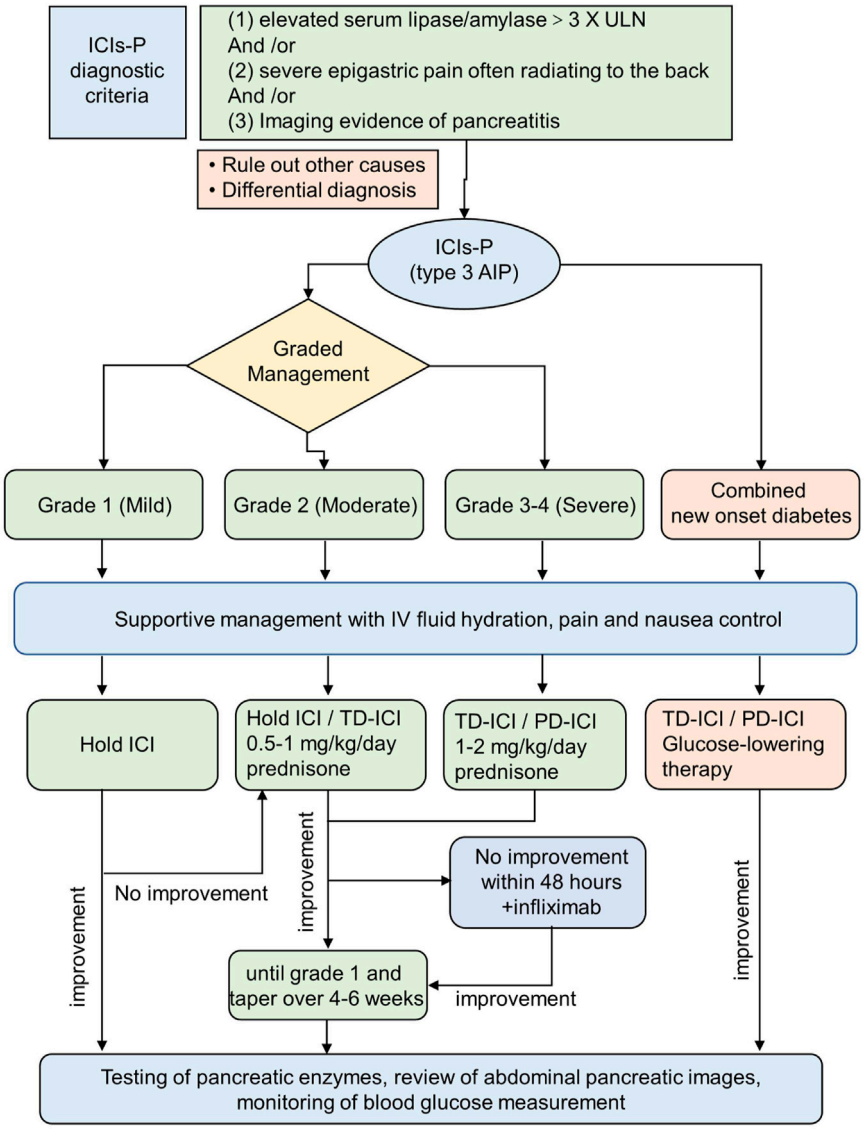


FIGURE 2
Scheme delineating the approach to the ICIs-P diagnosis and management. The recommended approach reconciles existing guidelines with the newest understanding from clinical experience. ICIs-P,Immune checkpoint inhibitors-induced pancreatitis; TD-ICI,temporary discontinuation of immune checkpoint inhibitors therapy; PD-ICI, permanent discontinuation of immune checkpoint inhibitors therapy.

survival than those who permanently discontinue ICIs treatment, suggesting that temporary interruption of ICIs followed by resumption after improvement in lipase values may potentially increase the anticancer effect of ICIs (Abu-Sbeih et al., 2019). Our study also found that several patients with G3 grade ICIs-P did not experience pancreatitis recurrence when ICIs was resumed after pancreatitis control (Kohlmann et al., 2019; Goyal et al., 2020; Yamamoto et al., 2021), whereas one patient experienced a new irAE after the resumption of ICIs during treatment (Pagan et al., 2019). Therefore, restarting ICIs therapy after the resolution of high-grade irAEs (e.g., pancreatitis) requires comprehensive consideration according to the condition. Among these, the response status seems to be a critical factor, and reboot immunotherapy should always be performed on a case-by-case basis, specifically in response-deficient or underresponsive patients.

There are no guidelines for the management of ICIs-P in patients with new-onset diabetes. A review study recommended against the use of glucocorticoids for the treatment of type 1 diabetes associated with ICIs because it may worsen type 1 diabetes and induce ketoacidosis (de Filette et al., 2019). Moreover, patients with acute pancreatitis may become dehydrated due to nausea and vomiting. Therefore, IV fluid is the primary treatment for acute pancreatitis (Waller et al., 2018). The current NCCN guidelines include IV hydration therapy for all ICIs-P grades. Abu-Sbeih et al. noted that aggressive IV rehydration has substantial utility in treating ICIs-P and appears to decrease the risk of long-term adverse events (Abu-Sbeih et al., 2019). We have provided our diagnostic algorithm and therapeutic suggestions based on the available guidelines, published evidence, and our medical practice (Figure 2).

4.5 Study limitations

This research has some limitations, mainly because of the retrospective nature of the case reports and FAERS database is a spontaneous reporting system: (1) Risk factors and treatment gaps: Details about risk factors, diagnostic workup, or ICIs-P management may have been missed; this incomplete data limits the identification of potential risk factors and the development of comprehensive strategies. (2) Publication bias: Minor or fatal cases may have been underreported, distorting the understanding of ICIs-P's true incidence and clinical features, which could misguide clinical decisions and patient counseling. (3) Methodological constraints: The limited sample size, retrospective nature, and prolonged inclusion time introduce heterogeneity in diagnosis and care standards, compromising result reliability, generalizability, and statistical power. (4) Causal inference limitations: The lack of comparator cohorts precludes causal inference and risk stratification in non-pancreatitis populations, hindering clinical interpretation of therapeutic effects and phenotypic correlations. (5) FAERS database limitations: Spontaneously reported adverse events lack proven causality between drugs and events. Incomplete data (e.g., patient history, dosage) further reduce analytical accuracy; FAERS only quantifies reported events, not actual incidence rates. Future studies require multicenter prospective cohorts with standardized data collection to enhance understanding of ICIs-P.

Despite these limitations, to our knowledge, this is the first study integrating FAERS data mining and literature review to assess ICIs-P's clinical characteristics and risk factors. Additionally, our systematic review includes the largest published cohort of ICI-treated cancer patients with pancreatitis, providing valuable evidence for further research and clinical practice.

5 Conclusion

ICIs-P is a rare, but potentially fatal irAEs. Therefore, clinicians should be aware of the risks of pancreatitis associated with immunotherapy and educate patients comprehensively. Early recognition of ICIs-P in the growing number of patients treated with ICIs is critical for its successful management. ICIs-P is an irreversible exocrine autoimmune impairment of the pancreas induced by ICIs that may manifest as asymptomatic, elevated pancreatic enzyme levels, or clinical pancreatitis. Patients with pancreatitis symptoms should have their lipase and amylase levels and radiology evaluated. The diagnosis should be determined by excluding other causes, and the differential diagnosis should consider other types of autoimmune pancreatitis. Steroids are commonly used to treat irAEs associated with checkpoint inhibitors; however, their role in the treatment and prevention of long-term complications of ICIs-P requires further investigation. Rational intravenous rehydration may be beneficial in the treatment of ICIs-P, particularly in combination with new-onset diabetes. Despite some conclusions and recommendations, we recognize the need for further prospective investigations to complement or re-evaluate current treatment policies and expand our understanding of the pathogenesis of pancreatitis associated with checkpoint inhibitors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

WF: Writing–original draft. HW: Writing–original draft. XZ: Writing–review and editing. HZ: Writing–review and editing. WY: Writing–review and editing. YG: Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was funded by the Sichuan Provincial Administration of Traditional Chinese Medicine research project (grant No. 2024MS414 and No. 2024MS313), Beijing Weiai Public Welfare Foundation - "Special Scientific Research on Diabetes and Related Metabolic Diseases (2024)". and Medical Research Project of Chengdu City (grant No. 2024313).

Acknowledgments

We are extremely grateful to Professor Xu Jie for his assistance in the analysis of The FAERS database. We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1426847/full#supplementary-material

References

Abu-Sbeih, H., Tang, T., Lu, Y., Thirumurthi, S., Altan, M., Jazaeri, A. A., et al. (2019b). Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *J. Immunother. Cancer* 7 (1), 31. doi:10.1186/s40425-019-0502-7

Abu-Sbeih, H., Tran, C. N., Ge, P. S., Bhutani, M. S., Alasadi, M., Naing, A., et al. (2019a). Case series of cancer patients who developed cholecystitis related to immune checkpoint inhibitor treatment. *J. Immunother. Cancer* 7 (1), 118. doi:10.1186/s40425-019-0604-2

Alessandrino, F., Sahu, S., Nishino, M., Adeni, A. E., Tirumani, S. H., Shinagare, A. B., et al. (2019). Frequency and imaging features of abdominal immune-related adverse events in metastatic lung cancer patients treated with PD-1 inhibitor. *Abdom. Radiol. (NY)* 44 (5), 1917–1927. doi:10.1007/s00261-019-01935-2

Bachiller, M. D., Piernavieja, L. C., Chico, P. T., et al. (2020). Pancreatitis induced by immunotherapy? Two case reports. *Eur. J. Hosp. Pharm.* 27 (Suppl. 1), A167–A168. doi:10.1136/ejhpharm-2020-eahpconf.356

Bai, X., Jiang, S., Zhou, Y., Zhen, H., Ji, J., Li, Y., et al. (2021). Common immune-related adverse events of immune checkpoint inhibitors in the gastrointestinal system: a study based on the us Food and drug administration adverse event reporting system. *Front. Pharmacol.* 12, 720776. doi:10.3389/fphar.2021.720776

Baldini, C., Martin, R. P., Voisin, A. L., Danlos, F. X., Champiat, S., Laghouati, S., et al. (2020). Impact of aging on immune-related adverse events generated by anti-programmed death (ligand)PD-(L)1 therapies. *Eur. J. Cancer* 129, 71–79. doi:10.1016/j.ejca.2020.01.013

Brahmer, J. R., Abu-Sbeih, H., Ascierto, P. A., Brufsky, J., Cappelli, L. C., Cortazar, F. B., et al. (2021). Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J. Immunother. Cancer* 9 (6), e002435. doi:10.1136/jitc-2021-002435

Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., et al. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J. Clin. Oncol.* 36 (17), 1714–1768. doi:10.1200/JCO.2017.77.6385

Capurso, G., Archibugi, L., Tessieri, L., Petrone, M. C., Laghi, A., and Arcidiacono, P. G. (2018). Focal immune-related pancreatitis occurring after treatment with programmed cell death 1 inhibitors: a distinct form of autoimmune pancreatitis? *Eur. J. Cancer* 95, 123–126. doi:10.1016/j.ejca.2018.02.006

Chandler, N., Dadlani, A., Bandikatla, S., et al. (2021). A rare case of asymptomatic pancreatitis due to atezolizumab, an immune checkpoint inhibitor. *J. Investigative Med.* 69 (5), 1099–1100. doi:10.1136/jim-2021-MW.36

Cinnor, B., Crossman, H., Kaplan, J., Mittal, C., Gerich, M. E., and Kao, D. J. (2017). First reported case of pembrolizumab-induced immune mediated hemorrhagic gastritis. *Gastroenterology* 152 (5), S891. doi:10.1016/s0016-5085(17)33042-1

Conforti, F., Pala, L., Bagnardi, V., De Pas, T., Martinetti, M., Viale, G., et al. (2018). Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. *Lancet Oncol.* 19 (6), 737–746. doi:10.1016/S1470-2045(18)30261-4

Das, J. P., Halpenny, D., Do, R. K., and Ulaner, G. A. (2019). Focal immunotherapy-induced pancreatitis mimicking metastasis on FDG PET/CT. *Clin. Nucl. Med.* 44 (10), 836–837. doi:10.1097/RLU.0000000000002692

Das, J. P., Postow, M. A., Friedman, C. F., Do, R. K., and Halpenny, D. F. (2020). Imaging findings of immune checkpoint inhibitor associated pancreatitis. *Eur. J. Radiol.* 131, 109250. doi:10.1016/j.ejrad.2020.109250

de Filette, J., Pen, J. J., Decoster, L., Vissers, T., Bravenboer, B., Van der Auwera, B. J., et al. (2019). Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. *Eur. J. Endocrinol.* 181 (3), 363–374. doi:10.1530/EJE-19-0291

Dehghani, L., Mikail, N., Kramkimel, N., Soyer, P., Lebtahi, R., Mallone, R., et al. (2018). Autoimmune pancreatitis after nivolumab anti-programmed death receptor-1 treatment. *Eur. J. Cancer* 104, 243–246. doi:10.1016/j.ejca.2018.09.014

Fang, W., Gao, Y., Shi, X., Zhang, X., Zhou, S., Zhu, H., et al. (2023). Immune checkpoint inhibitors-related pancreatitis with fulminant type 1 diabetes mellitus: case report and literature review. *Front. Immunol.* 14, 1243773. doi:10.3389/fimmu.2023.1243773

Freites-Martinez, A., Santana, N., Arias-Santiago, S., and Viera, A. (2021). Using the common terminology criteria for adverse events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr. Engl. Ed.* 112 (1), 90–92. doi:10.1016/j.ad.2019.05.009

George, J., Bajaj, D., Sankaramangalam, K., Yoo, J. W., Joshi, N. S., Gettinger, S., et al. (2019). Incidence of pancreatitis with the use of immune checkpoint inhibitors (ICI) in advanced cancers: a systematic review and meta-analysis. *Pancreatology* 19 (4), 587–594. doi:10.1016/j.pan.2019.04.015

Gomes, F., Lorigan, P., Woolley, S., Foden, P., Burns, K., Yorke, J., et al. (2021). A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients - the ELDERS study. *ESMO Open* 6 (1), 100042. doi:10.1016/j.esmoop.2020.100042

Goyal, P., Moyers, J. T., Hammami, M. B., et al. (2020). Immune checkpoint inhibitor-induced pancreatic injury: an atypical presentation. *Am. J. Gastroenterology* 115 (Suppl. L), S740–S741. doi:10.14309/01.ajg.0000707884.05320.32

Grover, S., Rahma, O. E., Hashemi, N., and Lim, R. M. (2018). Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for management. *Am. Soc. Clin. Oncol. Educ. Book* 38, 13–19. doi:10.1200/EDBK_100013

Guo, H., Guo, Q., Li, Z., and Wang, Z. (2024). Association between different GLP-1 receptor agonists and acute pancreatitis: case series and real-world pharmacovigilance analysis. *Front. Pharmacol.* 15, 1461398. doi:10.3389/fphar.2024.1461398

Haanen, J., Carbonnel, F., Robert, C., Kerr, K. M., Peters, S., Larkin, J., et al. (2018). Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 29 (Suppl. 4), iv264–iv266. doi:10.1093/annonc/mdy162

Hori, Y., Naitoh, I., Naiki-Ito, A., Kawai, T., Yoshida, M., Kato, A., et al. (2024). Incidence of pancreatic injury and pancreatitis in patients treated with immune checkpoint inhibitors. *Clin. Transl. Gastroenterol.* 15 (4), e00667. doi:10.14309/ctg.0000000000000667

Ikeuchi, K., Okuma, Y., and Tabata, T. (2016). Immune-related pancreatitis secondary to nivolumab in a patient with recurrent lung adenocarcinoma: a case report. *Lung Cancer* 99, 148–150. doi:10.1016/j.lungcan.2016.07.001

Jiang, R., Xu, L., Huang, Y., Fang, C., Guo, H., Li, S., et al. (2018). Anti-PD-1 drug (nivolumab) may induce acute and life-threatening pancreatitis in lung cancer patient: a case report. *Pancreas* 47 (8), e53–e54. doi:10.1097/MPA.0000000000001107

Jing, Y., Zhang, Y., Wang, J., Li, K., Chen, X., Heng, J., et al. (2021). Association between sex and immune-related adverse events during immune checkpoint inhibitor therapy. *J. Natl. Cancer Inst.* 113 (10), 1396–1404. doi:10.1093/jnci/djab035

Kakuwa, T., Hashimoto, M., Izumi, A., Naka, G., Takeda, Y., and Sugiyama, H. (2020). Pembrolizumab-related pancreatitis with elevation of pancreatic tumour markers. *Respirol. Case Rep.* 8 (2), e00525. doi:10.1002/rcr2.525

Kohlmann, J., Wagenknecht, D., Simon, J. C., and Ziemer, M. (2019). Immune-related pancreatitis associated with checkpoint blockade in melanoma. *Melanoma Res.* 29 (5), 549–552. doi:10.1097/CMR.0000000000000611

Kramer, S., van Hee, K., Blokzijl, H., van der Heide, F., and Visschedijk, M. C. (2023). Immune checkpoint inhibitor-related pancreatitis: a case series, review of the literature and an expert opinion. *J. Immunother.* 46 (7), 271–275. doi:10.1097/CJI.0000000000000472

Liu, Y., Zhang, H., Zhou, L., Li, W., Yang, L., Li, W., et al. (2021). Immunotherapy-associated pancreatic adverse events: current understanding of their mechanism, diagnosis, and management. *Front. Oncol.* 11, 627612. doi:10.3389/fonc.2021.627612

Ma, Z., Pei, J., Sun, X., Liu, L., Lu, W., Guo, Q., et al. (2021). Pericardial toxicities associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. *Front. Pharmacol.* 12, 663088. doi:10.3389/fphar.2021.663088

Michot, J. M., Ragou, P., Carbonnel, F., Champiat, S., Voisin, A. L., Mateus, C., et al. (2018). Significance of immune-related lipase increase induced by antiprogrammed death-1 or death ligand-1 antibodies: a brief communication. *J. Immunother.* 41 (2), 84–85. doi:10.1097/CJI.0000000000000202

Noguchi, Y., Tachi, T., and Teramachi, H. (2021). Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief. Bioinform* 22 (6), bbab347. doi:10.1093/bib/bbab347

Noseda, R., Bonaldo, G., Motola, D., Stathis, A., and Ceschi, A. (2021). Adverse event reporting with immune checkpoint inhibitors in older patients: age subgroup disproportionality analysis in VigiBase. *Cancers (Basel)* 13 (5), 1131. doi:10.3390/cancers13051131

Nwankwo, O. C., Lara-Salazar, F. M., Lara-Salazar, S., Abdulrahim, A. O., Chijioke, I., Singh, J., et al. (2024). Immune checkpoint inhibitors in cancer treatment and incidence of pancreatitis. *Cureus* 16 (8), e68043. doi:10.7759/cureus.68043

Ofuji, K., Hiramatsu, K., Nosaka, T., Naito, T., Takahashi, K., Matsuda, H., et al. (2021). Pembrolizumab-induced autoimmune side effects of colon and pancreas in a patient with lung cancer. *Clin. J. GASTROENTEROLOGY* 14 (6), 1692–1699. doi:10.1007/s12328-021-01499-z

Okazaki, K., Tomiyama, T., Mitsuyama, T., Sumimoto, K., and Uchida, K. (2014). Diagnosis and classification of autoimmune pancreatitis. *Autoimmun. Rev.* 13 (4-5), 451–458. doi:10.1016/j.autrev.2014.01.010

Paderi, A., Fancelli, S., Caliman, E., Pillozzi, S., Gambale, E., Mela, M. M., et al. (2021). Safety of immune checkpoint inhibitors in elderly patients: an observational study. *Curr. Oncol.* 28 (5), 3259–3267. doi:10.3390/curroncol28050283

Pagan, A., Gill, J., Arroyo, Y., and Bertran-Rodriguez, C. E. (2019). 1379 Immune checkpoint inhibitor-induced acute pancreatitis and colitis. *Am. J. Gastroenterology* 114, S763. doi:10.14309/01.ajg.0000595044.94402.db

Postow, M. A., Sidlow, R., and Hellmann, M. D. (2018). Immune-related adverse events associated with immune checkpoint blockade. *N. Engl. J. Med.* 378 (2), 158–168. doi:10.1056/NEJMra1703481

Quintero, O. L., Amador-Patarroyo, M. J., Montoya-Ortiz, G., Rojas-Villarraga, A., and Anaya, J. M. (2012). Autoimmune disease and gender: plausible mechanisms for the

female predominance of autoimmunity. *J. Autoimmun.* 38 (2-3), J109–J119. doi:10.1016/j.jaut.2011.10.003

Reese, S. W., Marchese, M., and McNabb-Baltar, J. (2020). Insights from pharmacovigilance: gastrointestinal-related immune checkpoint inhibitor adverse events. *Gastroenterology* 159 (4), 1195–1200. doi:10.1053/j.gastro.2020.06.093

Saito, H., and Ono, K. (2019). Nivolumab-induced pancreatitis: an immune-related adverse event. *Radiology* 293 (3), 521. doi:10.1148/radiol.2019191603

Sakaguchi, M., Nakaya, T., Tamada, K., Niki, T., Fukushima, N., Lefor, A. K., et al. (2024). Immune checkpoint inhibitor-induced pancreatitis with pancreatic enlargement mimicking autoimmune pancreatitis: a case report and review of the literature. *Intern Med.* 63 (6), 791–798. doi:10.2169/internalmedicine.1943-23

Santini, F. C., Rizvi, H., Plodkowski, A. J., Ni, A., Lacouture, M. E., Gambarin-Gelwan, M., et al. (2018). Safety and efficacy of Re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol. Res.* 6 (9), 1093–1099. doi:10.1158/2326-6066.CIR-17-0755

Sayed, A. A., Abreo, M., Thomas, A., and Chari, S. T. (2022). Type 3 autoimmune pancreatitis (immune checkpoint inhibitor-induced pancreatitis). *Curr. Opin. Gastroenterol.* 38 (5), 516–520. doi:10.1097/MOG.0000000000000873

Schadendorf, D., Wolchok, J. D., Hodi, F. S., Chiarion-Sileni, V., Gonzalez, R., Rutkowski, P., et al. (2017). Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J. Clin. Oncol.* 35 (34), 3807–3814. doi:10.1200/JCO.2017.73.2289

Shimosegawa, T., Chari, S. T., Frulloni, L., Kamisawa, T., Kawa, S., Mino-Kenudson, M., et al. (2011). International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 40 (3), 352–358. doi:10.1097/MPA.0b013e3182142fd2

Su, Q., Zhang, X. C., Hou, Y. L., Yao, Y. X., and Cao, B. W. (2018). Risk of immune-related pancreatitis in patients with solid tumors treated with immune checkpoint inhibitors: systematic assessment with meta-analysis. *J. Immunol. Res.* 2018, 1027323. doi:10.1155/2018/1027323

Sznol, M., Postow, M. A., Davies, M. J., Pavlick, A. C., Plimack, E. R., Shaheen, M., et al. (2017). Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. *Cancer Treat. Rev.* 58, 70–76. doi:10.1016/j.ctrv.2017.06.002

Tanabe, K., Yokoyama, K., Kanno, A., Ikeda, E., Ando, K., Nagai, H., et al. (2024). Immune checkpoint inhibitor-induced pancreatitis with pancreatic enlargement mimicking autoimmune pancreatitis: a case report and review of the literature. *Intern Med.* 63 (6), 791–798. doi:10.2169/internalmedicine.1943-23

Tanaka, T., Sakai, A., Shiomi, H., Masuda, A., Kobayashi, T., Tanaka, S., et al. (2021). An autopsy case of severe acute pancreatitis induced by administration of pazopanib following nivolumab. *Pancreatology* 21 (1), 21–24. doi:10.1016/j.pan.2020.11.002

Thompson, J. A., Schneider, B. J., Brahmer, J., Andrews, S., Armand, P., Bhatia, S., et al. (2019). Management of immunotherapy-related toxicities, version 1.2019. *J. Natl. Compr. Canc Netw.* 17 (3), 255–289. doi:10.6004/jnccn.2019.0013

Townsend, M. J., and Grover, S. (2021). S1653 Infliximab for steroid-refractory immune checkpoint inhibitor-induced pancreatitis. *Am. J. Gastroenterology* 116 (Suppl. L), S740–S741. doi:10.14309/01.ajg.0000780144.09245.72

Waller, A., Long, B., Koyfman, A., and Gottlieb, M. (2018). Acute pancreatitis: updates for emergency clinicians. *J. Emerg. Med.* 55 (6), 769–779. doi:10.1016/j.jemermed.2018.08.009

Wang, Z., Su, X., Shi, D., and Wei, L. (2024). Evaluate the renal system damage caused by zoledronic acid: a comprehensive analysis of adverse events from FAERS. *BMC Cancer* 24 (1), 1520. doi:10.1186/s12885-024-13284-5

Wright, J. J., Powers, A. C., and Johnson, D. B. (2021). Endocrine toxicities of immune checkpoint inhibitors. *Nat. Rev. Endocrinol.* 17 (7), 389–399. doi:10.1038/s41574-021-00484-3

Wu, S., Hu, W., Chen, M., Xiao, X., and Liu, R. (2024). A real-world pharmacovigilance study of FDA adverse event reporting system events for Lutetium-177-PSMA-617. *Sci. Rep.* 14 (1), 25712. doi:10.1038/s41598-024-77889-3

Yamamoto, K., Oka, K., Son, R., Honda, H., Sakae, H., Hasegawa, K., et al. (2021). Acute pancreatitis without abdominal pain induced by administration of nivolumab and ipilimumab. *Mod. Rheumatol. Case Rep.* 5 (2), 425–430. doi:10.1080/24725625.2021.1899444

Yazaki, T., Moriyama, I., Tobita, H., Sonoyama, H., Okimoto, E., Oka, A., et al. (2022). The simultaneous onset of pancreatitis and colitis as immune-related adverse events in a patient receiving nivolumab treatment for renal cell carcinoma. *Intern Med.* 61 (10), 1485–1490. doi:10.2169/internalmedicine.7911-21

Yilmaz, M., and Baran, A. (2022). Two different immune related adverse events occured at pancreas after nivolumab in an advanced RCC patient. *J. Oncol. Pharm. Pract.* 28 (1), 255–258. doi:10.1177/10781552211028636

Zen, Y. (2022). Type 2 autoimmune pancreatitis: consensus and controversies. *Gut Liver* 16 (3), 357–365. doi:10.5009/gnl210241

Zhang, Y., Fang, Y., Wu, J., Huang, G., Bin, J., Liao, Y., et al. (2022). Pancreatic adverse events associated with immune checkpoint inhibitors: a large-scale pharmacovigilance analysis. *Front. Pharmacol.* 13, 817662. doi:10.3389/fphar.2022.817662

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 16 April 2025
DOI 10.3389/fphar.2025.1510992

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Anoop Kumar,
Delhi Pharmaceutical Sciences and Research University, India
Adina Frum,
Lucian Blaga University of Sibiu, Romania

*CORRESPONDENCE
Wei Wei,
weiweieric0405@163.com

RECEIVED 14 October 2024
ACCEPTED 25 March 2025
PUBLISHED 16 April 2025

CITATION
Yang Y, Liu J and Wei W (2025) A real-world pharmacovigilance study of efgartigimod alfa in the FDA adverse event reporting system database.
Front. Pharmacol. 16:1510992.
doi: 10.3389/fphar.2025.1510992

A real-world pharmacovigilance study of efgartigimod alfa in the FDA adverse event reporting system database

Yunlin Yang[1], Jinfeng Liu[2] and Wei Wei[2,3,4]*

[1]Department of Clinical Pharmacy, Shifang People's Hospital, Shifang, Sichuan, China, [2]Department of Pharmacy, People's Hospital of Zhongjiang County, Deyang, Sichuan, China, [3]Department of Pharmacy and Evidence-Based Pharmacy Center, West China Second University Hospital, Chengdu, China, [4]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, China

Objective: Efgartigimod alfa, approved for treating generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive, has uncertain long-term safety in large populations This study analyzed adverse events (AEs) linked to efgartigimod alfa using data from the FDA Adverse Event Reporting System (FAERS).

Methods: We collected and analyzed efgartigimod alfa-related reports from the FAERS database from the first quarter of 2022 through the second quarter of 2024. Disproportionality analysis was used in data mining to quantify efgartigimod alfa-related AE signals.

Results: A total of 3,040 reports with efgartigimod alfa as the primary suspect and 12,487 AEs were retrieved from FAERS. The most frequently reported serious outcome was hospitalization (53.22%), and death occurred in 270 cases (8.88%). Disproportionality analysis detected 137 AE signals, with the most common in nervous system disorders (22.69%), general disorders and administration site conditions (16.90%), and infections and infestations (14.05%). Notably, in addition to infection-related AEs identified during clinical trials, this study detected unexpected signals, including inappropriate schedule of product administration (ROR 2.60, PRR 2.53, IC 1.34, EBGM 2.53) and nephrolithiasis (ROR 8.13, PRR 7.99, IC 2.99, EBGM 7.95). The median onset time of AEs was 81.0 days.

Conclusion: Our study provides a comprehensive assessment of the post-marketing safety of efgartigimod alfa and highlights the need for continued vigilance regarding infection-related adverse events. Additionally, the detection of inappropriate schedules of product administration underscores the importance of enhanced training and pharmacist involvement in medication management. Further research is warranted to explore the potential association between efgartigimod alfa and nephrolithiasis.

KEYWORDS

adverse event, data mining, FAERS, pharmacovigilance, efgartigimod alfa, generalized myasthenia gravis

1 Introduction

Generalized myasthenia gravis (gMG) is a rare chronic autoimmune neuromuscular disease (Gilhus, 2016; Beladakere Ramaswamy et al., 2021). The disease is characterized by generalized skeletal muscle weakness and exercise-induced weakness, which can have a significant negative impact on quality of life. gMG is treated with the goal of achieving complete remission, pharmacologic remission, or mild symptomatic status, while reducing adverse events (AEs) (Lascano and Lalive, 2021). Symptomatic therapy, such as acetylcholinesterase inhibitors, short-term salvage immunotherapy, such as plasma exchange and intravenous immunoglobulin, and long-term immunotherapy, such as corticosteroids and nonsteroidal immunosuppressants, comprise the standard treatment regimen for gMG (Lascano and Lalive, 2021; Menon and Bril, 2022; Habib et al., 2020). The symptoms of many patients can be effectively controlled with broad-spectrum nonspecific immunosuppressive drugs like corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, and tacrolimus; however, 10%–20% of patients are resistant or intolerant to these drugs, and many patients do not experience a complete or stable remission. Moreover, broad-spectrum nonspecific immunosuppressive drugs may need weeks to months to manifest their effects and are frequently linked to significant side effects (Alhaidar et al., 2022; Vanoli and Mantegazza, 2022).

Intravenous efgartigimod alfa is the inaugural neonatal Fc receptor (FcRn) antagonist authorized for the treatment of gMG (Heo, 2022). As one of several new targeted therapies, efgartigimod alfa is fast-acting, well-tolerated, and has the potential to provide sustained disease control in patients with gMG (Beladakere Ramaswamy et al., 2021; Menon and Bril, 2022; Habib et al., 2020). Clinical trials indicate that efgartigimod alfa is generally well tolerated in individuals with gMG, with most adverse responses classified as mild to moderate in intensity (Howard et al., 2021; Jacob et al., 2022). The most prevalent adverse events include headaches, upper respiratory tract infections, and urinary tract infections (Heo, 2022).

However, clinical trials generally have limited sample sizes and do not fully reflect the safety of efgartigimod alfa in real-world post-marketing applications. The FDA Adverse Event Reporting System (FAERS) database, on the other hand, is an invaluable resource for post-market monitoring and identification of drug safety issues (Feng et al., 2022), utilizing disproportionality analysis in a database of spontaneous reports of adverse drug events is an effective quantitative method for pharmacovigilance signal detection (Cutroneo et al., 2024).

Disproportionality analysis is a method employed to formulate hypotheses on potential causal associations between a medication and an adverse event (Tyagi and Kumar, 2024). Signal detection involves reviewing individual case safety reports and conducting statistical analyses while considering the nature of the data, its characteristics, and the type of drug (Jain et al., 2023). Multiple reports with high-quality information are needed to produce a signal (Javed and Kumar, 2024; Sharma et al., 2023). This study offers a thorough evaluation of the safety of egartigimod alfa in real-world settings through a detailed review of FAERS data, enhancing clinician knowledge and fostering safer medication utilization.

2 Materials and methods

2.1 Data source

We conducted a retrospective pharmacovigilance study using data from the FAERS database covering the first quarter of 2022 through the second quarter of 2024. The FAERS data file consists of seven types of datasets: patient demographics and management information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), reporting source (RPSR), start and end dates of drug therapy (THER), and indications for use/diagnosis (INDI). We downloaded each quarter's data from the FDA website [FAERS Quarterly Data Extract Files (www.fda.gov)] to import into MySQL for analysis. We obtained a total of 4,304,335 AE reports during the time period identified in this study. Due to the presence of duplicate reports, we removed the duplicates before performing further data analysis by selecting the most recent FDA_DT when the CASEID was the same, and selecting the larger PRIMARYID when the CASEID and FDA_DT were the same, as per FDA recommendations, resulting in 3,757,554 AE reports (Figure 1).

2.2 Adverse event and drug identification

FAERS is a database that contains information on adverse events and medication error reports submitted to the FDA (Rodriguez et al., 2001; Wysowski and Swartz, 2005). In addition to reports from manufacturers, healthcare professionals and the public can also submit reports. The FAERS structure follows the International Safety Reporting Guidelines ICH E2B issued by the International Conference on Harmonization (ICH) (Lomeli-Silva et al., 2024). AEs are coded as terms in the Medical Dictionary for Regulatory Activities (MedDRA) (Brown et al., 1999). MedDRA categorizes words into five hierarchical levels: System Organ Class (SOC), High-Level Group terms (HLGT), High-Level Terms (HLT), Preferred Term (PT), and Low Level Terms (LLT), enhancing data organization and searchability across different tiers (Omar et al., 2021). This study utilized MedDRA version 27.1, the most recent iteration at the time of analysis. FAERS allows reporting of any FDA-approved drug, and the drug names in this study were the generic and trade names, including efgartigimod, VYVGART, and VYVGART HYTRULO, respectively. To enhance the precision of the analysis, we chose to report only AEs for which efgartigimod alfa was the primary suspect (PS) drug for inclusion in this study.

2.3 Data mining

Disproportionality analysis is a basic analytical method used in pharmacovigilance studies that compares the proportion of the target drug that undergoes a specific AE with all other drugs (Hu et al., 2020). An AE signal is deemed created when the occurrence of a certain adverse event associated with a particular medicine substantially exceeds the background frequency in the database and beyond a defined threshold. In this study, frequentist

TABLE 1 Four major algorithms used for signal detection.

Algorithms	Equation	Criteria
ROR	ROR = ad/b/c	lower limit of 95% CI > 1, N ≥ 3
	95% CI = $e^{\ln(ROR) \pm 1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
PRR	PRR = a (c + d)/c/ (a + b)	PRR ≥ 2, $\chi^2 \geq 4$, N ≥ 3
	$\chi^2 = [(ad\text{-}bc)^2](a + b + c + d)/[(a + b)(c + d)(a + c)(b + d)]$	
BCPNN	$IC = \log_2 a(a + b + c + d)(a + c)(a + b)$	IC025 > 0
	95% CI = E (IC) ± 2V (IC)$^{0.5}$	
MGPS	EBGM = a (a + b + c + d)/ (a + c)/ (a + b)	EBGM05 > 2
	95% CI = $e^{\ln(EBGM) \pm 1.96(1/a+1/b+1/c+1/d)^{0.5}}$	

Equation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. 95% CI, 95% confidence interval; N, the number of reports; χ^2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E (IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

methods [reporting odds ratio (ROR) (van Puijenbroek et al., 2002) and proportional reporting ratio (PRR) (Evans et al., 2001)], Bayesian methods [information component (IC) (Bate et al., 1998) and empirical Bayes geometric mean (EBGM) (Szarfman et al., 2002)] of disproportionality analysis were applied to identify the potential AE signals associated with efgartigimod alfa. Each of these methods has distinct advantages: ROR and PRR are widely recognized and easily interpretable methods for disproportionality analysis, while IC and EBGM adjust for variability in the reporting rates and offer more robust estimates for signals where data might be sparse. In order to improve the accuracy of the analysis, the four algorithms mentioned above were only considered to satisfy the thresholds simultaneously when they produce a meaningful AE signal. Formulae and threshold conditions for the four methods are shown in Table 1.

In addition, time to AE and the proportion of serious outcomes were calculated in this study. Time to AE was defined as the interval between EVENT_DT (date of AE occurrence) and START_DT (date of initiation of treatment with efgartigimod alfa). We excluded reports with reporting errors (EVENT_DT before START_DT), inaccurate dates, or missing entries. Furthermore, we tallied the instances with serious outcomes and then divided them by the overall number of reports to get the ratio of serious outcomes. All data processing was performed using MYSQL 8.0, Navicat Premium 16, and Microsoft Excel 2021.

2.4 Subgroups analysis

A subgroup analysis was conducted to determine differences in adverse event signals associated with efgartigimod alfa among specific populations. The analysis was stratified by gender (i.e., male and female).

2.5 Sensitivity analysis

To assess the impact of concomitant medications on the observed outcomes, we conducted a sensitivity analysis focusing on the newly detected AE signals. Specifically, we excluded AE reports that involved the concurrent administration of other medications. This approach allowed us to determine whether the inclusion of these reports significantly influenced our results. The findings from the sensitivity analysis were compared to those of the primary analysis to evaluate the robustness of our study conclusions.

3 Results

3.1 Descriptive analysis

Excluding duplicate reports, we retrieved a total of 3,040 reports of efgartigimod alfa as PS and 12,487 cases of AEs induced by efgartigimod alfa from the first quarter of 2022 to the second quarter of 2024. After the drug was introduced to the market, there was a trend of increasing AE reports year by year, and the total number of reports in the first two quarters of 2024 has exceeded that of all of 2023. There was a significant amount of missing data in the age and sex fields in all reports, with 2,266 cases (75.54%) not reporting sex. In addition to this, patient age was not reported for 2,783 cases (91.55%). The vast majority of reports came from the United States (85.99%), followed by Japan (5.59%) and Germany (1.71%). Consumers submitted 79.54% of the reports and healthcare professionals submitted 19.34% of the reports. Myasthenia gravis was the most reported indication (68.52%), and as for reported serious outcomes, hospitalization was the most reported (53.22%), followed by other serious (important medical event) with 47.63%. In addition, death was reported in 270 cases (8.88%). For details, see Table 2.

3.2 Time to onset of efgartigimod alfa-associated adverse events

Excluding erroneous, absent, or unidentified reports of adverse event, a total of 992 AEs documented the time of commencement, with a median onset time of 81.0 days (interquartile range 15.0–220.5 days). As shown in Figure 2, efgartigimod alfa

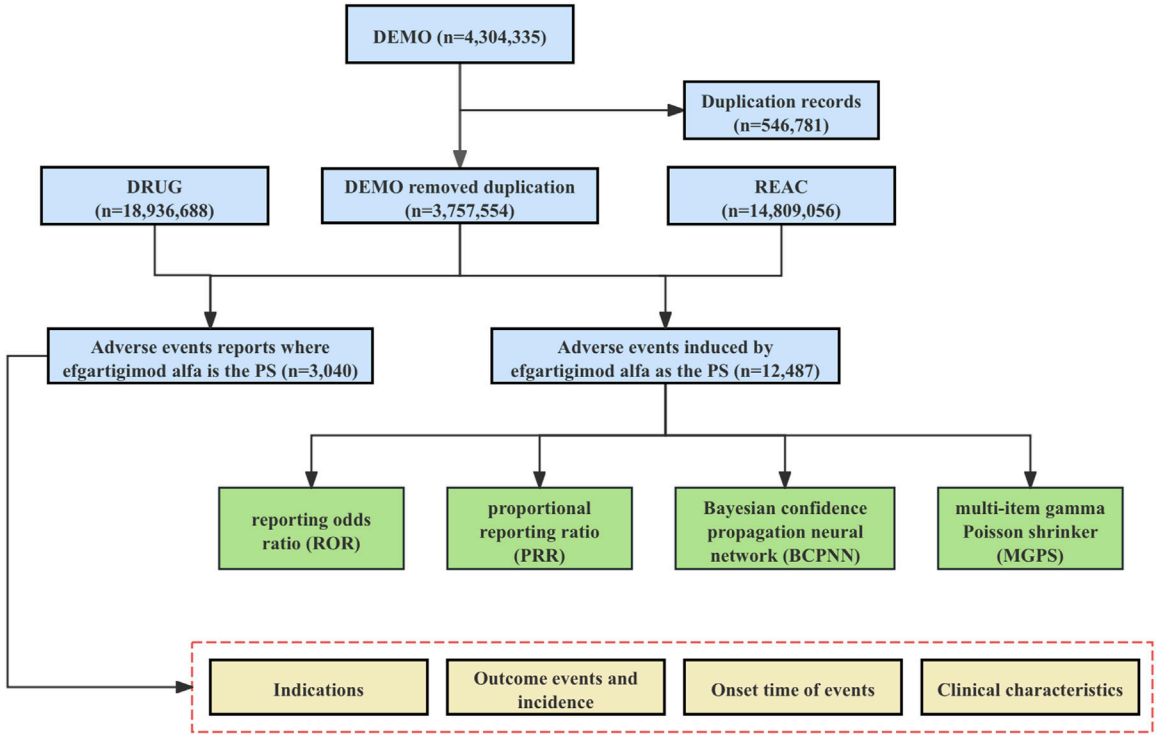


FIGURE 1
The flowchart for identifying efgartigimod alfa AEs in the FAERS database. Abbreviations: FAERS, United States Food and Drug Administration Adverse Event Reporting System; DEMO, demographic and administrative information file; DRUG, drug information file; REAC, adverse events file; PS, Primary Suspect.

resulted in the greatest number of AEs occurring in the first 1 month after initiation of therapy (342 cases, 34.48%), and in addition, 13.81% (137 cases) of AEs occurred after 1 year of dosing.

3.3 Disproportionality analysis

Figure 3 shows the percentage of AEs in each SOC classification. Efgartigimod alfa caused the most common AEs in nervous system disorders (22.69%), followed by general disorders and administration site conditions (16.90%) and infections and infestations (14.05%). A total of 137 AE signals were detected in 16 SOCs. The FAERS database collects information on all medical and healthcare-related AEs, so we excluded some AE signals that were related to the patient's primary disease and those that were not related to medication use, as outlined in Supplementary Table S1. Table 3 shows the number of AE signals detected at the AE signals detected at the preferred term (PT) level. In this study, the SOC detected a total of 20 AE signals: infection and invasion. This coincides with warnings and precautions on drug labels. The three AEs with the highest reporting rate were urinary tract infection (180 cases), pneumonia (130 cases), and nasopharyngitis (84 cases). In addition to this, we found some important and noteworthy AE signals. Inappropriate schedule of product administration was reported in 131 cases with signal intensities of ROR 2.60 (2.18–3.10), PRR 2.53 (122.93), IC 1.34 (1.05), and EBGM 2.53 (2.12). Another 58 cases reported nephrolithiasis with signal intensity of ROR 8.13 (6.26–10.55), PRR 7.99 (353.46), IC 2.99 (2.42), and EBGM 7.95 (6.12).

3.4 Subgroup analysis

Reports from male and female patients were collected and analyzed separately, and AE signals were calculated accordingly. Table 4 presents the distribution of AE signals based on ROR values across different genders. Overall, the number of AE signals associated with efgartigimod alfa was generally similar between male (23 signals) and female (22 signals) patients. Regarding the newly identified AE signal of nephrolithiasis, there were five reported cases in male patients with a signal strength of ROR 5.40 (2.23–13.05), PRR 5.34 (17.64), IC 2.41 (0.18), and EBGM 5.33 (2.20), while six cases were reported in female patients with a signal strength of ROR 6.12 (2.73–13.71), PRR 6.04 (25.27), IC 2.59 (0.49), and EBGM 6.03 (2.69). The signal strength of nephrolithiasis was comparable between male and female patients.

3.5 Sensitivity analysis

A sensitivity analysis was performed after excluding AE reports that documented concomitant medication use. The number of reports for inappropriate schedule of product administration decreased from 131 to 126, with a signal strength of ROR 2.49 (2.09–2.98), PRR 2.43 (107.89), IC 1.28 (0.99), and EBGM 2.43

TABLE 2 Clinical characteristics of reports with efgartigimod alfa from the FAERS database (January 2022 to June 2024).

Characteristics	Subgroups	Case number, n	Case proportion, %
Number of events		3,040	
Gender	Female	402	13.22
	Male	372	12.24
	Unknown	2,266	75.54
Age	<18 years	1	0.03
	18–44 years	34	1.12
	45–64 years	74	2.43
	≥65 years	148	4.87
	Unknown	2,783	91.55
Reporter	Consumer	2,418	79.54
	Health Professional	263	8.65
	Physician	263	8.65
	Pharmacist	62	2.04
	Unknown	34	1.12
Reported Countries	America	2,614	85.99
	Japan	170	5.59
	Germany	52	1.71
	Great Britain	32	1.05
	Canada	14	0.46
	Country not specified or others	158	5.20
Year	2024 q1-q2	1,468	48.29
	2023	1,227	40.36
	2022	345	11.35
Indications	Myasthenia gravis	2,083	68.52
	Immune thrombocytopenia	12	0.40
	Pemphigus	6	0.20
	Chronic inflammatory demyelinating polyradiculoneuropathy	4	0.13
	Muscular weakness	4	0.13
	Others and Unknown	931	30.63
Serious Outcome	Hospitalization	1,618	53.22
	Other Serious (Important Medical Event)	1,448	47.63
	Death	270	8.88
	Life-Threatening	174	5.72
	Required intervention to prevent permanent inmairment/damage	8	0.26
	Disability	7	0.23

Abbreviations: FAERS, United States Food and Drug Administration Adverse Event Reporting System; q1, quarter 1; q2, quarter 2.

(2.03). Similarly, the number of reports for nephrolithiasis decreased from 58 to 40, with a signal strength of ROR 5.56 (4.07–7.60), PRR 5.50 (147.05), IC 2.45 (1.81), and EBGM 5.48 (4.01). Overall, although the number of reports decreased, the sensitivity analysis did not substantially alter the conclusions of the primary analysis.

TABLE 3 Signal strength of reports of efgartigimod alfa at the Preferred Term (PT) level in the FAERS database.

SOC	Preferred terms (PTs)	Efgartigimod alfa cases reporting PT	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Vascular disorders	Poor venous access	26	9.81 (6.66–14.45)	9.73 (202.33)	3.27 (2.26)	9.67 (6.56)
Cardiac disorders	Atrial fibrillation	56	4.24 (3.25–5.53)	4.18 (135.70)	2.06 (1.57)	4.17 (3.20)
	Cardiac failure congestive	20	4.12 (2.65–6.40)	4.10 (46.73)	2.03 (1.13)	4.09 (2.63)
Gastrointestinal disorders	Dysphagia	139	11.53 (9.71–13.67)	11.04 (1263.74)	3.45 (3.09)	10.96 (9.23)
	Oesophageal stenosis	4	11.29 (4.22–30.24)	11.28 (37.14)	3.48 (0.27)	11.19 (4.18)
	Salivary hypersecretion	11	7.91 (4.37–14.33)	7.89 (65.79)	2.97 (1.36)	7.85 (4.33)
	Tongue disorder	5	6.73 (2.79–16.22)	6.72 (24.22)	2.74 (0.34)	6.69 (2.78)
Renal and urinary disorders	Nephrolithiasis[a]	58	8.13 (6.26–10.55)	7.99 (353.46)	2.99 (2.42)	7.95 (6.12)
	Micturition urgency	7	4.72 (2.25–9.93)	4.71 (20.41)	2.23 (0.47)	4.70 (2.24)
General disorders and administration site conditions	Symptom recurrence	152	70.70 (59.81–83.57)	67.21 (9410.28)	6.00 (5.25)	63.8 (53.97)
	Therapeutic product ineffective	21	19.31 (12.53–29.76)	19.18 (356.54)	4.24 (2.70)	18.91 (12.27)
	Pre-existing condition improved	7	11.58 (5.50–24.4)	11.56 (66.90)	3.52 (1.10)	11.46 (5.44)
	Infusion site extravasation	10	7.73 (4.15–14.41)	7.71 (58.05)	2.94 (1.25)	7.67 (4.11)
	Therapeutic response shortened	64	6.72 (5.24–8.61)	6.60 (303.15)	2.71 (2.21)	6.57 (5.12)
	Therapy non-responder	58	6.24 (4.81–8.10)	6.14 (249.12)	2.61 (2.09)	6.11 (4.71)
	Drug effect less than expected	27	5.72 (3.91–8.36)	5.67 (103.64)	2.50 (1.68)	5.65 (3.87)
	Asthenia	213	4.37 (3.80–5.03)	4.14 (513.81)	2.05 (1.81)	4.13 (3.59)
	Therapeutic product effect decreased	47	3.87 (2.90–5.16)	3.82 (98.08)	1.93 (1.40)	3.81 (2.86)
	Fatigue	332	2.84 (2.54–3.19)	2.64 (353.05)	1.40 (1.21)	2.64 (2.36)
Endocrine disorders	Thyroid mass	7	10.29 (4.89–21.67)	10.27 (58.08)	3.35 (1.03)	10.19 (4.84)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Thymoma	10	213.64 (109.10–418.36)	212.94 (1799.25)	7.51 (2.39)	181.77 (92.82)
Musculoskeletal and connective tissue disorders	Mastication disorder	26	71.65 (48.18–106.55)	71.04 (1698.01)	6.07 (3.67)	67.23 (45.21)
	Muscle fatigue	7	11.72 (5.56–24.7)	11.70 (67.86)	3.54 (1.11)	11.60 (5.51)
	Muscular weakness	153	11.01 (9.35–12.96)	10.50 (1310.86)	3.38 (3.04)	10.42 (8.85)
	Jaw disorder	4	10.18 (3.80–27.24)	10.16 (32.79)	3.33 (0.23)	10.09 (3.77)
	Muscle twitching	15	5.41 (3.25–8.99)	5.39 (53.38)	2.42 (1.26)	5.37 (3.23)

(Continued on following page)

TABLE 3 (*Continued*) Signal strength of reports of efgartigimod alfa at the Preferred Term (PT) level in the FAERS database.

SOC	Preferred terms (PTs)	Efgartigimod alfa cases reporting PT	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
	Musculoskeletal chest pain	10	4.56 (2.45–8.49)	4.55 (27.57)	2.18 (0.77)	4.53 (2.43)
	Back pain	88	2.73 (2.21–3.38)	2.68 (93.70)	1.42 (1.06)	2.68 (2.17)
Injury, poisoning and procedural complications	Inappropriate schedule of product[a] administration	131	2.60 (2.18–3.10)	2.53 (122.93)	1.34 (1.05)	2.53 (2.12)
Nervous system disorders	Bulbar palsy	11	368.50 (187.81–723.06)	367.17 (3096.43)	8.15 (2.60)	283.26 (144.36)
	Dysarthria	66	16.94 (13.25–21.65)	16.59 (955.44)	4.03 (3.36)	16.38 (12.82)
	Amyotrophic lateral sclerosis	4	15.85 (5.91–42.53)	15.83 (54.89)	3.97 (0.38)	15.65 (5.83)
	Tunnel vision	4	14.13 (5.27–37.89)	14.11 (48.20)	3.80 (0.35)	13.97 (5.21)
	Facial paresis	5	13.71 (5.68–33.13)	13.69 (58.19)	3.76 (0.69)	13.55 (5.61)
	Drooling	9	10.67 (5.53–20.58)	10.64 (77.93)	3.40 (1.37)	10.55 (5.47)
	Spinal cord compression	4	8.08 (3.02–21.62)	8.07 (24.63)	3.00 (0.13)	8.03 (3.00)
	Speech disorder	34	5.43 (3.87–7.62)	5.38 (121.06)	2.42 (1.72)	5.36 (3.82)
	Facial paralysis	7	5.05 (2.40–10.62)	5.04 (22.59)	2.33 (0.53)	5.02 (2.39)
	Hemiparesis	8	4.69 (2.34–9.41)	4.68 (23.11)	2.22 (0.60)	4.67 (2.33)
	Dysstasia	18	4.32 (2.72–6.88)	4.30 (45.56)	2.10 (1.13)	4.29 (2.70)
	Balance disorder	45	4.18 (3.11–5.62)	4.14 (107.02)	2.04 (1.49)	4.13 (3.07)
Infections and infestations	Herpes zoster reactivation	3	30.65 (9.74–96.42)	30.62 (83.88)	4.90 (0.02)	29.9 (9.51)
	Prostate infection	4	27.95 (10.37–75.33)	27.91 (101.5)	4.77 (0.52)	27.32 (10.13)
	Epididymitis	4	27.63 (10.25–74.48)	27.6 (100.30)	4.76 (0.52)	27.02 (10.02)
	Diverticulitis	46	11.91 (8.89–15.95)	11.74 (448.41)	3.54 (2.79)	11.64 (8.69)
	Respiratory syncytial virus infection	18	8.24 (5.18–13.12)	8.20 (113.08)	3.03 (1.82)	8.15 (5.12)
	Upper respiratory tract infection	53	8.05 (6.13–10.58)	7.93 (319.70)	2.98 (2.38)	7.89 (6.01)
	Urinary tract infection	180	7.03 (6.05–8.18)	6.67 (871.44)	2.73 (2.45)	6.64 (5.71)
	Urosepsis	8	6.13 (3.06–12.29)	6.11 (34.07)	2.61 (0.83)	6.09 (3.04)
	Meningitis	5	6.10 (2.53–14.69)	6.09 (21.17)	2.60 (0.28)	6.06 (2.52)
	Herpes zoster	48	5.49 (4.13–7.31)	5.42 (172.82)	2.43 (1.86)	5.40 (4.06)
	Respiratory tract infection	21	5.18 (3.37–7.96)	5.15 (69.97)	2.36 (1.43)	5.13 (3.34)
	Cellulitis	32	4.93 (3.48–6.99)	4.89 (98.83)	2.29 (1.57)	4.87 (3.44)
	Pneumonia aspiration	15	4.57 (2.75–7.61)	4.56 (41.54)	2.18 (1.08)	4.54 (2.73)

(Continued on following page)

TABLE 3 (*Continued*) Signal strength of reports of efgartigimod alfa at the Preferred Term (PT) level in the FAERS database.

SOC	Preferred terms (PTs)	Efgartigimod alfa cases reporting PT	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
	Sepsis	63	4.52 (3.52–5.80)	4.44 (168.25)	2.15 (1.68)	4.43 (3.45)
	Post procedural infection	6	4.49 (2.01–10.01)	4.48 (16.17)	2.16 (0.27)	4.47 (2.00)
	Staphylococcal infection	14	4.10 (2.42–6.94)	4.09 (32.56)	2.03 (0.91)	4.08 (2.41)
	Kidney infection	12	3.87 (2.19–6.82)	3.85 (25.31)	1.94 (0.74)	3.85 (2.18)
	Bronchitis	28	2.96 (2.04–4.30)	2.95 (36.01)	1.56 (0.87)	2.94 (2.03)
	Pneumonia	130	2.91 (2.44–3.48)	2.83 (156.19)	1.50 (1.21)	2.83 (2.37)
	Nasopharyngitis	84	2.67 (2.15–3.31)	2.62 (84.89)	1.39 (1.02)	2.62 (2.11)

[a]Emerging findings of efgartigimod alfa associated AEs from FAERS database.
ROR, reporting odds ratio; PRR, proportional reporting ratio; χ^2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

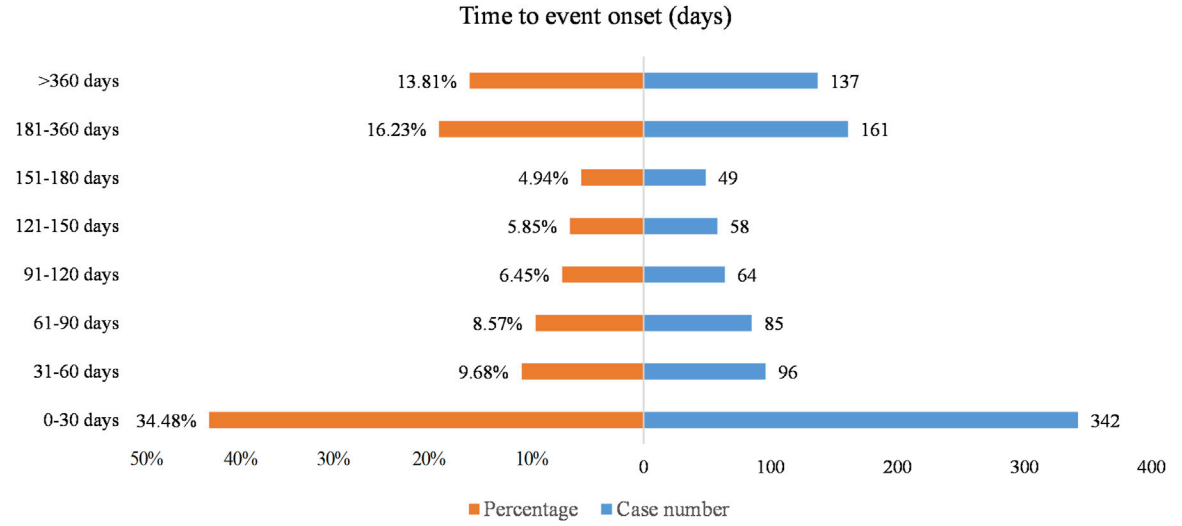


FIGURE 2
Time-to-onset of efgartigimod alfa-associated AEs.

4 Discussion

This study is the first and most extensive investigation to date of AEs related to efgartigimod alfa, using the FASRS database for post-marketing pharmacovigilance. Efgartigimod alfa is a first-of-its-kind novel human immunoglobulinG1 (IgG1) Fc fragment that binds with high affinity to the neonatal FcRn, thereby inhibiting its binding to FcRn and inhibiting its interaction with IgG. Efgartigimod alfa significantly reduces pathologic acetylcholine receptor antibodies, including serum IgG levels (Ulrichts et al., 2018) and thus exerts a therapeutic effect. A recent meta-analysis indicated that FcRn inhibitors (e.g., efgartigimod alfa) have favorable efficacy in patients with myasthenia gravis and do not carry increased safety risks (Li et al., 2024). However, further observations to determine the long-term safety of efgartigimod alfa remain critical, especially in the real-world application of the drug once it is on the market.

The warnings and precautions section of the drug labeling for efgartigimod alfa states that infections, hypersensitivity reactions, and infusion-related reactions are common AEs. This study emphasizes the importance of continuous monitoring and attention to these AEs, especially infection-related AEs, with efgartigimod alfa in the real world. In addition to this, some AEs that are not listed in the drug labeling are also cause for alarm.

The highest number of AE signals were observed in SOC: infections and infestations. The most common infections observed in pre-drug clinical trials were urinary tract infections and respiratory tract infections (Howard et al., 2021), which is consistent with the results of the present study. FcRn is associated with IgG circulation and antigen presentation in antigen-presenting cells (APC) (Baker et al., 2014; Ward and Ober, 2018) which may lead to autoimmune pathogenesis. Because IgG is one of the major immunoglobulins in the body, it is involved in neutralizing pathogens such as bacteria and viruses and removing pathogens

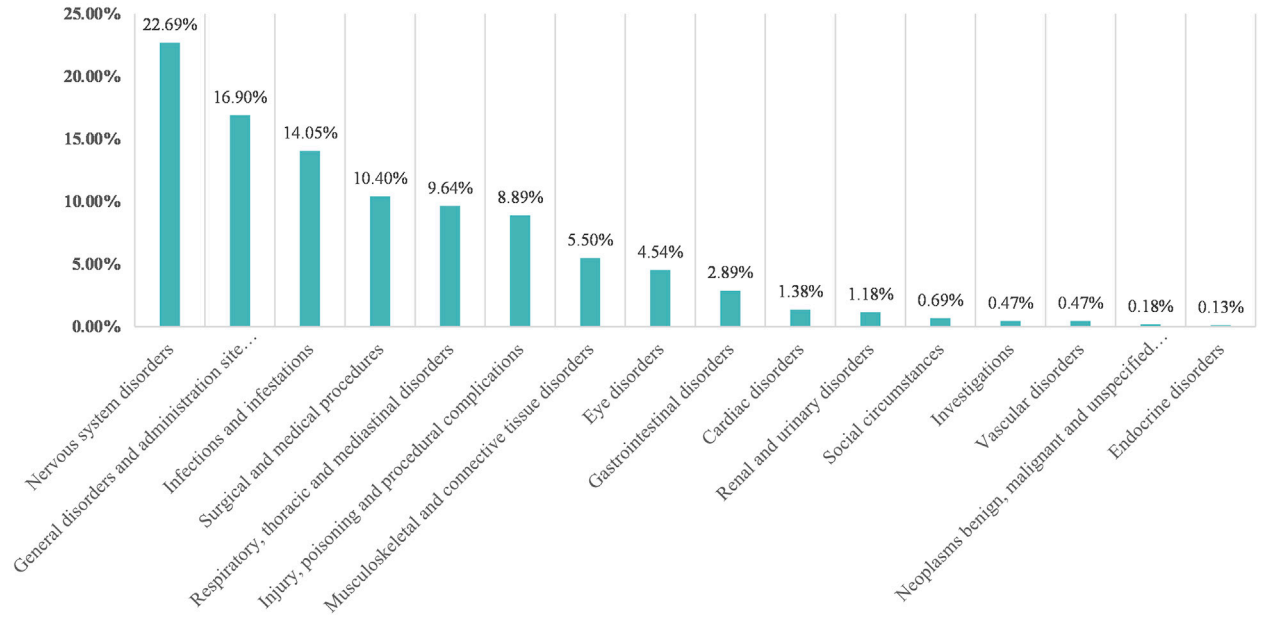


FIGURE 3
Proportion of efgartigimod alfa-associated AEs in different organ systems.

through activation of the complement system and conditioning. And blocking FcRn leads to a decrease in IgG levels, which in turn weakens the body's ability to cope with infections, making patients more susceptible to infection-related diseases (Zhou and Jiang, 2023). Therefore, we recommend that the administration of efgartigimod alfa should be delayed in patients with active infections until the infection is under control. And during treatment with efgartigimod alfa, it is crucial to monitor signs and symptoms associated with the infection.

For unexpected AEs, inappropriate schedule of product administration is a particularly important AE signal for healthcare professionals to be concerned about. Such events may indicate a failure to administer the drug at the correct time or frequency during actual use, which may compromise drug efficacy and increase the risk of adverse reactions. This study reveals the potential operational risks of efgartigimod alfa in the real world after its introduction to the market. Efgartigimod alfa has a complex preparation and administration process that requires strict adherence to a timeline (Heo, 2023). Any form of inappropriate dosing, such as delayed or too frequent administration, may lead to fluctuations in the patient's IgG levels, which in turn may affect their immunomodulatory function, thereby increasing the risk of adverse events such as infections and allergies (Zhou and Jiang, 2023). In addition, incidents of unscheduled medication administration tend to occur in healthcare settings with inadequately trained medical staff or limited resources (James, 2013; Bates et al., 1995; Reason, 2000). Therefore, during the administration of efgartigimod alfa, it is critical to enhance the training of healthcare professionals to ensure that they fully understand the administration protocols and that patients are continuously monitored. In addition, it is equally important for pharmacists to be involved in reviewing medication utilization and communicating with physicians in a timely manner throughout the course of treatment (Kaushal et al., 2008; Bladh et al., 2011).

Nephrolithiasis is one of the unexpected AEs not mentioned in the drug labeling found in this study. Nephrolithiasis is a common disease with a high incidence and recurrence rate, affecting approximately 10.6% of men and 7.1% of women in the United States, and its prevalence is comparable to that of diabetes mellitus (9.7%) (Sorokin et al., 2017; Scales et al., 2012; Ma et al., 2024). In China, the prevalence rates are 6.5% and 5.1% in men and women, respectively (Zeng et al., 2017), again not to be ignored. Currently, there is no evidence that efgartigimod alfa is associated with the development of kidney stones. However, renal adverse effects or metabolic problems may occur in the long-term treatment of patients with myasthenia gravis, especially when receiving immunosuppressive drugs or corticosteroids such as prednisone. And may lead to alterations in calcium, vitamin D, and bone metabolism, which may increase the risk of kidney stone formation (Compston et al., 2019; Oresta et al., 2021; Porter and Kaplan, 2011). Therefore, we further extracted will efgartigimod alfa as PS and reported AE reports of nephrolithiasis (Supplementary Table S2). Of these 58 reports, only nine reported prednisone as secondary suspect drug (SS) or concomitant (C), and two reported prednisone and mycophenolate mofetil as SS or C. The current study indicates that the correlation between efgartigimod alfa and nephrolithiasis is concerning, necessitating more high-quality research to validate or refute a causal link between the two.

This study still has some limitations that are worth exploring. First, the FAERS database is a self-reporting system, and due to its own limitations, there are omissions, duplicate reports, and incomplete case information, all of which may affect the results of the analysis (Sharma and Kumar, 2022). Second, even after implementing the FDA's suggested data cleaning and de-duplication processes, there is still a possibility of encountering

TABLE 4 Signal strength of reports of efgartigimod alfa at the Preferred Term (PT) level in the FAERS database based on gender.

SOC	PT	Male		Female	
		Number of reports	ROR (95% two-sided CI)	Number of reports	ROR (95% two-sided CI)
Eye disorders	Eyelid ptosis	4	35.62 (13.24–95.89)	5	23.48 (9.70–56.85)
Gastrointestinal disorders	Dysphagia	13	8.26 (4.75–14.38)	10	6.07 (3.24–11.37)
Renal and urinary disorders	Nephrolithiasis[a]	5	5.40 (2.23–14.05)	6	6.12 (2.73–13.71)
General disorders and administration site conditions	Asthenia	—	—	25	3.48 (2.23–5.22)
	Symptom recurrence	9	35.79 (18.41–69.55)	22	76.12 (49.37–117.36)
	Therapeutic product ineffective	3	32.14 (10.27–100.61)	—	—
	Therapy non-responder	—	—	9	7.06 (3.64–13.67)
	Drug effect less than expected	—	—	4	7.09 (2.65–19.01)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	29	3.79 (2.59–5.53)	31	3.07 (2.14–4.41)
	Choking	13	51.54 (29.52–89.96)	12	34.23 (19.23–60.91)
	Pharyngeal swelling	—	—	5	11.10 (4.59–26.83)
Surgical and medical procedures	Hospitalisation	19	5.00 (3.15–7.93)	19	5.75 (3.63–9.12)
	Mechanical ventilation	4	117.04 (43.01–318.47)	6	294.67 (128.41–676.22)
	Endotracheal intubation	—	—	5	119.36 (48.87–291.53)
	Thymectomy	—	—	3	4679.54 (941.63–23255.53)
Musculoskeletal and connective tissue disorders	Muscular weakness	16	9.95 (6.03–16.44)	—	—
	Mastication disorder	3	71.78 (22.79–226.11)	—	—
Injury, poisoning and procedural complications	Infusion related reaction	12	12.75 (7.17–22.68)	—	—
	Procedural headache	4	2056.76 (599.51–7055.64)	4	407.93 (146.15–1138.57)
Nervous system disorders	Myasthenia gravis crisis	44	1996.24 (1369.15–2910.56)	51	2712.79 (1905.73–3861.63)
	Myasthenia gravis	24	125.06 (82.17–190.33)	32	234.97 (162.49–339.77)
	Dysarthria	7	12.73 (6.02–26.92)	—	—
	Facial paresis	3	98.78 (31.23–312.48)	—	—
	Bulbar palsy	—	—	3	638.11 (190.23–2140.50)
Infections and infestations	Urinary tract infection	12	6.23 (3.50–11.07)	29	6.19 (4.24–9.03)
	Sepsis	9	4.46 (2.30–8.65)	—	—
	Pneumonia	—	—	20	3.35 (2.14–5.27)
	Respiratory tract infection	—	—	8	12.66 (6.28–25.51)
	Cellulitis	7	8.55 (4.05–18.09)	5	5.55 (2.30–13.42)
	Diverticulitis	5	13.83 (5.71–33.49)	—	—
	Upper respiratory tract infection	4	6.81 (2.54–18.26)	—	—

[a]Emerging findings of efgartigimod alfa associated AEs from FAERS database.
Abbreviations: ROR, reporting odds ratio.

duplicate reports. This might potentially result in an overestimation of the intensity of some AE signals (Cutroneo et al., 2024; Schilder et al., 2023).Third, this study could not establish a cause-and-effect link between efgartigimod alfa and particular AEs due to the use of disproportionality analyses. These analyses only give an evaluation of the strength of the signal, which is merely statistically significant. To validate the findings of this investigation, more high-quality studies are required. Furthermore, the FAERS database lacks racial and ethnicity data, which are crucial for evaluating drug-related adverse events considering both ecological and genetic factors (Yu et al., 2021). Additionally, due to a substantial proportion of missing age data, we were unable to conduct further subgroup analyses to determine the differences in AE occurrence across different age groups. Although there are certain limitations, the findings of this study will serve as a significant point of reference for healthcare practitioners to attentively observe any negative events that may occur in patients receiving efgartigimod alfa treatment.

5 Conclusion

This pharmacovigilance research investigated AEs linked to efgartigimod alfa in the FAERS database, which is a comprehensive assessment of the long-term safety of efgartigimod alfa after it has been approved and marketed. Our findings suggest that infection-related illnesses caused by efgartigimod alfa continue to require a high degree of vigilance in real-world applications after marketing. In addition, healthcare professionals should be vigilant in recognizing and preventing inappropriate schedules of product administration, and efforts should be made to enhance related education and training. And more research is needed to clarify the causal relationship between efgartigimod alfa and nephrolithiasis.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://figshare.com/articles/dataset/Adverse_events_associated_with_efgartigimod_use/27123546?file=49460241.

Author contributions

YY: Formal Analysis, Resources, Validation, Visualization, Writing – original draft, Writing – review and editing. JL: Conceptualization, Investigation, Software, Writing – review and editing. WW: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We appreciate the linguistic assistance provided by TopEdit (www.topeditsci.com) during the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1510992/full#supplementary-material

References

Alhaidar, M. K., Abumurad, S., Soliven, B., and Rezania, K. (2022). Current treatment of myasthenia gravis. *J. Clin. Med.* 11 (6), 1597. doi:10.3390/jcm11061597

Baker, K., Rath, T., Pyzik, M., and Blumberg, R. S. (2014). The role of FcRn in antigen presentation. *Front. Immunol.* 5, 408. doi:10.3389/fimmu.2014.00408

Bate, A., Lindquist, M., Edwards, I. R., Olsson, S., Orre, R., Lansner, A., et al. (1998). A Bayesian neural network method for adverse drug reaction signal generation. *Eur. J. Clin. Pharmacol.* 54 (4), 315–321. doi:10.1007/s002280050466

Bates, D. W., Cullen, D. J., Laird, N., Petersen, L. A., Small, S. D., Servi, D., et al. (1995). Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 274 (1), 29–34. doi:10.1001/jama.1995.03530010043033

Beladakere Ramaswamy, S., Singh, S., Hooshmand, S., Junsang, C., Sweeney, M., and Govindarajan, R. (2021). Current and upcoming treatment modalities in myasthenia gravis. *J. Clin. Neuromuscul. Dis.* 23 (2), 75–99. doi:10.1097/cnd.0000000000000377

Bladh, L., Ottosson, E., Karlsson, J., Klintberg, L., and Wallerstedt, S. M. (2011). Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. *BMJ Qual. Saf.* 20 (9), 738–746. doi:10.1136/bmjqs.2009.039693

Brown, E. G., Wood, L., and Wood, S. (1999). The medical dictionary for regulatory activities (MedDRA). *Drug Saf.* 20 (2), 109–117. doi:10.2165/00002018-199920020-00002

Compston, J. E., McClung, M. R., and Leslie, W. D. (2019). Osteoporosis. *Lancet* 393 (10169), 364–376. doi:10.1016/s0140-6736(18)32112-3

Cutroneo, P. M., Sartori, D., Tuccori, M., Crisafulli, S., Battini, V., Carnovale, C., et al. (2024). Conducting and interpreting disproportionality analyses derived from spontaneous reporting systems. *Front. Drug Saf. Regul.* 3, 1323057. doi:10.3389/fdsfr.2023.1323057

Evans, S. J., Waller, P. C., and Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* 10 (6), 483–486. doi:10.1002/pds.677

Feng, Z., Li, X., Tong, W. K., He, Q., Zhu, X., Xiang, X., et al. (2022). Real-world safety of PCSK9 inhibitors: a pharmacovigilance study based on spontaneous reports in FAERS. *Front. Pharmacol.* 13, 894685. doi:10.3389/fphar.2022.894685

Gilhus, N. E. (2016). Myasthenia gravis. *N. Engl. J. Med.* 375 (26), 2570–2581. doi:10.1056/NEJMra1602678

Habib, A. A., Ahmadi Jazi, G., and Mozaffar, T. (2020). Update on immune-mediated therapies for myasthenia gravis. *Muscle Nerve* 62 (5), 579–592. doi:10.1002/mus.26919

Heo, Y. A. (2022). Efgartigimod: first approval. *Drugs* 82 (3), 341–348. doi:10.1007/s40265-022-01678-3

Heo, Y. A. (2023). Efgartigimod alfa in generalised myasthenia gravis: a profile of its use. *CNS Drugs* 37 (5), 467–473. doi:10.1007/s40263-023-01000-z

Howard, J. F., Jr., Bril, V., Vu, T., Karam, C., Peric, S., Margania, T., et al. (2021). Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol.* 20 (7), 526–536. doi:10.1016/s1474-4422(21)00159-9

Hu, Y., Gong, J., Zhang, L., Li, X., Li, X., Zhao, B., et al. (2020). Colitis following the use of immune checkpoint inhibitors: a real-world analysis of spontaneous reports submitted to the FDA adverse event reporting system. *Int. Immunopharmacol.* 84, 106601. doi:10.1016/j.intimp.2020.106601

Jacob, S., Howard, J., Bril, V., Peric, S., De Bleecker, J., T'joen, C., et al. (2022). Long-term assessment of efgartigimod in patients with generalised myasthenia gravis: ADAPT+ study interim results. *J. Neurol. Neurosurg. Psychiatry* 93 (9), e2.112. doi:10.1136/jnnp-2022-abn2.2

Jain, D., Sharma, G., and Kumar, A. (2023). Adverse effects of proton pump inhibitors (PPIs) on the renal system using data mining algorithms (DMAs). *Expert Opin. Drug Saf.* 22 (8), 741–752. doi:10.1080/14740338.2023.2189698

James, J. T. (2013). A new, evidence-based estimate of patient harms associated with hospital care. *J. Patient Saf.* 9 (3), 122–128. doi:10.1097/PTS.0b013e3182948a69

Javed, F., and Kumar, A. (2024). Identification of signal of clindamycin associated renal failure acute: a disproportionality analysis. *Curr. Drug Saf.* 19 (1), 123–128. doi:10.2174/1574886318666230228142856

Kaushal, R., Bates, D. W., Abramson, E. L., Soukup, J. R., and Goldmann, D. A. (2008). Unit-based clinical pharmacists' prevention of serious medication errors in pediatric inpatients. *Am. J. Health Syst. Pharm.* 65 (13), 1254–1260. doi:10.2146/ajhp070522

Lascano, A. M., and Lalive, P. H. (2021). Update in immunosuppressive therapy of myasthenia gravis. *Autoimmun. Rev.* 20 (1), 102712. doi:10.1016/j.autrev.2020.102712

Li, J., Wu, X., Chu, T., Tan, X., Wang, S., Qu, R., et al. (2024). The efficacy and safety of FcRn inhibitors in patients with myasthenia gravis: a systematic review and meta-analysis. *J. Neurol.* 271 (5), 2298–2308. doi:10.1007/s00415-024-12247-x

Lomeli-Silva, A., Contreras-Salinas, H., Barajas-Virgen, M. Y., Romero-Lopez, M. S., and Rodríguez-Herrera, L. Y. (2024). Harmonization of individual case safety reports transmission requirements among PAHO reference authorities: a review of their current regulation. *Ther. Adv. Drug Saf.* 15, 20420986241228119. doi:10.1177/20420986241228119

Ma, Y., Cheng, C., Jian, Z., Wen, J., Xiang, L., Li, H., et al. (2024). Risk factors for nephrolithiasis formation: an umbrella review. *Int. J. Surg.* 110 (9), 5733–5744. doi:10.1097/js9.0000000000001719

Menon, D., and Bril, V. (2022). Pharmacotherapy of generalized myasthenia gravis with special emphasis on newer biologicals. *Drugs* 82 (8), 865–887. doi:10.1007/s40265-022-01726-y

Omar, N. E., Fahmy Soliman, A. I., Eshra, M., Saeed, T., Hamad, A., and Abou-Ali, A. (2021). Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS). *ESMO Open* 6 (6), 100315. doi:10.1016/j.esmoop.2021.100315

Oresta, B., Braga, D., Lazzeri, M., Frego, N., Saita, A., Faccani, C., et al. (2021). The microbiome of catheter collected urine in males with bladder cancer according to disease stage. *J. Urol.* 205 (1), 86–93. doi:10.1097/ju.0000000000001336

Porter, R. S., Kaplan, J. L. (2011). *The Merck Manual of Diagnosis and Therapy* (19th ed). Whitehouse Station, NJ: Merck Sharp and Dohme Corp.

Reason, J. (2000). Human error: models and management. *BMJ* 320 (7237), 768–770. doi:10.1136/bmj.320.7237.768

Rodriguez, E. M., Staffa, J. A., and Graham, D. J. (2001). The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Saf.* 10 (5), 407–410. doi:10.1002/pds.615

Scales, C. D., Jr., Smith, A. C., Hanley, J. M., Saigal, C. S., and Urologic Diseases in America Project (2012). Prevalence of kidney stones in the United States. *Eur. Urol.* 62 (1), 160–165. doi:10.1016/j.eururo.2012.03.052

Schilder, J. M., Golembesky, A., Boyle, T. A. C., Ye, G. L., and Kuplast, J. (2023). Commentary: adverse event profiles of PARP inhibitors: analysis of spontaneous reports submitted to FAERS. *Front. Pharmacol.* 14, 1241524. doi:10.3389/fphar.2023.1241524

Sharma, A., and Kumar, A. (2022). Identification of novel signal of clobazam-associated drug reaction with eosinophilia and systemic symptoms syndrome: a disproportionality analysis. *Acta Neurol. Scand.* 146 (5), 623–627. doi:10.1111/ane.13690

Sharma, A., Roy, S., Sharma, R., and Kumar, A. (2023). Association of antiviral drugs and their possible mechanisms with DRESS syndrome using data mining algorithms. *J. Med. Virol.* 95 (3), e28671. doi:10.1002/jmv.28671

Sorokin, I., Mamoulakis, C., Miyazawa, K., Rodgers, A., Talati, J., and Lotan, Y. (2017). Epidemiology of stone disease across the world. *World J. Urol.* 35 (9), 1301–1320. doi:10.1007/s00345-017-2008-6

Szarfman, A., Machado, S. G., and O'Neill, R. T. (2002). Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf.* 25 (6), 381–392. doi:10.2165/00002018-200225060-00001

Tyagi, S., and Kumar, A. (2024). Safety of immune checkpoint inhibitors: an updated comprehensive disproportionality analysis and meta-analysis. *Crit. Rev. Oncol. Hematol.* 200, 104398. doi:10.1016/j.critrevonc.2024.104398

Ulrichts, P., Guglietta, A., Dreier, T., van Bragt, T., Hanssens, V., Hofman, E., et al. (2018). Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. *J. Clin. Invest.* 128 (10), 4372–4386. doi:10.1172/jci97911

Vanoli, F., and Mantegazza, R. (2022). Antibody therapies in autoimmune neuromuscular junction disorders: approach to myasthenic crisis and chronic management. *Neurotherapeutics* 19 (3), 897–910. doi:10.1007/s13311-022-01181-3

van Puijenbroek, E. P., Bate, A., Leufkens, H. G., Lindquist, M., Orre, R., and Egberts, A. C. (2002). A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 11 (1), 3–10. doi:10.1002/pds.668

Ward, E. S., and Ober, R. J. (2018). Targeting FcRn to generate antibody-based therapeutics. *Trends Pharmacol. Sci.* 39 (10), 892–904. doi:10.1016/j.tips.2018.07.007

Wysowski, D. K., and Swartz, L. (2005). Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch. Intern Med.* 165 (12), 1363–1369. doi:10.1001/archinte.165.12.1363

Yu, R. J., Krantz, M. S., Phillips, E. J., and Stone, C. A., Jr. (2021). Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA adverse event reporting system (FAERS). *J. Allergy Clin. Immunol. Pract.* 9 (2), 819–829.e2. doi:10.1016/j.jaip.2020.09.021

Zeng, G., Mai, Z., Xia, S., Wang, Z., Zhang, K., Wang, L., et al. (2017). Prevalence of kidney stones in China: an ultrasonography based cross-sectional study. *BJU Int.* 120 (1), 109–116. doi:10.1111/bju.13828

Zhou, Y., and Jiang, S. (2023). Roles of FcRn in antigen-presenting cells during autoimmunity and a clinical evaluation of efgartigimod as an FcRn blocker. *Pathogens* 12 (6), 817. doi:10.3390/pathogens12060817

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 22 April 2025
DOI 10.3389/fonc.2025.1520770

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Fabio Maria Turazza,
National Cancer Institute Foundation (IRCCS), Italy
Amudha Ganapathy,
University of Illinois Chicago, United States
Shuqi Dai,
Qujing Medical College, China

*CORRESPONDENCE
Ya-Kun Wu
353827514@qq.com

†These authors share first authorship

RECEIVED 31 October 2024
ACCEPTED 31 March 2025
PUBLISHED 22 April 2025

CITATION
Luo L, Liang H, Yuan L and Wu Y-K (2025) Potential synergistic effects of lenvatinib and aspirin in aortic dissection: a case report and literature review.
Front. Oncol. 15:1520770.
doi: 10.3389/fonc.2025.1520770

Potential synergistic effects of lenvatinib and aspirin in aortic dissection: a case report and literature review

Lan Luo[1†], Hao Liang[2†], Lin Yuan[1] and Ya-Kun Wu[2*]

[1]Department of Pharmacy, Suining Central Hospital, Suining, Sichuan, China, [2]Department of Hepatobiliary Surgery, Suining Central Hospital, Suining, Sichuan, China

Background: Although numerous anticancer drugs targeting vascular endothelial growth factor (VEGF) are commonly used in clinical practice, life-threatening drug-drug interactions (DDIs) involving these drugs are rarely reported.

Case summary: A male patient had been taking aspirin for two years following a stroke. He was subsequently diagnosed with hepatocellular carcinoma (HCC) and initiated lenvatinib therapy. Shortly after, he developed lenvatinib-induced hypertension (191/102 mmHg) and was prescribed amlodipine for blood pressure control. At his first routine follow-up for HCC treatment, he was asymptomatic but was incidentally diagnosed with acute aortic dissection (AD). The patient declined endovascular treatment, and his AD lesions remained temporarily stable. Although lenvatinib is generally considered a safe and effective option for advanced HCC, this case raises concerns about a potential link between lenvatinib and aspirin in the development of AD due to their temporal association. This case highlights the need for increased clinical awareness regarding possible DDIs between these two drugs, particularly in patients with untreated acute AD.

Conclusion: The concurrent use of lenvatinib and aspirin may increase the risk of AD in patients with cancer. To prevent life-threatening complications, patients receiving both therapies should be closely monitored and strictly adhere to treatment guidelines. For patients who decline invasive AD treatment, continued lenvatinib therapy might be a cost-effective option to improve prognosis, though the continuation of aspirin therapy requires careful consideration.

KEYWORDS

lenvatinib, aspirin, adverse reactions, drug-drug interactions, hepatocellular carcinoma, aortic dissection

1 Introduction

With the rapid advancement of anticancer therapies, an increasing number of novel drugs have been introduced into clinical practice within a short period. Among them, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors inhibitors, such as lenvatinib, have been widely adopted in cancer treatment. However, an increasing number of physicians have recorded unexpected adverse events (AEs) associated with these drugs (1). In particular, drug-drug interactions (DDIs) between newly developed anticancer drugs and pre-existing medications have raised concerns due to their potential to cause severe, life-threatening complications. Notably, evaluating these AEs through prospective randomized controlled studies remains challenging.

Aortic dissection (AD) is a rare but life-threatening disease. Recently, cases of AD linked to VEGF inhibitors have been reported by pharmacists, prompting increasing attention from clinicians (2). A 2024 retrospective study involving a large patient cohort reported a significantly elevated risk of AD in patients receiving VEGF inhibitor treatment (3). However, the complexity of clinical scenarios remains unanswered. Some patients undergoing VEGF treatment have a history of long-term medication use, particularly antiplatelet agents. Thus, the potential DDIs between VEGF inhibitors and antiplatelet therapy in AD may be complex.

Herein, we report an intriguing case of a patient incidentally diagnosed with acute abdominal AD while receiving lenvatinib therapy for advanced hepatocellular carcinoma (HCC) and long-term aspirin therapy. Additionally, we review existing literature on potential DDIs between lenvatinib and aspirin in the context of AD.

2 Case description

A 59-year-old man, asymptomatic at the time of presentation, was admitted to the Department of Vascular Surgery following the incidental detection of AD during a routine assessment for HCC treatment.

Two years prior, the patient had experienced a large-artery atherosclerosis-related stroke and had undergone stent implantation in his middle cerebral artery (Figure 1). Initially, he was prescribed dual antiplatelet therapy with ticagrelor and aspirin for six months. Due to post-angioplasty restenosis in the middle cerebral artery, dual antiplatelet therapy was extended to one year, after which he continued aspirin monotherapy (0.1 g once daily). The patient tolerated aspirin well without any adverse effects.

Approximately one month before admission, the patient was diagnosed with unresectable HCC and hepatitis C virus (HCV) infection. A computed tomography (CT) scan of the abdominal aorta at the time showed no abnormalities (Figure 2). He was subsequently discharged after starting treatment with aspirin and lenvatinib (8 mg once daily). Tramadol was prescribed for moderate-to-severe cancer-related pain. A few days after initiating lenvatinib and aspirin treatment, the patient developed hypertension (191/102 mmHg), which was potentially associated with lenvatinib use. He visited his physician and was prescribed amlodipine (5 mg once daily) to manage his blood pressure. His blood pressure stabilized within the normal range the following day. Until the day of admission, the patient did not report any new or worsening symptoms, including pain. Apart from lenvatinib-induced hypertension, no other side effects of lenvatinib were observed.

The patient had no significant medical history or common risk factors for AD. His blood sugar and lipid levels were within normal limits, and he had no history of arrhythmia, infective endocarditis, coronary heart disease, or heart failure. Additionally, there was no family history of rare diseases.

On admission, the patient was afebrile, with a body temperature of 36.5°C. His respiratory rate was 20 breaths/min, pulse rate was 64 beats/min, and blood pressure was 117/71 mmHg. He remained cooperative during the examination and reported no pain upon abdominal palpation. At the time of admission, he had been receiving aspirin for two years, lenvatinib for over one month, and amlodipine for nearly one month.

Several abnormal blood test results were observed. The patient's hemoglobin level was 111 g/L (reference range: 130-175 g/L), while his platelet count remained within the normal range at 154 $\times 10^9$/L (reference range: 100-350). C-reactive protein level was elevated at 58.26 mg/L, and the D-dimer level was slightly increased at 0.57 μg/mL (reference range: 0–0.5). Activated partial thromboplastin time was within normal limits. The HCV antibody test was positive, whereas the HCV RNA test result was negative.

Electrocardiography showed no ischemic changes. CT imaging revealed a large tumor-like lesion in the left hepatic lobe, with multiple small lesions scattered throughout the liver (Figure 2). A Stanford type B AD was observed, extending from the infrarenal abdominal aorta to the common iliac artery (Figures 3a, b).

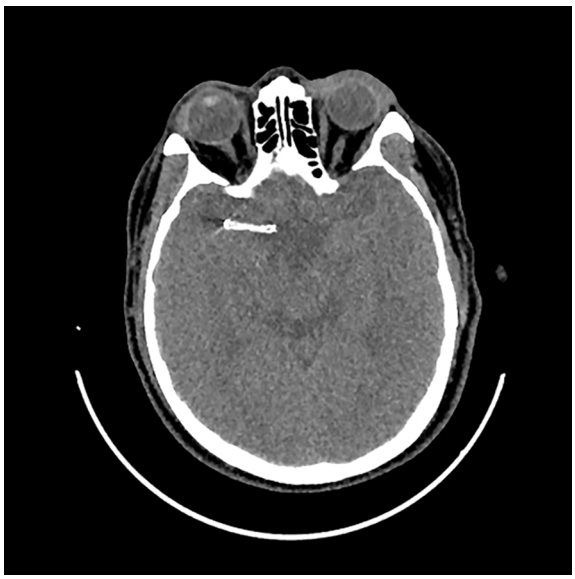


FIGURE 1
Implantation of stent in his middle cerebral artery in the computed tomography examination.

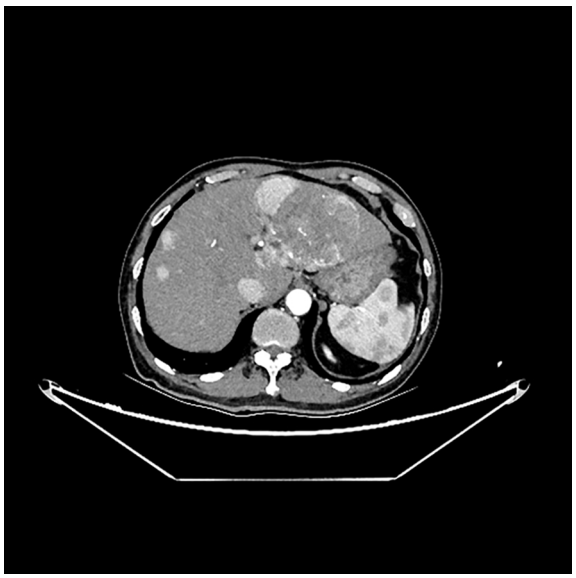


FIGURE 2
Tumor lesions in his left liver and normal outline of abdominal aorta in the computed tomography examination.

Additionally, thrombi were detected in the inferior mesenteric and left common iliac arteries, and stenosis was observed in the celiac trunk.

The patient was diagnosed with acute abdominal aortic dissection (AAD). As he declined endovascular treatment, optimal medical therapy was initiated and appeared to be effective. Lenvatinib, amlodipine, and aspirin were temporarily discontinued during hospitalization, and his blood pressure remained stable throughout his admission. Follow-up CT imaging one week later revealed that the AAD lesions remained unchanged. The patient was subsequently discharged. However, post-discharge, the concurrent use of lenvatinib and aspirin, along with their potential DDIs, remained a concern for his physicians, who strongly advised the patient to keep regular follow-up evaluations. A review of similar cases and relevant literature has been conducted (Table 1).

3 Discussion

We report a case of a patient who was incidentally diagnosed with AAD after receiving lenvatinib and aspirin therapy. AAD is a life-threatening vascular disease. However, cases of AAD induced by the combined use of lenvatinib and aspirin in patients without a history of hypertension are rare.

In this case, the patient developed AAD approximately one month after initiating lenvatinib and aspirin therapy despite well-controlled lenvatinib-induced hypertension. The temporal association between these medications and AAD suggests a potential interaction. We hypothesize that aspirin use may have contributed to the onset and progression of AAD. While aspirin plays a crucial role in reducing the risk of stroke recurrence (4), its use in untreated AAD may inadvertently accelerate disease progression and increase the risk of rupture. This presents a complex clinical challenge, emphasizing the need for a careful risk-benefit assessment when considering aspirin therapy in such patients.

Several VEGF inhibitors are used in clinical practice, and their association with aortic dissection has been documented. One study reported that 49 out of 16,441 patients (0.3%) treated with VEGF inhibitors developed AD, a rate 30 times higher than in those who did not receive VEGF inhibitor therapy (5). According to the World Health Organization's centralized database of drug reactions (2), bevacizumab was associated with the highest risk of promoting AD (222 cases, 44.9%), while lenvatinib-related AD was reported in 11 cases (2.2%).

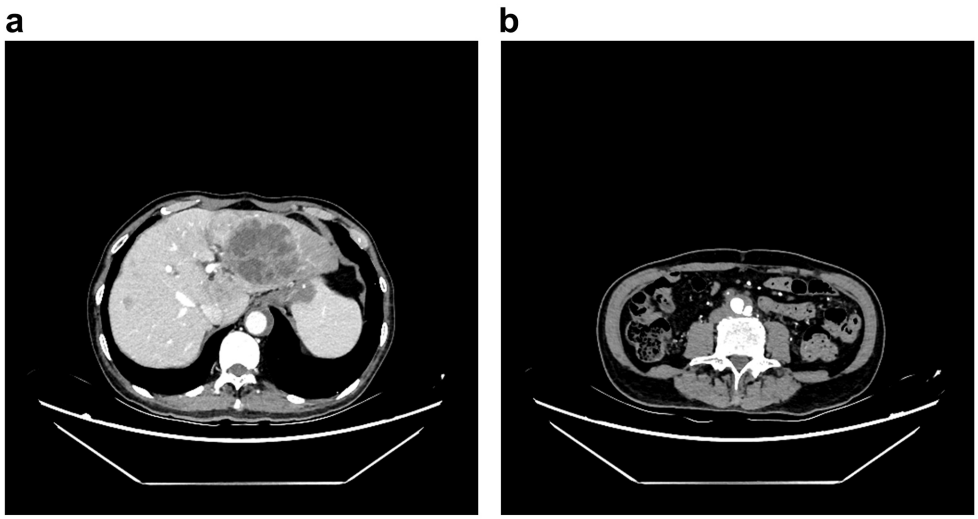


FIGURE 3
Signs of abdominal aortic dissection in the computed tomography examination, **(a)** abnormal outline of abdominal aorta in the level of liver, **(b)** outline of aortic dissection in the level of lower abdomen.

TABLE 1 Patients without history of hypertension diagnosed with AD after received VEDFI treatments for cancer.

Article	Age (yeas)	Sex	Type of cancer	Stage of cancer	Type of VEGFI	Type of AD	BP at admission (mmHg)	Treatment for AD	Drugs in the following treatments	OS from diagnosis of AD (month)
(Jiang, Li et al. 2020) (13)	58	Male	Lung squamous cell carcinoma	IV	Anlotinib	Stanford type A	180/120	Stent-graft intervention	Anticoagulant, Nitroglycerin, Nivolumab	2
(Takada, Yasui et al. 2018) (10)	66	Male	Metastatic renal cell carcinoma	IV	Sorafenib and Axitinib	Stanford type A	130/ N/A	Non-invasive treatment	Carvedilol, Nivolumab	N/A
(Tsuchiya, Ogawa et al. 2018) (11)	65	Male	Advanced hepatocellular carcinoma	BCLC C	Sorafenib	Stanford type A	128/54	Ascending aorta replacement	ACEI, 5-fluorouracil, Cisplatin	34
(Hatem, Bebawi et al. 2017) (14)	63	Female	Recurrence of gastrointestinal tumor	N/A	Sunitinib	Stanford type A	N/A	Aortic replacement	Sunitinib	recovered
(Formiga and Fanelli 2015) (9)	68	Male	Metastatic renal clear cell carcinoma	IV	Sunitinib	Stanford type B	210/120	Endoprosthesis	Metoprolol, Temsirolimus	Over 2
(Serrano, Suárez et al. 2010) (12)	77	Female	Renal cell carcinoma	IV	Sorafenib	Stanford type B	200/106	Non-invasive treatment	β-blocker, ACEI, Diuretic	N/A

AD: Aortic dissection; **VEGFI**: Vascular endothelial growth factor tyrosine kinase inhibitor; **BCLC**: Barcelona Clinic Liver Cancer staging; **BP**: Blood pressure; **OS**: Overall survival; **ACEI**: Angiotensin converting enzyme inhibitors; **N/A**: Not available.

Lenvatinib has demonstrated safety and efficacy in the treatment of advanced HCC (6). Its mechanism of action involves inhibiting angiogenesis and tumor proliferation while also exerting immunomodulatory effects (7). A preclinical study in mice suggested that the combination of lenvatinib and aspirin may have a synergistic anticancer effect against HCC (8). However, clinical evidence supporting this synergy in humans remains limited. Conversely, some VEGF inhibitors (9–14), such as anlotinib have been associated with AD when co-administered with anticoagulants. Given that lenvatinib inhibits PDGF receptors, potential DDIs with aspirin warrants further investigation.

One hypothesis suggests that lenvatinib-induced hypertension may contribute to vascular endothelial injury (15), while also impairing the formation of nutrient vessels within the arterial wall. This could lead to microscopic tears in the aortic intima (16). Simultaneously, aspirin inhibits platelet aggregation and adhesion, potentially impairing vascular repair mechanisms. The combined use of aspirin and lenvatinib may, therefore, exacerbate endothelial damage, increasing the risk of AD. Although this hypothesis is based on limited data, clinicians should exercise caution when prescribing lenvatinib alongside aspirin. Close monitoring for AD in these patients is recommended to mitigate potential risks.

The pathological mechanisms underlying AD remain unclear. Factors such as pre-existing vascular disease, genetic predisposition, and blood pressure variability may contribute to its development (17, 18). In this patient, there was no documented history of vascular disease or genetic predisposition. However, fluctuations in blood pressure may have played a role in the onset of AD. Lenvatinib-induced hypertension was effectively controlled upon discontinuation of lenvatinib. During follow-up, when lenvatinib was reintroduced for the treatment of HCC, amlodipine was prescribed to manage hypertension associated with its use.

Lenvatinib-induced hypertension requires careful management, as it is the most common adverse effect, occurring in 42.2% of patients (6). Calcium channel blockers and potassium-sparing diuretics can help control this hypertension (19). However, the risk of AD in these patients remains unpredictable (10, 11). Current guidelines recommend β-Receptor blockers as first-line agents for managing lenvatinib-induced hypertension (9, 20). In cases of uncontrolled hypertension, adjusting lenvatinib dosage or discontinuing treatment should be considered (21). However, as lenvatinib is an effective treatment for advanced HCC (6), its withdrawal could reduce survival time, presenting a complex clinical challenge that warrants further investigation.

The use of aspirin in this patient requires careful cardiovascular risk assessment. Currently, no high-quality evidence supports either the continuation or discontinuation of aspirin in patients with AD. Existing data on the effects of antithrombotic therapy in patients with AD remain inconclusive (22, 23). In this patient, aspirin treatment was discontinued during the acute phase of AD. However, once the AD lesions stabilized and considering the patient's reliable adherence to follow-up, aspirin therapy was reconsidered—despite the

patient's refusal to undergo invasive treatment for AD. In a case report, antiplatelet therapy might not significantly increase cardiovascular risks (24). Using newer antiplatelet agents with a lower cardiovascular risk might be more beneficial.

Regarding prognosis, the occurrence of AAD can negatively impact clinical outcomes (25). Many patients diagnosed with advanced cancer have limited treatment options, and discontinuation of VEGF inhibitors can lead to disease progression (13). However, in clinical practice, physicians often recommend stopping VEGF inhibitors following an AD diagnosis (9–14), even in patients who have undergone invasive treatment. Consequently, the tumor's malignancy grade may considerably influence the patient's overall prognosis.

4 Conclusion

Patients with cancer receiving lenvatinib and aspirin should be closely monitored due to the potential risk of AD. The combination of these therapies may contribute to AD development, particularly in those with lenvatinib-induced hypertension, which could serve as a predisposing factor. The concurrent use of lenvatinib and aspirin may lead to microscopic tears in the aorta intima, increasing the risk of AD rupture. For patients who decline invasive treatment for AD, continuing lenvatinib may be a cost-effective strategy for improving prognosis. However, the safety of aspirin therapy in such cases requires further evaluation. Clinicians should remain vigilant regarding potential DDIs between lenvatinib and aspirin, as a deeper understanding of these interactions is crucial for optimizing patient outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Suining Central Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. HL: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. LY: Writing – review & editing. YW: Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Project administration, Visualization.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

1. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann oncology: Off J Eur Soc Med Oncol.* (2022) 33:1217–38. doi: 10.1016/j.annonc.2022.10.001

2. Guyon J, Gouverneur A, Maumus-Robert S, Bérard X, Pariente A, Bikfalvi A, et al. Association between antiangiogenic drugs used for cancer treatment and artery dissections or aneurysms. *JAMA Oncol.* (2021) 7:775–8. doi: 10.1001/jamaoncol.2021.0210

3. Wu CW, Huang HY, Lin SY, Wang CC, Huang CF, Wu IH. Vascular endothelial growth factor inhibitors and the risk of aortic aneurysm and aortic dissection. *JAMA network Open.* (2024) 7:e240940. doi: 10.1001/jamanetworkopen.2024.0940

4. Shah J, Liu S, Yu W. Contemporary antiplatelet therapy for secondary stroke prevention: a narrative review of current literature and guidelines. *Stroke Vasc Neurol.* (2022) 7:406–14. doi: 10.1136/svn-2021-001166

5. Oshima Y, Tanimoto T, Yuji K, Tojo A. Association between aortic dissection and systemic exposure of vascular endothelial growth factor pathway inhibitors in the Japanese adverse drug event report database. *Circulation.* (2017) 135:815–7. doi: 10.1161/CIRCULATIONAHA.116.025144

6. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet (London England)*. (2018) 391:1163–73. doi: 10.1016/S0140-6736(18)30207-1

7. Zhao Y, Zhang YN, Wang KT, Chen L. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. *Biochim Biophys Acta Rev Cancer*. (2020) 1874:188391. doi: 10.1016/j.bbcan.2020.188391

8. Yan X, Yu H, Liang J, Hu Z, Li X, Liu H, et al. Synergistic antitumor efficacy of aspirin plus lenvatinib in hepatocellular carcinoma via regulating of diverse signaling pathways. *Cell Death Discov*. (2023) 9:416. doi: 10.1038/s41420-023-01664-y

9. Formiga MN, Fanelli MF. Aortic dissection during antiangiogenic therapy with sunitinib. A case report. *Sao Paulo Med J = Rev paulista medicina*. (2015) 133:275–7. doi: 10.1590/1516-3180.2013.7380002

10. Takada M, Yasui T, Oka T, Shioyama W, Kuroda T, Nakai Y, et al. Aortic dissection and cardiac dysfunction emerged coincidentally during the long-term treatment with angiogenesis inhibitors for metastatic renal cell carcinoma. *Int Heart J*. (2018) 59:1174–9. doi: 10.1536/ihj.17-461

11. Tsuchiya A, Ogawa M, Watanabe Y, Kimura N, Hayashi K, Suda T, et al. Successful treatment of aortic dissection during sorafenib therapy for hepatocellular carcinoma. *Clin Case Rep*. (2018) 6:1643–4. doi: 10.1002/ccr3.2018.6.issue-8

12. Serrano C, Suárez C, Andreu J, Carles J. Acute aortic dissection during sorafenib-containing therapy. *Ann Oncol*. (2010) 21:181–2. doi: 10.1093/annonc/mdp468

13. Jiang B, Li J, Chen J, Xiang X, Xiong J, Deng J. Aortic dissection in a patient treated with anlotinib for metastatic lung squamous cell carcinoma. *Thoracic Cancer*. (2020) 11:461–4. doi: 10.1111/1759-7714.13288

14. Hatem R, Bebawi E, Schampaert E. Potential sunitinib-induced coronary artery and aortic dissections. *Can J Cardiol*. (2017) 33:830.e817–830.e818. doi: 10.1016/j.cjca.2017.03.002

15. Hutter R, Carrick FE, Valdiviezo C, Wolinsky C, Rudge JS, Wiegand SJ, et al. Vascular endothelial growth factor regulates reendothelialization and neointima formation in a mouse model of arterial injury. *Circulation*. (2004) 110:2430–5. doi: 10.1161/01.CIR.0000145120.37891.8A

16. Sueta D, Suyama K, Sueta A, Tabata N, Yamashita T, Tomiguchi M, et al. Lenvatinib, an oral multi-kinases inhibitor, -associated hypertension: Potential role of vascular endothelial dysfunction. *Atherosclerosis*. (2017) 260:116–20. doi: 10.1016/j.atherosclerosis.2017.03.039

17. Raunsø J, Song RJ, Vasan RS, Bourdillon MT, Nørager B, Torp-Pedersen C, et al. Familial clustering of aortic size, aneurysms, and dissections in the community. *Circulation*. (2020) 142:920–8. doi: 10.1161/CIRCULATIONAHA.120.045990

18. Song C, Yu G, Feng X, Feng R, Bao J, Zhao Z, et al. Impact of high blood pressure variability on the occurrence of acute type B aortic dissection. *Vascular*. (2020) 28:413–20. doi: 10.1177/1708538120902630

19. Waliany S, Sainani KL, Park LS, Zhang CA, Srinivas S, Witteles RM. Increase in blood pressure associated with tyrosine kinase inhibitors targeting vascular endothelial growth factor. *JACC CardioOncology*. (2019) 1:24–36. doi: 10.1016/j.jaccao.2019.08.012

20. Dai S, Zhong Y, Cui H, Zhao J, Li S. Aortic dissection induced by vascular endothelial growth factor inhibitors. *Front Pharmacol*. (2023) 14:1189910. doi: 10.3389/fphar.2023.1189910

21. Matsumoto K, Shiroyama T, Miyake K, Yamamoto Y, Kuge T, Yoneda M, et al. Management of severe hypertension due to lenvatinib in patients with advanced thymic carcinoma: A case report. *Medicine*. (2022) 101:e28476. doi: 10.1097/MD.0000000000028476

22. Hori K, Morikawa N, Tayama E, Fukumoto Y. Use of anti-thrombotic drugs and in-hospital mortality in acute aortic dissection patients. *Diagnostics (Basel Switzerland)*. (2022) 12(10):2322. doi: 10.3390/diagnostics12102322

23. Masumoto A, Azumi Y, Kaji S, Miyoshi Y, Kim K, Kitai T, et al. Impact of antithrombotic therapy on clinical outcomes in patients with type B acute aortic syndrome. *JTCVS Open*. (2023) 14:36–45. doi: 10.1016/j.xjon.2023.02.017

24. Bocchino PP, De Filippo O, Piroli F, Scacciatella P, Imazio M, D'Ascenzo F, et al. Anticoagulant and anti-thrombotic therapy in acute type B aortic dissection: when real-life scenarios face the shadows of the evidence-based medicine. *BMC Cardiovasc Disord*. (2020) 20:29. doi: 10.1186/s12872-020-01342-2

25. Alivon M, Giroux J, Briet M, Goldwasser F, Laurent S, Boutouyrie P. Large artery stiffness and hypertension after antiangiogenic drugs: influence on cancer progression. *J hypertension*. (2015) 33:1310–7. doi: 10.1097/HJH.0000000000000550

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 April 2025
DOI 10.3389/fphar.2025.1498191

OPEN ACCESS

EDITED BY
Maxine Deborah Gossell-Williams,
University of the West Indies, Jamaica

REVIEWED BY
Anoop Kumar,
Delhi Pharmaceutical Sciences and Research University, India
Moetaza M Soliman,
Mansoura University, Egypt

*CORRESPONDENCE
Jia Feng Tang,
57094644@qq.com
Tao Tao,
tt1435502957@163.com

†These authors have contributed equally to this work

RECEIVED 18 September 2024
ACCEPTED 08 April 2025
PUBLISHED 24 April 2025

CITATION
Li X, Wang SW, Zhang Z-J, Luo ZY, Tang JF and Tao T (2025) Real-world pharmacovigilance analysis of drug-related cataracts using the FDA adverse event reporting system database. *Front. Pharmacol.* 16:1498191. doi: 10.3389/fphar.2025.1498191

Real-world pharmacovigilance analysis of drug-related cataracts using the FDA adverse event reporting system database

Xiang Li[1,2†], Shu Wen Wang[1†], Zhi-Jie Zhang[1], Zhan Yang Luo[3], Jia Feng Tang[2*] and Tao Tao[1*]

[1]Eye Institute & Affiliated Xiamen Eye Center, School of Medicine, Xiamen University, Xiamen, Fujian, China, [2]Chongqing Key Laboratory of Development and Utilization of Genuine Medicinal Materials in Three Gorges Reservoir Area, Chongqing Three Gorges Medical College, Wan Zhou, China, [3]Shanghai Pudong Hospital, Fudan University Pudong Medical Center, Shanghai, China

Objective: Although numerous drugs have been associated with cataracts, the risk for most drugs remains unclear. This study aimed to investigate the risk factors for drug-induced cataracts by analyzing large-scale data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: We used the reporting odds ratio (ROR) to evaluate reports of drug-induced cataracts in FAERS from the first quarter of 2004 to the third quarter of 2024. A univariate analysis, LASSO (least absolute shrinkage and selection operator) regression, and a multivariate regression analysis were performed to identify drug-related risk factors for cataracts, and Bonferroni correction was applied for multiple comparisons.

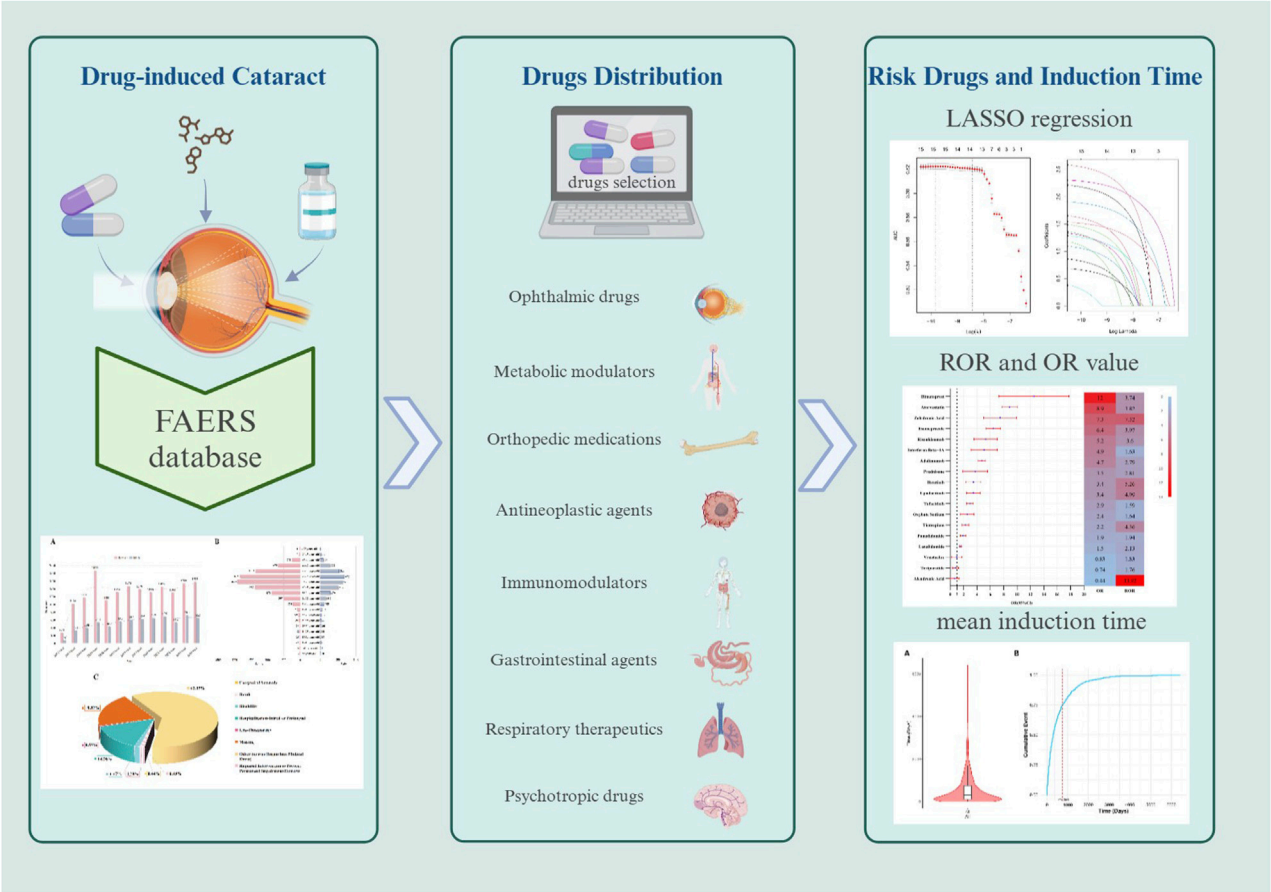
Results: Multivariate logistic regression ultimately identified 15 drugs as independent risk factors, including immunomodulators (6/15), antineoplastic drugs (3/15), psychotropic drugs (1/15), respiratory drugs (1/15), gastrointestinal drugs (1/15), orthopedic drugs (1/15), metabolic regulators (1/15), and ophthalmic drugs (1/15). The median time to onset of drug-induced cataracts was 449 days (interquartile range [IQR]: 150–901 days), with approximately 75% of adverse events occurring within 747 days.

Conclusion: These findings may help clinicians detect drug-related cataracts at an early stage and provide valuable insights for future research on the mechanisms of drug-induced cataracts.

KEYWORDS

FAERS, cataracts, drug, cataract prevention, adverse event

10.3389/fphar.2025.1498191



GRAPHICAL ABSTRACT

Introduction

The eye lens is an optically transparent structure situated posterior to the iris and anterior to the vitreous body and retina. Its distinctive morphology and refractive properties enable the precise focusing of light onto the retina (Thakur and Panda, 2000). With advancing age, the eye lens gradually becomes denser and thicker. Cataracts develop when eye lens transparency is compromised, typically manifesting clinically as decreased visual acuity, reduced contrast sensitivity, impaired color perception, and heightened glare sensitivity (Tewari et al., 2019). Common risk factors for cataract formation include aging, smoking, ultraviolet radiation exposure, diabetes mellitus, ocular trauma, and adverse drug reactions (Congdon, 2001). Additionally, certain medications may induce drug-related cataracts through mechanisms primarily involving direct drug toxicity, metabolic disturbances within the eye lens, and oxidative stress reactions (Szostakiewicz-Grabek et al., 2016). While most drug-induced cataracts result from prolonged systemic medication use (e.g., glucocorticoids), rare cases have been reported following chronic topical ocular application of glucocorticoid-containing eye drops.

Although cataracts are generally considered treatable, they remain one of the leading causes of blindness worldwide (Hashemi et al., 2009). Cataracts continue to pose a significant public health challenge in ophthalmology, affecting both developed and developing countries. The World Health Organization (WHO) estimates that approximately 180 million individuals worldwide experience some degree of visual impairment, with cataracts accounting for approximately 46% of blindness cases (GBD, 2019 Blindness and Vision Impairment CollaboratorsVision Loss Expert Group of the Global Burden of Disease Study, 2021). The burden of cataract-related diseases is expected to escalate further due to global population growth and aging.

Although drug-induced cataracts are clinically prevalent, systematic research on this condition remains insufficient, with existing knowledge primarily derived from case reports. This research gap limits a comprehensive understanding of cataract pathogenesis, epidemiological characteristics, and clinical management strategies. Furthermore, as novel medications continue to emerge and drug administration routes diversify, the pharmacological spectrum and clinical manifestations of drug-induced cataracts may evolve accordingly. This underscores the need for continuous pharmacovigilance and in-depth research to refine and update clinical evidence and practice guidelines.

Currently, a clinical consensus exists regarding the cataractogenic risks associated with both local and systemic drug use, particularly with glucocorticoids (Szostakiewicz-Grabek et al., 2016), anti-neoplastic agents (Uboweja et al., 2006), psychotropic medications (Fang et al., 2019), and statins (Mach et al., 2018). However, systematic research on drug-induced cataracts remains

limited. With the ongoing introduction of new drugs and the diversification of administration routes, the spectrum of cataractogenic medications and their clinical presentations is expected to change. This highlights an urgent need for sustained pharmacovigilance and in-depth investigations to enhance the existing knowledge base and improve patient safety.

Given the limitations of previous research, the analysis of adverse drug events using large-scale databases holds significant practical implications for clinical practice. FAERS serves as a comprehensive and information-rich pharmacovigilance database, collecting spontaneous post-marketing reports of adverse drug events associated with medical products (Li et al., 2025a). As a crucial tool for drug safety monitoring, FAERS provides essential data for epidemiological studies of adverse drug reactions and post-marketing surveillance. In this study, we systematically evaluate the occurrence of drug-induced cataracts using extensive real-world data, encompassing both topical ocular and systemic drug applications. Additionally, this study may reveal previously unidentified associations between specific medications and cataracts, offering novel insights for improving drug safety management.

Methodology

Research design and data sources

This study is a retrospective observational pharmacovigilance analysis based on the FAERS. The research methods and procedures strictly follow the relevant guidelines and standards set forth in Recommendations for the Evaluation of Adverse Drug Reaction Signals Using Individual Case Safety Reports (READUS-PV) (Fusaroli et al., 2024). Because the FAERS database is publicly available and all patient information is anonymized, this study does not require ethical approval or patient informed consent.

Data extraction and processing

All adverse events were systematically coded using the internationally recognized and clinically validated Medical Dictionary for Regulatory Activities (MedDRA). Employing Open Vigil 2.1–MedDRA software, we searched for adverse event reports related to "cataract" and extracted detailed information based on Primary Identifier (PRIMARYID), including individual case safety reports (ISRs), demographic data (patient age, sex, reporting country, etc.), adverse event descriptions, medication usage, reporting date, and clinical outcomes. Between January 2004 and September 2024, FAERS recorded a total of 21, 964, 449 initial reports. After deduplication, 18, 278, 243 records were included. Through further consolidation of duplicate brand-name drugs, 1,117 distinct drugs were identified. The detailed process of data screening and cleaning is illustrated in Figure 1. To reduce uncertainty and ensure specificity, this study included only drugs classified as "primary suspected." Cases concurrently labeled as concomitant medications, secondary suspected drugs, or interacting drugs were excluded. Regarding demographic information, only cases with complete age, sex, and weight data were retained, while cases in which the reported age exceeded 120 years or weight was over 400 kg were excluded.

Statistical analysis

Individuals who used the target drugs constituted the experimental group, while those who used non-target drugs served as the control group, forming a 2 × 2 contingency table for analysis (Supplementary Table 1). We used the ROR and its corresponding 95% confidence interval (CI) to conduct disproportionality analysis, aiming to evaluate the association between the drugs and cataracts while excluding medications specifically intended for cataract treatment. A potential risk signal was considered present if the ROR exceeded 3 and the lower limit of the 95% CI was greater than 1 (Li et al., 2025b). The calculation formula is as follows:

$$ROR = \frac{a/c}{b/d} ROR_{95\%CI} = e^{ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

In this study, we extracted complete data on patient sex, age, and weight from FAERS, including only cases with all required data. Patients who were older than 120 years or weighed more than 400 kg were excluded. First, we performed a univariate analysis using the ROR. Drugs were selected if the 95% CI lower limit was greater than 1, the ROR exceeded 3, and the adjusted p-value was below 0.01.

Subsequently, drugs with $p < 0.01$ in the univariate analysis were included in a LASSO regression model for variable selection. We then conducted a multivariable logistic regression analysis, incorporating demographic variables, to further assess the independent association between specific drugs and cataracts.

Finally, demographic characteristics (sex, age, and weight) were analyzed after excluding extreme values (age >120 years or weight >400 kg). All statistical analyses were carried out using R software (version 4.2.2), and data extraction and processing were performed with Open Vigil 2.1–MedDRA. The univariate analysis included drugs with ROR >3, a 95% CI lower limit greater than 1, and a significance threshold of $p < 0.01$. All statistical analyses were conducted using R software (version 4.2.2) and Post-Ingres Structured Query Language (PostgreSQL).

Results

Baseline characteristics of cataract patients

A total of 23,680 patients with cataract-related adverse event reports were included in this study. The number of reports peaked in 2015 (n = 2,419), exhibiting an overall increasing trend over the years (Figure 2A). Notably, a significant gender disparity was observed, with female patients accounting for 71.2% of the cases (Figure 2B). The mean age of patients with drug-related cataracts was 66.92 ± 11.95 years. The age distribution trends were similar between genders, with most reports concentrated in the 65–70 age group (females: 1,912 cases; males: 626 cases). Regarding clinical outcomes,

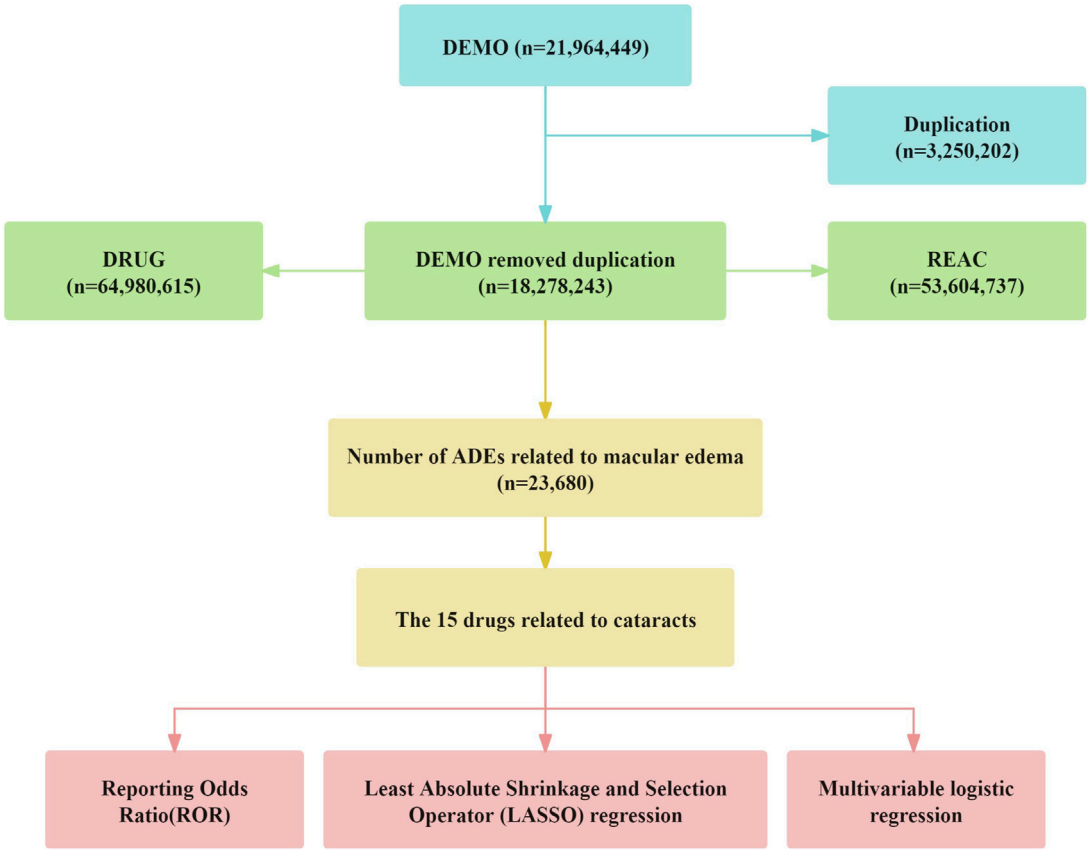


FIGURE 1
The flow diagram of screening reports containing Cataracts elicited by diverse agents from the FAERS database.

62.05% of patients (n = 14,693) experienced serious medical events (Figure 2C). The detailed information is shown in Table 1.

Drugs associated with cataracts

A volcano plot was constructed to evaluate the potential associations between medications and cataracts (Figure 3). In this plot, the x-axis represents the logarithmic ROR, where higher values indicate a stronger proportional association between adverse event reporting and cataracts. The y-axis represents the negative logarithm of the adjusted P-value (P-adjusted) after Fisher's exact test with Bonferroni correction, with higher values signifying greater statistical significance. The color of each point corresponds to the logarithmic number of reported cases, with redder shades indicating a higher number of cases. Therefore, medications positioned in the upper-right quadrant of the volcano plot exhibit stronger signal intensity and higher statistical significance.

According to the analysis, the top five medications associated with an increased risk of cataracts were Alendronic Acid (ROR = 13.92, 95% CI: 12.51–15.48, P < 0.01), Ibrutinib (ROR = 5.26, 95% CI: 4.85–5.70, P < 0.01), Upadacitinib (ROR = 4.99, 95% CI: 4.52–5.51, P < 0.01), Tiotropium (ROR = 4.36, 95% CI: 3.97–4.97, P < 0.01), and Adalimumab (ROR = 2.79, 95% CI: 2.65–2.94, P < 0.01).

Risk factors for drug-related cataracts

This study performed univariate analysis on medications reported in more than 100 cases, selecting those with a lower bound of the 95% CI for ROR greater than 1 and a Bonferroni-adjusted P-value (P-adjusted) < 0.01. Subsequently, medications with P < 0.01 in the univariate analysis were further screened using a Least Absolute Shrinkage and Selection Operator LASSO regression model, identifying 18 candidate drugs (Figure 4).

Multivariate logistic regression analysis, incorporating demographic data, was conducted for these candidate medications (Figure 5). The results identified 15 drugs (Bimatoprost, Atorvastatin, Zoledronic Acid, Esomeprazole, Risankizumab, Interferon β-1, Adalimumab, Prednisone, Ibrutinib, Upadacitinib, Tofacitinib, Sodium Oxybate, Tiotropium, Pomalidomide, and Lenalidomide) as independent risk factors for drug-induced cataracts. Based on pharmacological characteristics, these medications were further classified into eight distinct drug categories (Figure 6).

The predictive performance of the multivariate logistic regression model yielded an area under the ROC-AUC of 0.737 (Figure 7).

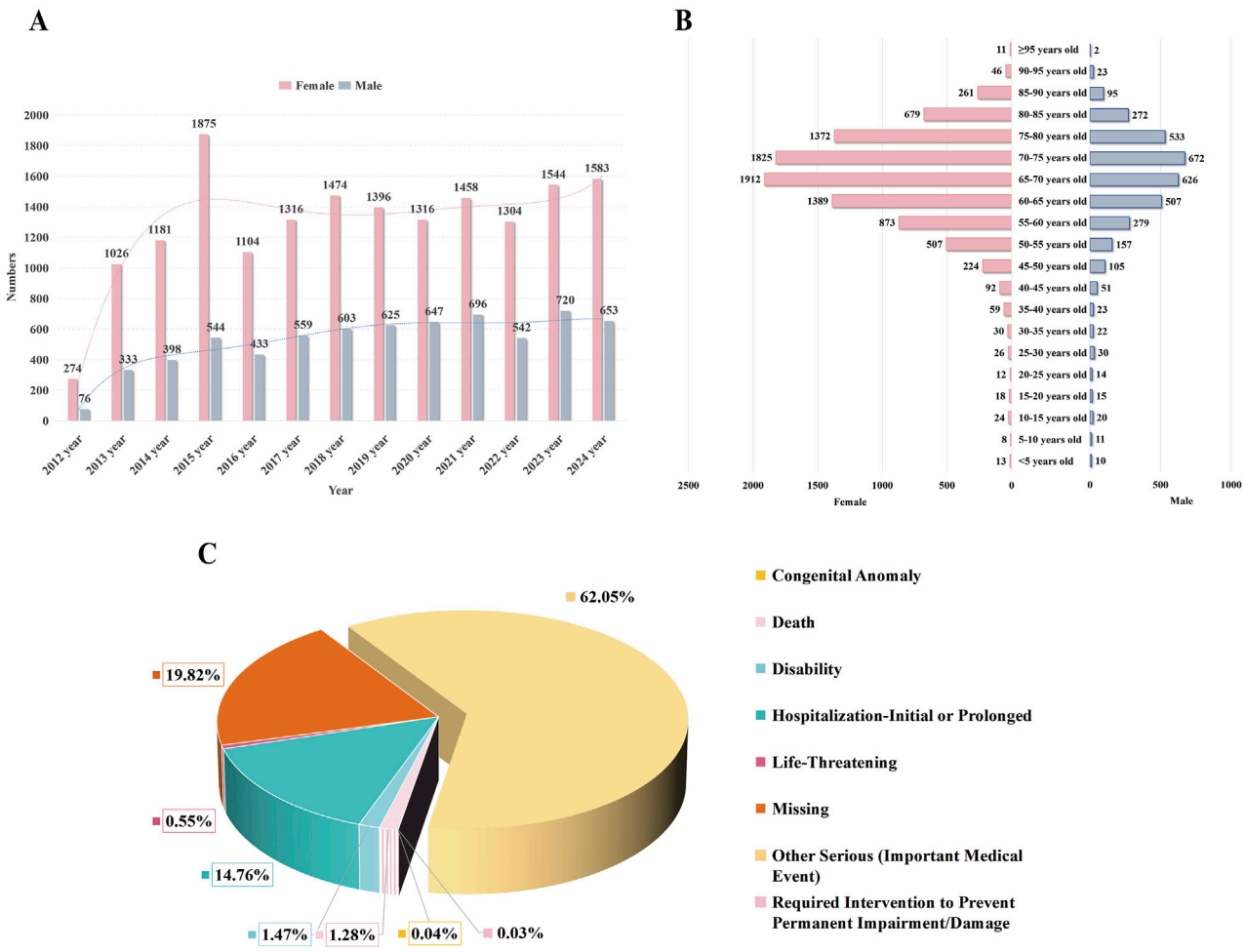


FIGURE 2
Characteristics of reports involved in drug-indued cataracts from the FAERS database. Notes: **(A)** displays a timeline chart showing the distribution of reported adverse events of cataracts over time. **(B)** depicts a pyramid chart of age distribution among patients reporting adverse events of cataracts, categorized by gender. **(C)** illustrates a pie chart representing the distribution of outcomes among patients experiencing adverse events of cataracts.

Onset time

This study also analyzed the time interval between medication use and cataract onset. The results indicated a median onset time of 449 days (interquartile range: 150–901 days) for drug-induced cataracts, with approximately 75% of cases occurring within 747 days after medication initiation (Figure 8).

Discussion

Drug-induced cataracts are increasingly recognized as significant adverse events associated with various medications (Zhao et al., 2021). In recent years, a growing number of case reports have documented drug-induced cataracts, correlating with the expanding use of medications and ongoing drug development. This trend has raised awareness of drug-induced cataracts; however, public awareness of ocular adverse drug reactions remains insufficient.

This study systematically reviewed anonymized cataract case reports from FAERS, comprehensively identifying medications potentially associated with cataract risk. By leveraging this extensive real-world database, disproportionality analysis, univariate analysis, and multivariate regression analysis identified 15 drugs as independent risk factors for drug-induced cataracts, thereby providing critical insights into medication-related cataract risk.

Notably, the proportion of female patients (71.16%) was significantly higher than that of male patients, possibly reflecting longer female life expectancy, estrogen fluctuations during menopause, and greater visual burden in daily life (Zou et al., 2024). Consequently, particular attention should be given to females when assessing cataract risk associated with medication use.

The 15 identified medications were classified into eight drug categories, with ophthalmic drugs being the first group, represented by Bimatoprost. Bimatoprost, a prostaglandin analog commonly prescribed for ocular conditions, may induce cataracts by increasing melanocyte activity in iris melanocytes, leading to iris hyperpigmentation (reported in approximately 7%–16% of patients). This pigmentation alteration may indirectly contribute to cataract formation by modifying the eye lens microenvironment, promoting oxidative stress, and facilitating free radical accumulation. Additionally,

TABLE 1 Baseline data of cataracts patients reported in the FAERS database.

	Variables	Value
	Age (year)	66.92 ± 11.95
	Weight (kg)	72.44 ± 22.53
Gender		
	Female	16,851 (71.16%)
	Male	6,829 (28.84%)
Outcome		
	Congenital Anomaly	9 (0.04%)
	Death	302 (1.28%)
	Disability	348 (1.47%)
	Hospitalization-Initial or Prolonged	3,496 (14.76%)
	Life-Threatening	130 (0.55%)
	Missing	4,693 (19.82%)
	Other Serious (Important Medical Event)	14,694 (62.05%)
	Required Intervention to Prevent Permanent Impairment/Damage	8 (0.03%)
Country		
	United States	23,680 (100%)

Notes: Continuous numerical variables are expressed as mean ± standard deviation, and categorical variables are presented as n (%).

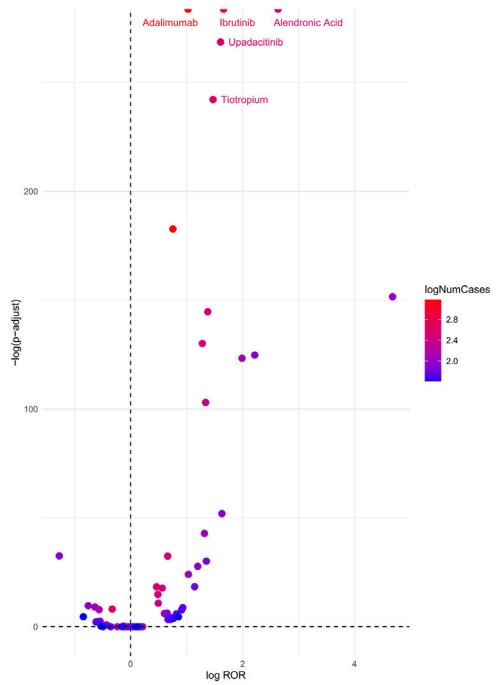


FIGURE 3
Cataracts-related drug volcano plots. Notes: ROR, reporting odds ratio; P-adjust, p-value after Bonferroni correction.

prostaglandin analogs may contribute to cataractogenesis through altered eye lens microenvironments or increased exposure to free radicals. Future research should integrate molecular investigations (such as apoptosis pathways in eye lens epithelial cells) with epidemiological studies to elucidate the underlying pathogenic mechanisms and identify high-risk populations.

Atorvastatin, a widely used 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitor, effectively reduces cholesterol synthesis and lowers low-density lipoprotein cholesterol (LDL-C) levels, thereby decreasing the risk of atherosclerosis and associated cardiovascular events. It is extensively prescribed for hypercholesterolemia, coronary heart disease, and both primary and secondary prevention of cardiovascular diseases (Liao and Laufs, 2005). Two pharmacovigilance studies have previously identified a significant association between statin use and an increased risk of cataracts (Erie et al., 2016; Klein et al., 2006). Consistent with these findings, our multivariate logistic regression analysis indicated that atorvastatin may be an independent risk factor for drug-induced cataracts (Odds Ratio (OR) [95% CI]: 12 [7.6–18]). However, existing research is not entirely consistent. Some studies have reported conflicting results, suggesting that statins may exert potential protective effects against cataracts, diabetic retinopathy, diabetic retinopathy progression, and non-infectious uveitis (Wagner and Rein, 2013; Kurinami et al., 2018). Given these contradictory findings, further research—ideally through large-scale randomized controlled trials (RCTs)—is necessary to clarify the relationship between statins and cataracts.

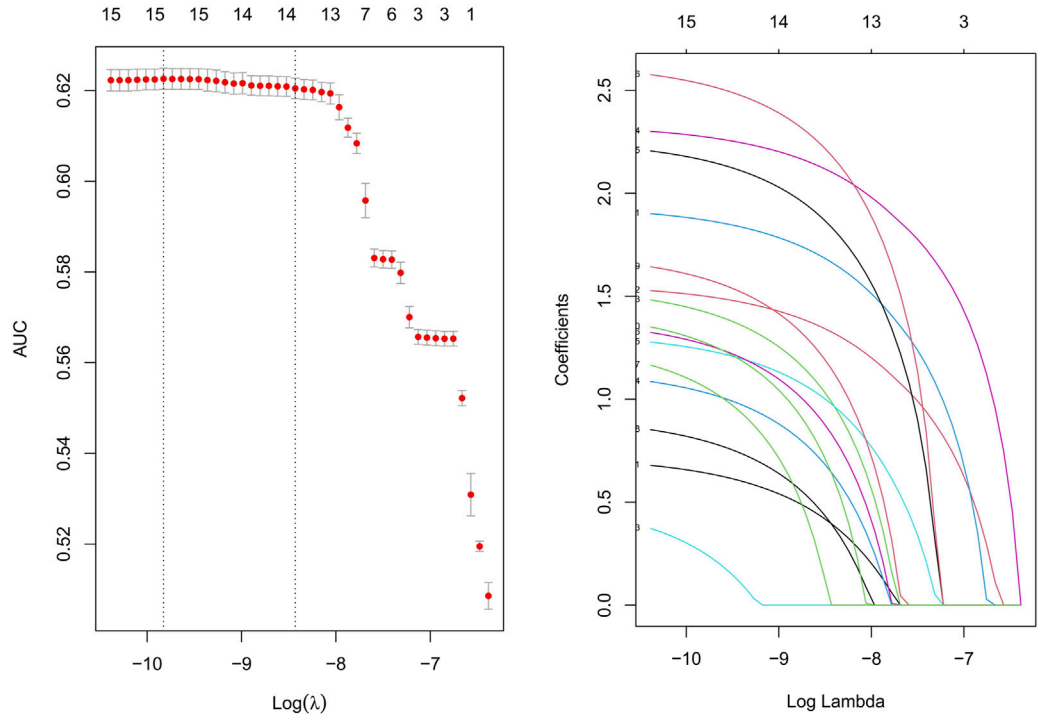


FIGURE 4
Results of the LASSO regression analysis. Note: LASSO, least absolute shrinkage and selection operator.

Zoledronic acid is a potent bisphosphonate primarily used to inhibit osteoclast activity, thereby reducing bone resorption. It is commonly prescribed for osteoporosis, bone metastases from cancer, and hypercalcemia (Major et al., 2001; Black et al., 2007). A study based on Optum and MarketScan databases reported a potential association between zoledronic acid treatment and an increased risk of cataracts (ROR [95% CI]: 12 [7.6–18]). The proposed mechanisms suggest that zoledronic acid may impair eye lens epithelial cell function by inducing local inflammation and protein denaturation, ultimately contributing to cataract formation (Lee et al., 2020). However, clinical evidence remains limited. Further research is warranted to elucidate the underlying mechanisms and explore the epidemiology of bisphosphonate-related cataracts.

Esomeprazole, a widely used proton pump inhibitor (PPI) for gastroesophageal reflux disease (GERD) and peptic ulcers, reduces gastric acid secretion by inhibiting H^+/K^+-ATPase activity (Qi et al., 2015). While its product labeling mentions occasional blurred vision as a potential adverse effect, comprehensive ophthalmic side effects remain poorly characterized. Our analysis suggests that esomeprazole may be an independent risk factor for cataracts. However, given the limited current evidence, further large-scale RCTs are warranted to elucidate this potential risk and assess its clinical implications comprehensively.

Atorvastatin, a widely used HMG-CoA reductase inhibitor, effectively inhibits cholesterol synthesis and lowers LDL-C levels, thereby reducing cardiovascular risk (Liao and Laufs, 2005). Two pharmacovigilance studies have previously reported a significant association between statin use and an increased risk of cataracts (Erie et al., 2016; Klein et al., 2006). Consistently, our multivariate logistic regression analysis identified atorvastatin as an independent risk factor for drug-induced cataracts (OR [95% CI]: 12 [7.6–18]). However, existing studies have yielded conflicting results regarding the relationship between statins and cataracts, with some evidence suggesting potential ocular protective effects against diabetic retinopathy, uveitis, and other ocular conditions (Wagner and Rein, 2013; Kurinami et al., 2018). Therefore, further RCTs are warranted to clarify this association.

Risankizumab, a monoclonal antibody targeting interleukin-23A (IL-23A), is primarily indicated for the treatment of plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis (Gordon et al., 2018). Previous pharmacovigilance studies have identified cataracts as a reported adverse reaction. Consistently, our multivariate logistic regression analysis suggested that Risankizumab may be an independent risk factor for cataracts. However, the precise pathogenic mechanisms remain unclear and warrant further investigation.

Interferon Beta-1A, indicated for multiple sclerosis, was also identified as potentially associated with drug-induced cataracts. Given the limited availability of direct clinical studies or case reports, further ocular monitoring in patients receiving Interferon Beta-1A is recommended to facilitate early detection and management of ocular complications.

Adalimumab, commonly used for the treatment of severe uveitis associated with juvenile idiopathic arthritis, has been reported to contribute to cataracts and glaucoma, leading to significant visual impairment (Lu et al., 2021; Fleischmann et al., 2022). However, in our study, the cataract signal associated with Adalimumab may represent a false positive, potentially influenced by underlying diseases or inadequate treatment responses. Therefore, further research is necessary to establish a definitive causal relationship between Adalimumab and cataracts.

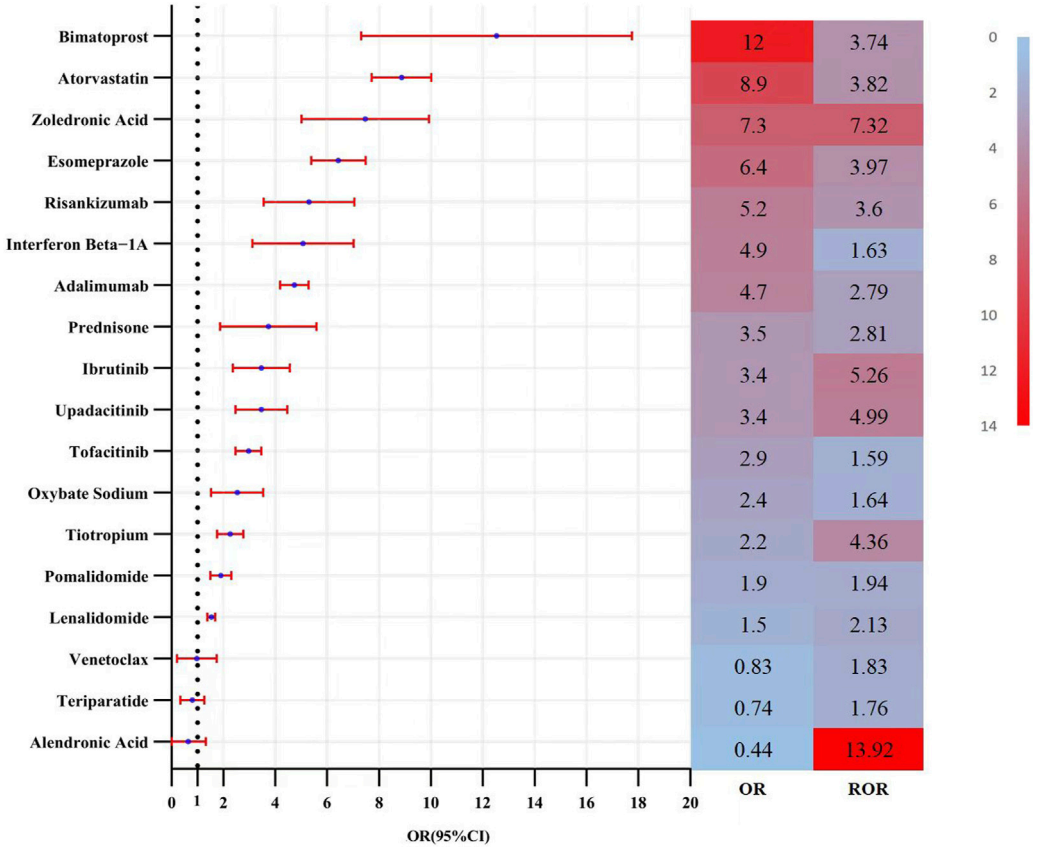


FIGURE 5
Results of the multi-factor logistic regression analysis and ROR value. Note: CI, confidence interval; OR, odds ratio; P-adjust, p-value after bonferroni correction; P-adjust <0.01, statistically significant. ROR, Reporting Odds Ratio.

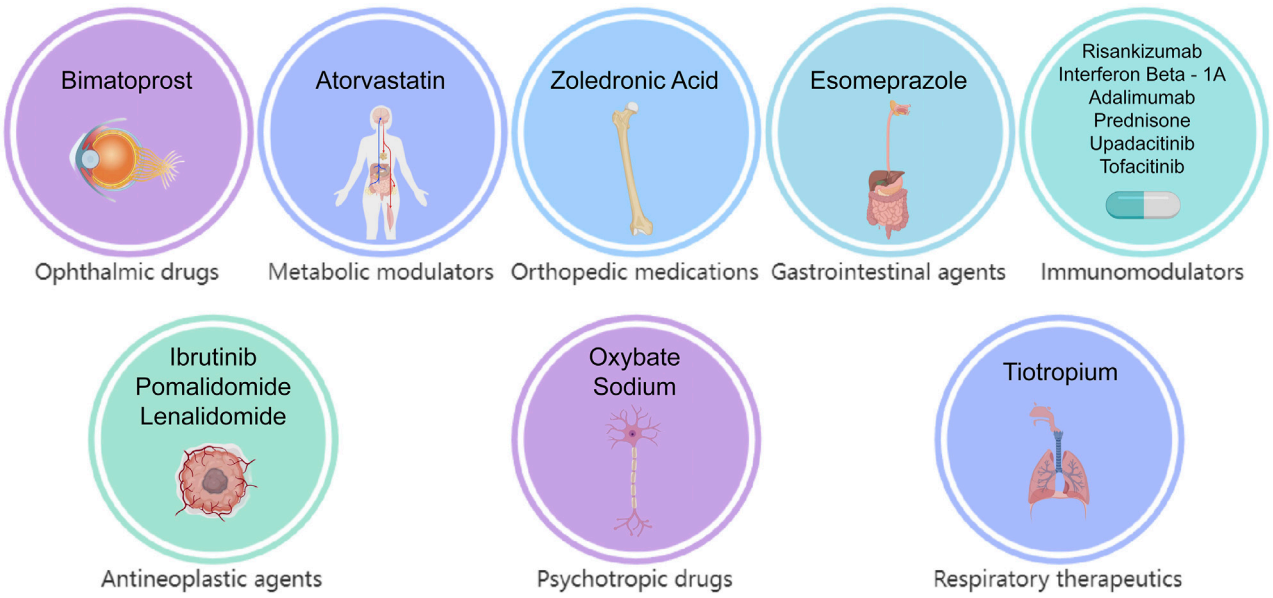


FIGURE 6
The identification and classification of drugs associated with cataracts.

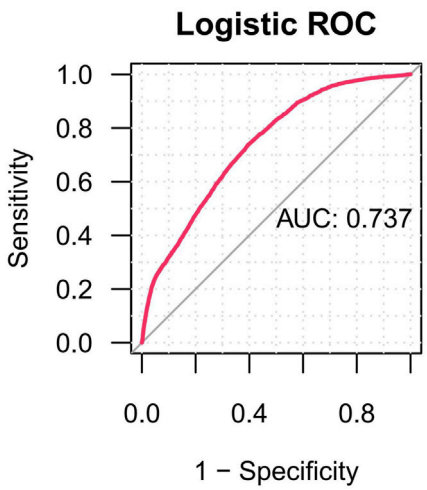


FIGURE 7
The ROC curves of drug-related cataracts risk factors. Notes: ROC, receiver operating characteristic; AUC, area under curve.

Glucocorticoids have long been associated with cataract development, first reported by Wang (Wang et al., 2009). Since then, extensive evidence has demonstrated that both systemic and topical glucocorticoids, such as dexamethasone, prednisone, and hydrocortisone, significantly increase cataract risk (Black et al., 2016). Posterior subcapsular cataract (PSC) is the predominant clinical presentation of glucocorticoid-induced cataracts, distinguishing it from age-related and other cataract types. The underlying mechanism likely involves disruption of eye lens epithelial cell function, specifically interfering with proliferation, differentiation, migration, and apoptotic processes, ultimately leading to eye lens protein denaturation and opacity formation (Mishra et al., 2023).

Upadacitinib and Tofacitinib are selective Janus kinase (JAK) inhibitors that exert anti-inflammatory and immunomodulatory effects by inhibiting the JAK/signal transducer and activator of transcription (STAT) signaling pathway (Loftus et al., 2023). Recent pharmacovigilance studies have identified ocular adverse events, including cataracts, macular holes, and scleritis, as potential new safety signals not previously documented in Upadacitinib's labeling (Wu et al., 2023). This finding aligns with our results, suggesting that the JAK/STAT pathway may contribute to cataract formation by influencing eye lens epithelial cell proliferation. Currently, no dedicated research has explored the relationship between Tofacitinib and cataracts; therefore, close ophthalmic monitoring in clinical practice is recommended.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, irreversibly binds to BTK, thereby suppressing B-cell proliferation and survival (Li et al., 2021). In the RESONATE phase III multicenter trial, among approximately 400 patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) receiving Ibrutinib, 10% reported blurred vision, and 3% developed cataracts. Researchers have cautioned that the risk of ocular adverse events may increase with prolonged treatment (Li et al., 2021). Additionally, a case report suggested that Ibrutinib may penetrate the blood-aqueous barrier, altering the ocular microenvironment and causing platelet dysfunction and impaired fibrinolysis, potentially leading to anterior chamber fibrinoid syndrome following cataract surgery (Wang et al., 2025). Further prospective studies and molecular investigations are warranted to clarify the causal relationship

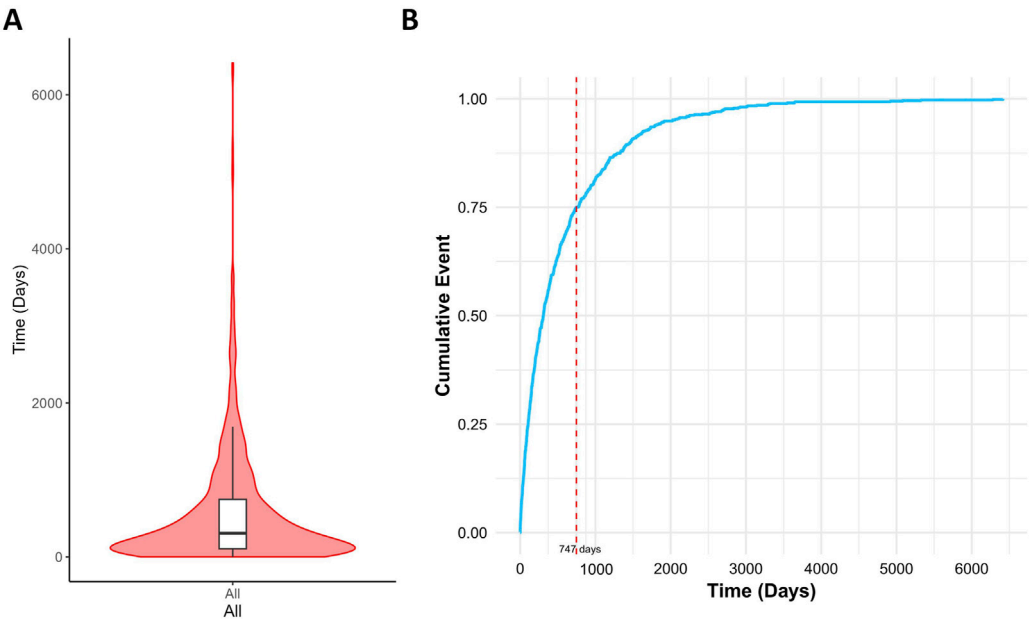


FIGURE 8
Time interval between drug intake and the onset of drug-related cataracts. Notes: **(A)** Violin plot of time to drug-related cataracts occurrence; **(B)** Cumulative incidence of drug-related cataracts.

between Ibrutinib and cataracts. Moreover, predictive risk models should be developed to optimize patient management.

Pomalidomide and Lenalidomide are primarily used for the treatment of relapsed or refractory multiple myeloma (Dimopoulos et al., 2021). Although no direct association between Pomalidomide and cataracts has been reported, a prospective study involving vitreoretinal lymphoma patients receiving intravitreal methotrexate (MTX), Rituximab, and Lenalidomide (R^2 regimen) as maintenance therapy identified notable ocular toxicities, including cataracts, suggesting a potential increase in ocular toxicity risk (Zhang et al., 2021). Our findings further support the hypothesis that both drugs may independently contribute to cataract risk. Future clinical research is warranted to elucidate their pathogenic mechanisms and assess cataract risk, aiming to optimize treatment strategies and ocular monitoring.

Sodium Oxybate, a central nervous system depressant and the sodium salt of γ-hydroxybutyric acid (GHB), is primarily used to treat narcolepsy-related symptoms, including cataplexy and disrupted nighttime sleep. Its mechanism of action involves modulating gamma-aminobutyric acid (GABA) receptor activity to enhance sleep quality and regulate the circadian rhythm (Avidan and Kushida, 2020). Currently, no studies have reported an association between Sodium Oxybate and ocular adverse events. However, our findings suggest a potential cataractogenic risk, highlighting the need for future ophthalmic safety monitoring and large-scale clinical studies to elucidate the associated risks and underlying mechanisms.

Tiotropium, a long-acting anticholinergic agent, is widely used for the long-term management of chronic obstructive pulmonary disease (COPD) and asthma (Blair, 2019). Currently, limited evidence directly links Tiotropium to cataractogenesis. Cataract formation is typically influenced by multiple factors, including aging, UV exposure, diabetes, and prolonged corticosteroid use (Yong et al., 2022). Tiotropium exerts its effects by antagonizing M3 cholinergic receptors, thereby reducing airway smooth muscle constriction. However, this mechanism does not directly impact eye lens metabolism or structure. Although no conclusive evidence currently supports a causal relationship, regular ophthalmologic examinations during prolonged Tiotropium treatment are advisable. Future large-scale longitudinal studies are needed to further investigate the potential cataractogenic risk and underlying mechanisms of Tiotropium, aiming to optimize drug safety evaluations and clinical management strategies.

This study identified a median onset time of drug-induced cataracts as 449 days (interquartile range: 150–901 days), with over 75% of cases occurring within 747 days following drug initiation. This finding suggests a significant latency period for drug-induced cataracts, accompanied by considerable inter-individual variability.

Previous studies support this observation. For instance, Cumming et al. demonstrated that prolonged inhaled glucocorticoid use is associated with an increased cataract risk, typically requiring months to years of cumulative exposure (Wang et al., 2009). Similarly, studies by Klein et al. and Smeeth et al. highlighted prolonged intervals between drug exposure and cataract onset, ranging from months to years (Smeeth et al., 2003). Collectively, these findings align with our results, indicating a slow progression and high variability in the onset timing of drug-related cataracts. Consequently, patients undergoing long-term treatment with high-risk medications require continuous ophthalmologic monitoring to facilitate early detection and intervention, ultimately reducing the risk of vision impairment associated with drug-induced cataracts.

Nevertheless, this study has several limitations. First, the FAERS relies on voluntary submissions from healthcare professionals, patients, and pharmaceutical companies, which may lead to underreporting or reporting bias. Second, as FAERS was not specifically designed to establish causality, its case-report-based data lack standardized follow-up and control groups, limiting the ability to draw direct causal inferences between drug exposure and cataract development (Li et al., 2025a). This limitation is a common challenge in pharmacovigilance and observational cohort studies. Additionally, FAERS often contains missing information, including specific drug dosages, patient comorbidities, cataract onset timing, and other critical clinical variables, which may compromise analytical accuracy (Li et al., 2025b). Furthermore, FAERS does not specify cataract subtypes (e.g., cortical, nuclear, or posterior subcapsular cataracts), reducing the specificity of study outcomes. Therefore, caution is warranted when interpreting data-mining results, and conclusions should be corroborated through comprehensive evidence-based assessments to ensure clinical reliability and applicability.

Conclusion

This study utilized FAERS data to compile a comprehensive list of drugs potentially associated with drug-induced cataracts. The findings provide valuable insights for the early identification of drug-related cataracts and serve as a reference for future research on the pathogenesis of drug-induced cataracts. However, all reported findings require further validation through additional clinical studies and animal experiments.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

XL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. SW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review and editing. Z-JZ: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Formal Analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft. ZL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review and editing. JT: Funding acquisition, Project administration, Resources, Supervision, Writing – original draft,

Writing – review and editing, Conceptualization, Data curation, Formal Analysis. TT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. The study described was supported by grants from a Key Project and a Lab Project at Chongqing Three Gorges Medical College, China (SYS20210021), and a project supported by the Chongqing Education Commission Science and Technology Research Program (KJQN202302715).

Acknowledgments

The authors would like to thank all reviewers for their valuable comments.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1498191/full#supplementary-material

References

Avidan, A. Y., and Kushida, C. A. (2020). The sodium in sodium oxybate: is there cause for concern? *Sleep. Med.* 75, 497–501. doi:10.1016/j.sleep.2020.09.017

Black, D. M., Delmas, P. D., Eastell, R., Reid, I. R., Boonen, S., Cauley, J. A., et al. (2007). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* 356, 1809–1822. doi:10.1056/NEJMoa067312

Black, R. J., Hill, C. L., Lester, S., and Dixon, W. G. (2016). The association between systemic glucocorticoid use and the risk of cataract and glaucoma in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLoS One* 11, e0166468. doi:10.1371/journal.pone.0166468

Blair, H. A. (2019). Tiotropium/olodaterol: a review in COPD. *Drugs* 79, 997–1008. doi:10.1007/s40265-019-01133-w

Congdon, N. G. (2001). Prevention strategies for age related cataract: present limitations and future possibilities. *Br. J. Ophthalmol.* 85, 516–520. doi:10.1136/bjo.85.5.516

Dimopoulos, M. A., Terpos, E., Boccadoro, M., Delimpasi, S., Beksac, M., Katodritou, E., et al. (2021). Daratumumab plus Pomalidomide and dexamethasone versus Pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 22, 801–812. doi:10.1016/S1470-2045(21)00128-5

Erie, J. C., Pueringer, M. R., Brue, S. M., Chamberlain, A. M., and Hodge, D. O. (2016). Statin use and incident cataract surgery: a case-control study. *Ophthalmic Epidemiol.* 23, 40–45. doi:10.3109/09286586.2015.1077258

Fang, S.-C., Huang, C.-Y., Liao, D.-L., Hsu, C.-C., and Shao, Y.-H. J. (2019). Associations among antipsychotics, metabolism-related diseases, and cataracts in patients with schizophrenia: a retrospective cohort study. *Schizophr. Res.* 212, 150–156. doi:10.1016/j.schres.2019.07.049

Fleischmann, R., Mysler, E., Bessette, L., Peterfy, C. G., Durez, P., Tanaka, Y., et al. (2022). Long-term safety and efficacy of Upadacitinib or Adalimumab in patients with rheumatoid arthritis: results through 3 Years from the SELECT-COMPARE study. *RMD Open* 8, e002012. doi:10.1136/rmdopen-2021-002012

Fusaroli, M., Salvo, F., Begaud, B., AlShammari, T. M., Bate, A., Battini, V., et al. (2024). The REporting of a disproportionality analysis for DrUg safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration. *Drug Saf.* 47, 585–599. doi:10.1007/s40264-024-01423-7

GBD 2019 Blindness and Vision Impairment CollaboratorsVision Loss Expert Group of the Global Burden of Disease Study (2021). Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob. Health* 9, e144–e160. doi:10.1016/S2214-109X(20)30489-7

Gordon, K. B., Strober, B., Lebwohl, M., Augustin, M., Blauvelt, A., Poulin, Y., et al. (2018). Efficacy and safety of Risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 392, 650–661. doi:10.1016/S0140-6736(18)31713-6

Hashemi, H., Hatef, E., Fotouhi, A., Feizzadeh, A., and Mohammad, K. (2009). The prevalence of lens opacities in tehran: the tehran eye study. *Ophthalmic Epidemiol.* 16, 187–192. doi:10.1080/09286580902863031

Klein, B. E. K., Klein, R., Lee, K. E., and Grady, L. M. (2006). Statin use and incident nuclear cataract. *JAMA* 295, 2752–2758. doi:10.1001/jama.295.23.2752

Kurinami, N., Sugiyama, S., Ijima, H., Yoshida, A., Hieshima, K., Miyamoto, F., et al. (2018). Clinical usefulness of the body muscle-to-fat ratio for screening obstructive sleep apnea syndrome in patients with inadequately controlled type 2 diabetes mellitus. *Diabetes Res. Clin. Pract.* 143, 134–139. doi:10.1016/j.diabres.2018.07.008

Lee, H., Jin, Y., Roh, M., Tsacogianis, T. N., Park, S., Choi, N.-K., et al. (2020). Risk of cataract surgery and age-related macular degeneration after initiation of denosumab vs zoledronic acid for osteoporosis: a multi-database cohort study. *Drugs Aging* 37, 311–320. doi:10.1007/s40266-020-00745-2

Li, W., Ali, T., He, K., Liu, Z., Shah, F. A., Ren, Q., et al. (2021). Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. *Brain Behav. Immun.* 92, 10–24. doi:10.1016/j.bbi.2020.11.008

Li, X., Sun, Y.-Q., Huang, Q.-L., Zhang, Z.-J., Shi, L.-Q., Tang, J.-F., et al. (2025a). Drug-related macular edema: a real-world FDA adverse event reporting system database study. *BMC Pharmacol. Toxicol.* 26, 23. doi:10.1186/s40360-025-00856-9

Li, X., Wu, S.-N., Zhang, S.-Q., Zhang, Z.-J., Wang, M.-Y., Chen, C.-T., et al. (2025b). Real-world analysis of medications inducing meibomian gland dysfunction: based on the FDA adverse event reporting system database. *Expert Opin. Drug Saf.*, 1–9. doi:10.1080/14740338.2024.2446430

Liao, J. K., and Laufs, U. (2005). Pleiotropic effects of statins. *Annu. Rev. Pharmacol. Toxicol.* 45, 89–118. doi:10.1146/annurev.pharmtox.45.120403.095748

Loftus, E. V., Panés, J., Lacerda, A. P., Peyrin-Biroulet, L., D'Haens, G., Panaccione, R., et al. (2023). Upadacitinib induction and maintenance therapy for Crohn's disease. *N. Engl. J. Med.* 388, 1966–1980. doi:10.1056/NEJMoa2212728

Lu, X., Hu, R., Peng, L., Liu, M., and Sun, Z. (2021). Efficacy and safety of Adalimumab biosimilars: current critical clinical data in rheumatoid arthritis. *Front. Immunol.* 12, 638444. doi:10.3389/fimmu.2021.638444

Mach, F., Ray, K. K., Wiklund, O., Corsini, A., Catapano, A. L., Bruckert, E., et al. (2018). Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur. Heart J.* 39, 2526–2539. doi:10.1093/eurheartj/ehy182

Major, P., Lortholary, A., Hon, J., Abdi, E., Mills, G., Menssen, H. D., et al. (2001). Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J. Clin. Oncol.* 19, 558–567. doi:10.1200/JCO.2001.19.2.558

Mishra, D., Kashyap, A., Srivastav, T., Yadav, A., Pandey, S., Majhi, M. M., et al. (2023). Enzymatic and biochemical properties of lens in age-related cataract versus diabetic cataract: a narrative review. *Indian J. Ophthalmol.* 71, 2379–2384. doi:10.4103/ijo.IJO_1784_22

Qi, Q., Wang, R., Liu, L., Zhao, F., and Wang, S. (2015). Comparative effectiveness and tolerability of esomeprazole and omeprazole in gastro-esophageal reflux disease: a systematic review and meta-analysis. *Int. J. Clin. Pharmacol. Ther.* 53, 803–810. doi:10.5414/CP202396

Smeeth, L., Hubbard, R., and Fletcher, A. E. (2003). Cataract and the use of statins: a case-control study. *QJM* 96, 337–343. doi:10.1093/qjmed/hcg064

Szostakiewicz-Grabek, B., Juszkiewicz-Borowiec, M., and Krasowska, D. (2016). The effect of drugs used in treatment of skin disorders on visual system. *Pol. Merkur Lek.* 40, 269–272.

Tewari, D., Samoilă, O., Gocan, D., Mocan, A., Moldovan, C., Devkota, H. P., et al. (2019). Medicinal plants and natural products used in cataract management. *Front. Pharmacol.* 10, 466. doi:10.3389/fphar.2019.00466

Thakur, S. K., and Panda, A. (2000). Susruta's role in the development of cataract surgery. *Surv. Ophthalmol.* 44, 541–542. doi:10.1016/s0039-6257(00)00128-4

Uboweja, A., Malhotra, S., and Pandhi, P. (2006). Effect of inhaled corticosteroids on risk of development of cataract: a meta-analysis. *Fundam. Clin. Pharmacol.* 20, 305–309. doi:10.1111/j.1472-8206.2006.00397.x

Wagner, L. D., and Rein, D. B. (2013). Attributes associated with eye care use in the United States: a meta-analysis. *Ophthalmology* 120, 1497–1501. doi:10.1016/j.ophtha.2012.12.030

Wang, J. J., Rochtchina, E., Tan, A. G., Cumming, R. G., Leeder, S. R., and Mitchell, P. (2009). Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 116, 652–657. doi:10.1016/j.ophtha.2008.12.001

Wang, S., Wang, X., Ding, J., Zhang, X., Zhu, H., Fan, Y., et al. (2025). Disproportionality analysis of upadacitinib-related adverse events in inflammatory bowel disease using the FDA adverse event reporting system. *Front. Pharmacol.* 16, 1436183. doi:10.3389/fphar.2025.1436183

Wu, X.-P., Lu, X.-K., Wang, Z.-T., Huang, L., Cai, R.-W., Yu, H.-M., et al. (2023). Post-marketing safety concerns with Upadacitinib: a disproportionality analysis of the FDA adverse event reporting system. *Expert Opin. Drug Saf.* 22, 975–984. doi:10.1080/14740338.2023.2223952

Yong, G.-Y., Mohamed-Noor, J., Salowi, M. A., Adnan, T. H., and Zahari, M. (2022). Risk factors affecting cataract surgery outcome: the Malaysian cataract surgery registry. *PLoS One* 17, e0274939. doi:10.1371/journal.pone.0274939

Zhang, Y., Zhang, X., Zou, D., Yin, J., Zhang, L., Wang, X., et al. (2021). Lenalidomide and Rituximab regimen combined with intravitreal methotrexate followed by Lenalidomide maintenance for primary vitreoretinal lymphoma: a prospective phase II study. *Front. Oncol.* 11, 701507. doi:10.3389/fonc.2021.701507

Zhao, L., Wang, H., and Du, X. (2021). The therapeutic use of quercetin in ophthalmology: recent applications. *Biomed. Pharmacother.* 137, 111371. doi:10.1016/j.biopha.2021.111371

Zou, M., Chen, A., Liu, Z., Jin, L., Zheng, D., Congdon, N., et al. (2024). The burden, causes, and determinants of blindness and vision impairment in asia: an analysis of the global burden of disease study. *J. Glob. Health* 14, 04100. doi:10.7189/jogh.14.04100

Glossary

FDA	U.S.Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
ROR	Ratio of Odds Ratios
LASSO	least absolute shrinkage and selection operator
IQR	Interquartile Range
WHO	World Health Organization
READUS-PV	Recommendations for the Evaluation of Adverse Drug Reaction Signals Using Individual Case Safety Reports
MedDRA	Medical Dictionary for Regulatory Activities
PRIMARYID	Primary Identifier
ISRs	Individual Case Safety Reports
CI	Confidence Interval
PostgreSQL	Post-Ingres Structured Query Language
ROC-AUC	Receiver Operating Characteristic - Area Under the Curve
HMG-CoA	3-Hydroxy-3-methylglutaryl-Coenzyme A
LDL-C	Low-Density Lipoprotein Cholesterol
OR	Odds Ratio
RCTs	Randomized Controlled Trials
PPI	Proton Pump Inhibitor
GERD	Gastroesophageal Reflux Disease
IL-23A	Interleukin-23A
PSC	Posterior Subcapsular Cataract
JAK	Janus kinase
STAT	Signal Transducer and Activator of Transcription
BTK	Bruton's Tyrosine Kinase
CLL	Chronic Lymphocytic Leukemia
SLL	Small Lymphocytic Lymphoma
MTX	Methotrexate
GHB	γ-hydroxybutyric acid
GABA	Gamma-Aminobutyric Acid
COPD	Chronic Obstructive Pulmonary Disease.

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 May 2025
DOI 10.3389/fphar.2025.1529342

OPEN ACCESS

EDITED BY
Miao Yan,
Central South University, China

REVIEWED BY
Umamaheswaran Gurusamy,
Nationwide Children's Hospital, United States
Luyang Su,
Hebei General Hospital, China
Mokshal Porwal,
Allegheny Health Network, United States

*CORRESPONDENCE
Sheng Liu,
lslhtcm@163.com
Jin-Zhou Zheng,
zjzhssll@163.com
You-Yang Shi,
syyshutcm@163.com

†These authors have contributed equally to this work

RECEIVED 16 November 2024
ACCEPTED 28 April 2025
PUBLISHED 14 May 2025

CITATION
Wu Y-Y, Huang Q-L, Luo Z-Y, Song X-Y, Shi Y-Y, Zheng J-Z and Liu S (2025) Evaluation of dermatologic adverse events associated with aromatase inhibitors: insights from the FAERS database.
Front. Pharmacol. 16:1529342.
doi: 10.3389/fphar.2025.1529342

Evaluation of dermatologic adverse events associated with aromatase inhibitors: insights from the FAERS database

Yuan-Yuan Wu[1†], Qiong-Lian Huang[1†], Zhan-Yang Luo[2†], Xiao-Yun Song[1], You-Yang Shi[1*], Jin-Zhou Zheng[1*] and Sheng Liu[1*]

[1]Institute of Chinese Traditional Surgery, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2]Shanghai Pudong Hospital, Fudan University Pudong Medical Center, Shanghai, China

Background: This study evaluates the risk of dermatologic adverse events (AEs) associated with aromatase inhibitors (AIs) through an analysis of data from the FDA Adverse Event Reporting System (FAERS).

Methods: FAERS data from Q1 2004 to Q2 2024 were analyzed for dermatologic AEs related to AIs. A disproportionality analysis using reporting odds ratio (ROR) assessed AE risk, and the time to onset of these AEs was examined.

Results: Out of 21,035,995 AE reports, 2,237 involved skin impairment. Sixty-one preferred terms (PTs) presented positive signals, including nail disorders, onychoclasis, and abnormal hair growth in patients on anastrozole, exemestane, or letrozole. The highest associations were with pseudo cellulitis (ROR = 57.73), anhidrosis (ROR = 48.68), and nail toxicity (ROR = 38.40). Strong associations were observed for anastrozole (ROR = 1.07, 95% confidence interval: 1.03–1.11) and exemestane (ROR = 1.1, 95% CI: 1.04–1.16), but not for letrozole. Eleven dermatologic PTs had onset times under 50 days, with the earliest at 2 days; the latest, skin ulcer, appeared at 241.5 days with exemestane.

Conclusion: The findings provide substantial evidence of dermatologic AEs associated with AIs, particularly anastrozole and exemestane, emphasizing the importance of dermatologic monitoring during AI therapy and the need for further research into AI-induced dermatologic AEs.

KEYWORDS

aromatase inhibitors, dermatologic adverse events, FDA adverse event reporting system, disproportionality analysis, real-world

1 Introduction

Aromatase, present in both gonadal and extra-gonadal tissues, catalyzes the conversion of testosterone to estrogens (Stocco, 2012; Kharb et al., 2020). Excessive estrogen levels have been implicated in various diseases, notably contributing to the high malignancy rate of breast cancer (BC) in postmenopausal women (Diamond et al., 2015; Patel, 2017; Rižner and Romano, 2023). Consequently, inhibiting estrogen synthesis or blocking estrogenic activity is a key strategy in BC treatment, underlying the development of aromatase inhibitors (AIs) (Kharb et al., 2020). AIs

are a class of drugs that target the aromatase enzyme, which is responsible for converting androgens to estrogens. AIs have evolved through three generations, each improving upon the limitations of the previous. First-generation AIs, such as aminoglutethimide, were introduced in the 1970s but lacked selectivity and specificity (Buzdar et al., 2001). Second-generation AIs, like fadrozole and formestane, offered more selectivity but still had limitations in targeting aromatase efficiently (Dellapasqua and Colleoni, 2010). The third-generation AIs, including exemestane, anastrozole and letrozole, were developed to address these shortcomings, offering greater potency and specificity, and have shown efficacy in high-risk BC patients (Kharb et al., 2020). For instance, two clinical trials involving 5,738 patients demonstrated that AIs moderately reduced distant recurrences in premenopausal BC patients, leading to improved progression-free survival (PFS) across a broad population of BC patients (Francis et al., 2018; Robertson et al., 2021). However, adverse events (AEs) associated with AIs, such as cardiovascular events, dizziness, dyslipidemia, fatigue, headache, hot flushes, joint pain, muscle pain, nausea, osteoporosis, sweating, and vaginal dryness, pose significant clinical challenges, particularly for postmenopausal BC patients (Zhang et al., 2024), thus impacting the optimal use of AIs in BC therapy. Increasingly, attention has turned to the frequent occurrence of AIs' adverse effects.

Among the AEs associated with AIs, dermatologic reactions are particularly prevalent. For example, erythematous patches, papules, and plaques have been reported (with a median onset of 2 months) in an estrogen- and progesterone-receptor-positive BC patient receiving anastrozole (Santoro et al., 2011). Among the AEs associated with AIs, dermatologic reactions are particularly prevalent. For example, erythematous patches, papules, and plaques have been reported in an estrogen and progesterone receptor-positive BC patient receiving anastrozole, with a median onset of 2 months (Sonke et al., 2018). In an international, multicenter, randomized, double-blind, placebo-controlled phase III trial with 720 BC patients receiving exemestane, rash was the second most common AE, with other skin-related reactions also reported (Pritchard et al., 2013). These findings underscore growing concerns regarding the dermatologic safety of AIs.

Given the confirmed association between dermatologic AEs and AIs such as anastrozole, exemestane, and letrozole, it is essential to clarify the relationship between specific AI agents and dermatologic AEs. The FDA Adverse Event Reporting System (FAERS), a global spontaneous reporting system, provides extensive real-world data to identify AE risk signals (Gu et al., 2023). In this chapter, we analyze standardized FAERS data to assess the potential risk of dermatologic toxicity linked to key AI agents, aiming to inform safer options for BC therapy.

Abbreviations: BC, breast cancer; AIs, aromatase inhibitors; PFS, progression-free survival; AE, adverse event; FAERS, FDA Adverse Event Reporting System; SOC, system organ class; ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayes geometric mean; BCPNN, Bayesian confidence propagation neural network; TTO, time to onset; CI, confidence interval; PT, preferred term; ER, estrogen receptor; EBGM05, the lower limit of 95% CI of EBGM. IC, information component; IC025, the lower limit of 95%CI of the IC; $\chi 2$, chi-squared.

2 Materials and methods

2.1 Data source

The FAERS, accessible at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html, is a global pharmacovigilance database that records AEs, medication errors, and product quality complaints (Yang et al., 2022). This system supports the monitoring of post-marketing drugs and therapeutic biological products, helping to identify emerging safety concerns.

The FAERS database contains 21,035,995 raw AE reports from Q1 2004 to Q2 2024. To ensure data accuracy, duplicate records were removed following the FDA-recommended deduplication process (Tregunno et al., 2014). Specifically, among records sharing the same CASEID in the DEMO table, only the report with the most recent FDA_DT was retained. If both CASEID and FDA_DT were identical, the entry with the highest PRIMARYID was preserved. After deduplication, 2,237 dermatologic AE cases related to AI agents. Further analysis focused on anastrozole (n = 725), exemestane (n = 310), and letrozole (n = 1,202). Figure 1 illustrates the deduplication process.

2.2 Data extraction

AE cases linked to three AI agents (anastrozole, exemestane, and letrozole) were identified in the FAERS DRUG file using both generic and FDA-approved brand names. Dermatologic AEs were categorized under the system organ class (SOC) code 10040785 to assess dermatologic toxicities. Additionally, the time to onset (TTO) of dermatologic AEs for each AI was calculated as the interval from treatment initiation to AE occurrence. Cases with an onset time greater than zero days were included in the analysis (Ando et al., 2019). Reports with erroneous dates (e.g., administration date after the event date) or missing dates were excluded from the dataset.

2.3 Signal analysis

Disproportionality analysis, also known as case/non-case analysis, is widely used in pharmacovigilance for detecting drug-adverse reaction signals (Almenoff et al., 2007). This method includes several metrics for cross-validation to enhance the robustness of signal detection and minimize false positives, such as the reporting odds ratio (ROR), proportional reporting ratio (PRR), empirical Bayes geometric mean (EBGM), and Bayesian confidence propagation neural network (BCPNN); Further statistical details are provided in Supplementary Tables S1, S2. In this study, we used ROR, a commonly accepted standard in disproportionality analysis, to identify signals of dermatologic AEs associated with AIs (Evans et al., 2001). Specifically, we calculated RORs (where the lower limit of the 95% confidence interval (CI) > 1 to evaluate the association between AIs and dermatologic AEs in FAERS data. The TTO of AIs-related AEs was calculated as the interval from AI treatment initiation (as recorded in the THER file) to AE occurrence. We modeled changes in AE incidence using the Weibull distribution (Sauzet et al., 2013).

Additionally, we performed a multivariate logistic regression model considering hospitalization, age and body weight as potential factors influencing dermatologic AEs. Incomplete reports were

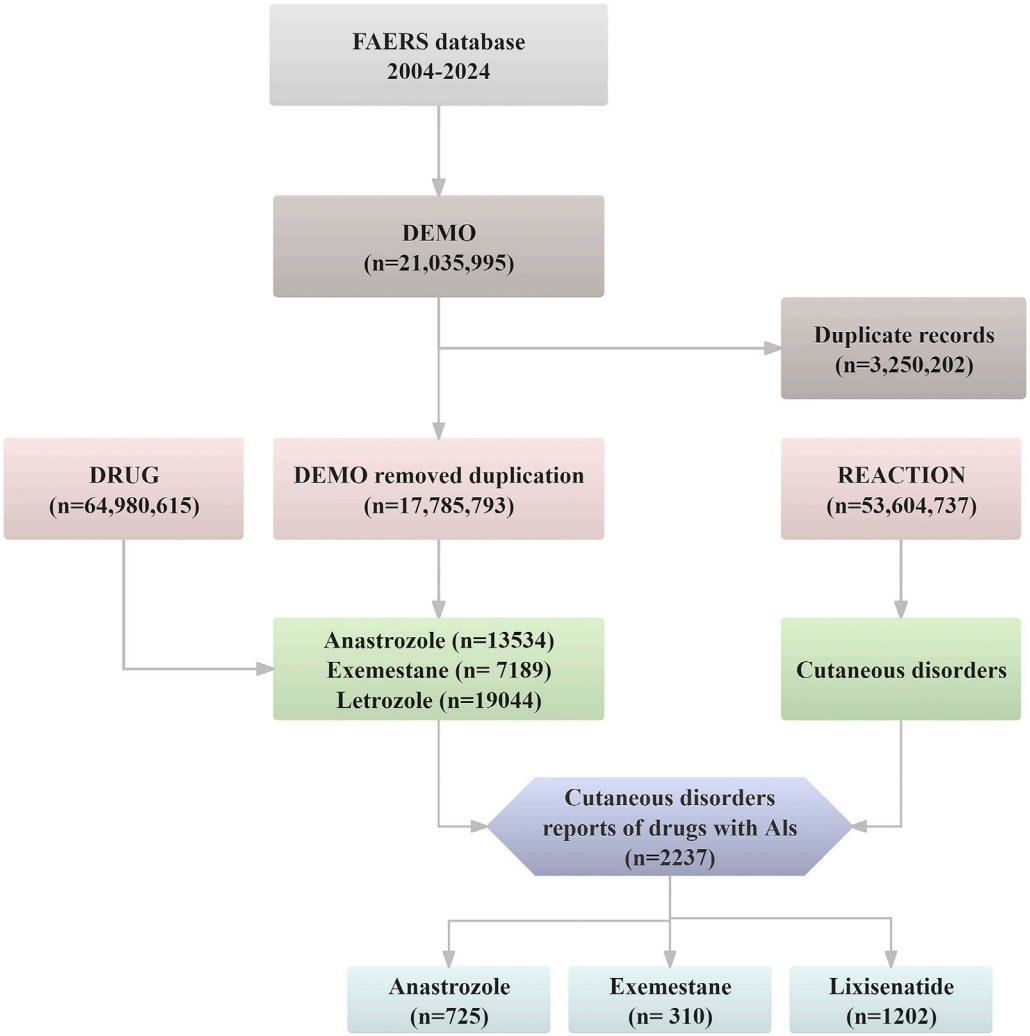


FIGURE 1
The flow diagram of confirming dermatologic AEs elicited by aromatase inhibitors from FAERS database.

excluded, and categorical variables were further analyzed to identify potential risk factors.

Two authors independently conducted all data analyses, with data extraction performed using SQLiteStudio (*version 3.3.3*) and statistical analyses conducted in IBM® SPSS® Statistics (*version 27.0*) and R software (*version 4.3*).

3 Results

3.1 Descriptive analysis

We systematically screened and analyzed the relationship between dermatologic AEs and aromatase inhibitor (AI) agents. Reports of dermatologic AEs associated with anastrozole (n = 725), exemestane (n = 310), and letrozole (n = 1,202) were identified according to their respective market approval dates. Table 1 summarizes the clinical characteristics of dermatologic AEs for each AI. Notably, dermatologic AEs were significantly more common in female patients (n = 2,164, 96.74%) than in male patients (n = 17, 0.76%), with 56 cases (2.50%) of unspecified gender, likely reflecting the use of AIs primarily in postmenopausal women with BC (Francis et al., 2018). Over half of the patients had a body weight below 80 kg (n = 120, 50.07%), with a median weight of 68 kg. The majority of patients were over 65 years of age (n = 759, 33.93%), and only 1.43% were under 18 years. The median age across the cohort was 66 years, consistent across anastrozole, exemestane, and letrozole. Most AE reports were submitted by physicians (n = 981, 43.85%), followed by consumers (n = 511, 22.84%). The United States represented approximately one-third of the reports (n = 585, 26.15%). Among serious outcomes, important medical events were most common (n = 1,102, 49.26%), followed by hospitalization (n = 504, 22.53%).

3.2 Different AI-related signals

Our analysis highlights the occurrence of dermatologic AEs across different AI treatment regimens. As shown in Table 2,

TABLE 1 Characteristics of reports involved dermatologic AEs of AIs from the FAERS database. (from Q1 2004 to Q1 2024).

Characteristics	All (*n* = 2,237)	Anastrozole (*n* = 725)	Exemestane (*n* = 310)	Letrozole (*n* = 1,202)
Gender, *n* (%)				
Female	2,164 (96.74)	700 (96.55)	299 (96.45)	1,165 (96.92)
Male	17 (0.76)	12 (1.66)	0 (0.00)	5 (0.42)
Unknown	56 (2.50)	13 (1.79)	11 (3.55)	32 (2.66)
Weight (kg), *n* (%)				
<80	1,120 (50.07)	362 (49.93)	157 (50.65)	601 (50.00)
80–100	354 (15.82)	100 (13.79)	39 (12.58)	215 (17.89)
>100	37 (1.65)	17 (2.34)	3 (0.97)	17 (1.41)
Unknown	726 (32.45)	246 (33.93)	111 (35.81)	369 (30.70)
Median (kg)	68 (23.04–176)	68 (23.04–176)	69 (25.10–150)	68 (27.78–132)
Age (years), *n* (%)				
<18	32 (1.43)	24 (3.31)	0 (0.00)	8 (0.67)
18–44	60 (2.68)	23 (3.17)	17 (5.48)	20 (1.66)
45–65	616 (27.54)	232 (32.00)	98 (31.61)	286 (23.79)
>65	759 (33.93)	286 (39.45)	119 (38.39)	354 (29.45)
Unknown	770 (34.42)	160 (22.07)	76 (24.52)	534 (44.43)
Median (years)	66 (1–93)	66 (3.33–89)	66 (25–93)	66 (1–93)
Occupation of reporters, *n* (%)				
Consumer (CN)	511 (22.84)	220 (30.34)	85 (27.42)	206 (17.14)
Physician (MD)	981 (43.85)	231 (31.86)	126 (40.65)	624 (51.91)
Pharmacist (PH)	125 (5.59)	41 (5.66)	24 (7.74)	60 (4.99)
Other health-professional (OT)	411 (18.37)	85 (11.72)	58 (18.71)	268 (22.30)
Unknown	209 (9.34)	148 (20.41)	17 (5.48)	44 (3.66)
Reported countries, *n* (%)				
US	585 (26.15)	348 (48.00)	100 (32.26)	137 (11.40)
Non-US	1,596 (71.35)	351 (48.41)	203 (65.48)	1,042 (86.69)
Unknown	56 (2.50)	26 (3.59)	7 (2.26)	23 (1.91)
Outcomes, *n* (%)				
Death (DE)	116 (5.19)	31 (4.28)	10 (3.23)	75 (6.24)
Disability (DS)	77 (3.44)	34 (4.69)	13 (4.19)	30 (2.50)
Hospitalization (HO)	504 (22.53)	115 (15.86)	66 (21.29)	323 (26.87)
Life-threatening (LT)	66 (2.95)	20 (2.76)	11 (3.55)	35 (2.91)
Other serious (Important medical event, OT)	1,102 (49.26)	308 (42.48)	153 (49.35)	641 (53.33)
Required intervention to prevent permanent impairment/damage (RI)	10 (0.45)	9 (1.24)	0 (0.00)	1 (0.08)
Unknown	362 (16.18)	208 (28.69)	57 (18.39)	97 (8.07)

Notes: Continuous numerical variables are expressed as mean ± standard deviation, and categorical variables are presented as n (%).

TABLE 2 Signal strength of reports of dermatologic adverse events related to aromatase inhibitors in FAERS database.

Aromatase inhibitors	The report number	ROR (95%CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC_{025})
Anastrozole	2,986	1.07 (1.03–1.11)	1.07 (12.71)	1.07 (1.03)	0.09 (−1.57)
Exemestane	1,331	1.1 (1.04–1.16)	1.1 (11.7)	1.1 (1.05)	0.13 (−1.53)
Letrozole	3,975	0.94 (0.91–0.98)	0.95 (12.29)	0.95 (0.92)	−0.08 (−1.74)

Note: ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC_{025}, the lower limit of 95%CI, of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI, of EBGM.

both anastrozole (ROR, 1.07; 95% CI, 1.03–1.11) and exemestane (ROR, 1.10; 95% CI, 1.04–1.16) demonstrated significant signals associated with dermatologic AEs, suggesting a strong link with dermatologic toxicity. In contrast, letrozole (ROR, 0.94; 95% CI, 0.91–0.98) showed no positive association with dermatologic AEs.

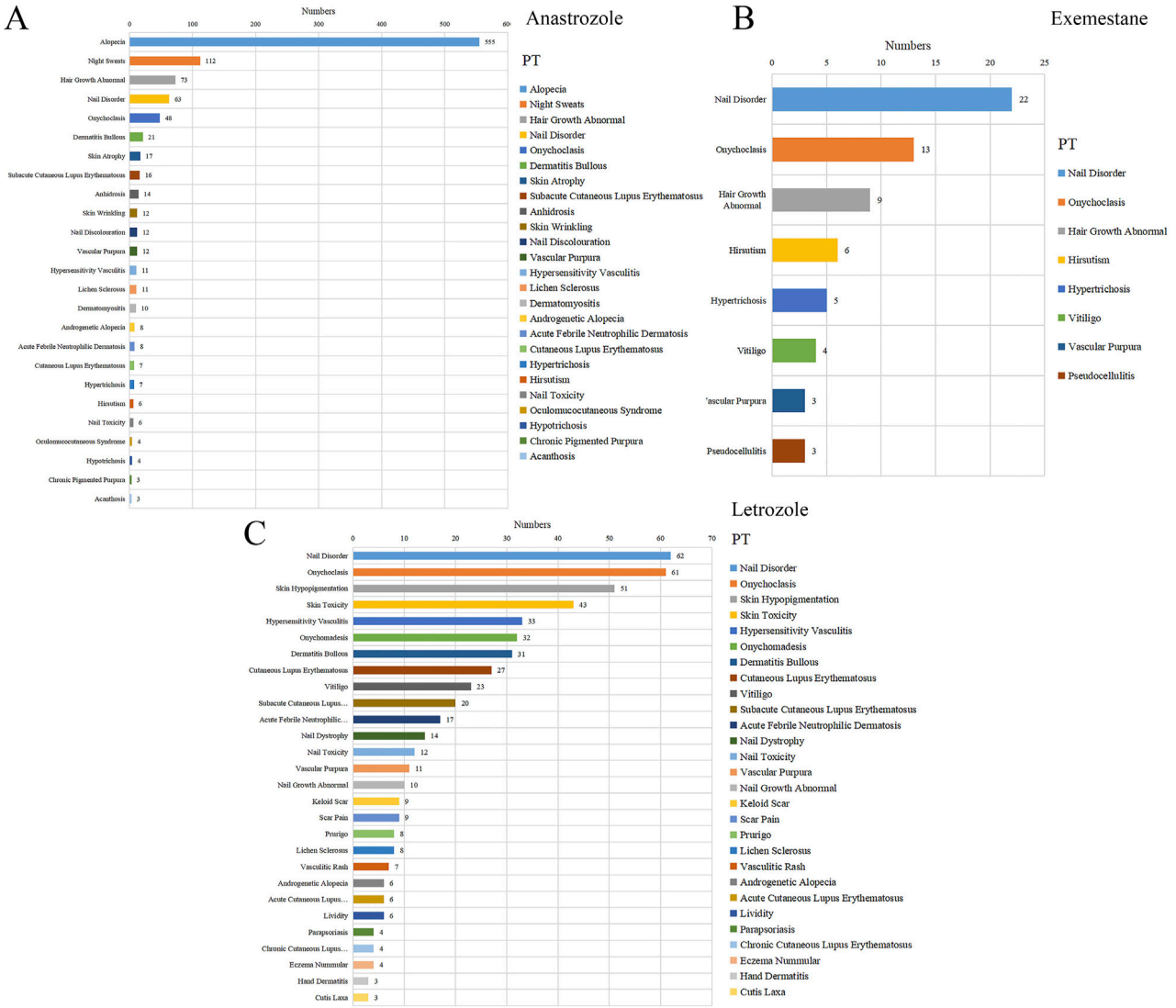


FIGURE 2
The statistics for different PTs in reports with dermatologic adverse events associated with several aromatase inhibitors. **(A)** Anastrozole, **(B)** Exemestane, **(C)** Letrozole.

3.3 The spectrum of dermatologic adverse effects at the preferred term (PT) levels

A total of 61 positive PT-level signals were identified (Figure 2). Significant PT signals were observed for three selected AI agents: anastrozole (25 PTs), exemestane (8 PTs), and letrozole (28 PTs). Anastrozole was strongly associated with dermatologic alopecia (n = 555), night sweats (n = 112), and abnormal hair growth (n = 173). For exemestane, nail disorder (n = 22), onychoclasis (n = 13), and abnormal hair growth (n = 9) were prominent signals. Notably, nail disorder (n = 22) and onychoclasis (n = 13) were the top two signals for letrozole among its 28 positive PTs, showing a marked association across all three AIs.

Disproportionality analysis on these PTs, indicated by ROR values > 1, confirmed a significant association between AIs and skin-related adverse reactions. Specifically, 25 positive signals (ROR = 1.07, 95% CI = 1.03–1.11) for anastrozole, 8 signals (ROR = 1.1, 95% CI = 1.04–1.16) for exemestane, and 28 signals (ROR = 0.94, 95% CI = 0.91–0.98) for letrozole were detected. As shown in Figure 3, the highest-ranked associations were anhidrosis for anastrozole (ROR = 48.68, CI = 28.48–83.22), pseudo cellulitis for exemestane (ROR = 57.73, CI = 18.36–181.48), and nail toxicity for letrozole (ROR = 38.40, CI = 21.47–68.68).

Logistic regression analysis (Table 3) indicated that hospitalization and age were significant protective factors for dermatologic AEs associated with anastrozole and exemestane (P < 0.05). However, body weight was not a significant factor for dermatologic AEs (P > 0.05).

3.4 TTO analysis of dermatologic AEs by AIs

The onset times for 10 PTs (alopecia, bullous dermatitis, dry skin, erythema, abnormal hair growth, hyperhidrosis, night sweats,

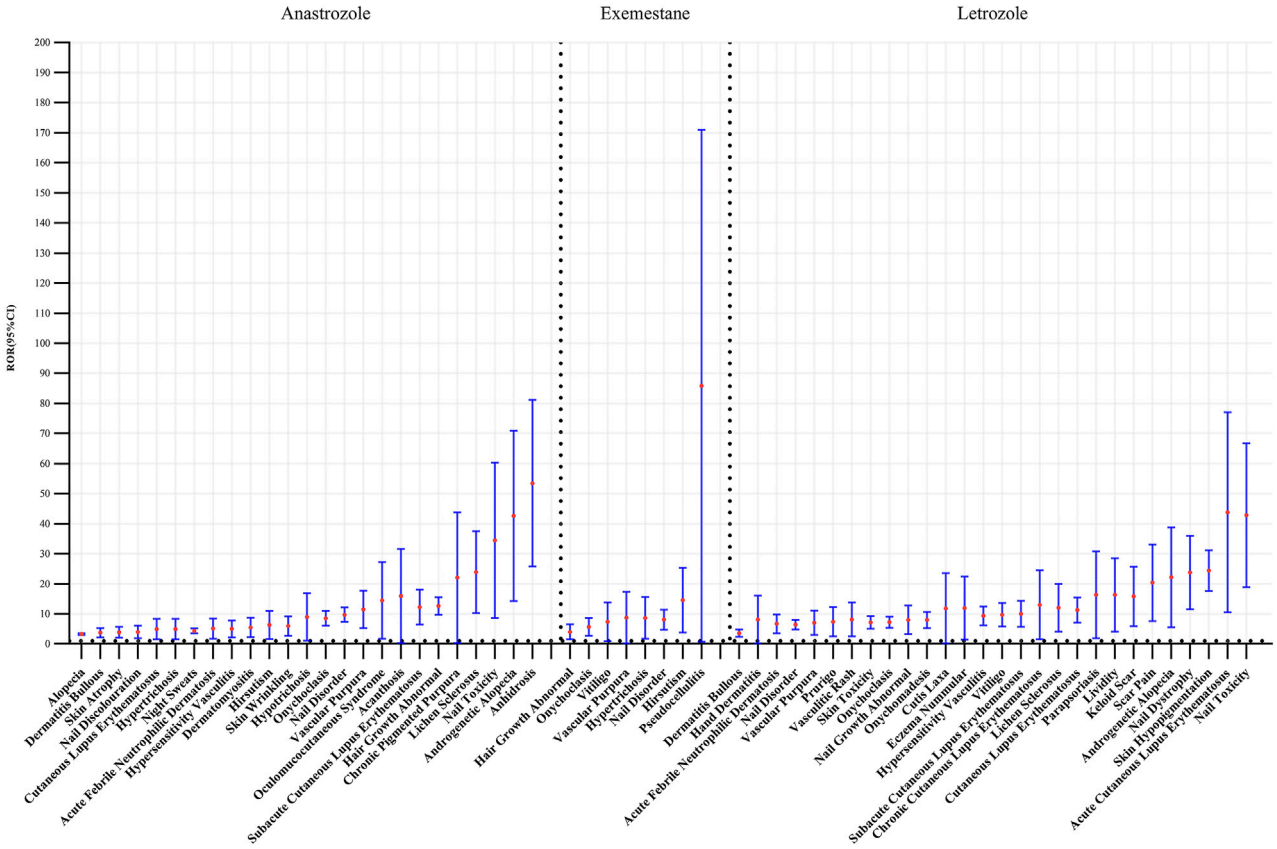


FIGURE 3
Forest plots of different aromatase inhibitors agents inducing dermatologic toxicity.

pruritus, rash, and urticaria) were significantly associated with anastrozole. Among these, night sweats had the shortest median onset time at 20.5 days, while bullous dermatitis had the longest at 212 days. In the letrozole group, 10 PTs (alopecia, angioedema, dry skin, erythema, hyperhidrosis, pruritus, rash, maculopapular rash, skin ulcer, and urticaria) were observed. Urticaria showed the shortest onset time with a median of 2 days, and skin ulcer had the longest at 241.5 days. For exemestane, onset times were noted for alopecia, dry skin, erythema, hyperhidrosis, night sweats, onychoclasis, pruritus, rash, pruritic rash, and urticaria. Urticaria presented the shortest onset time at a median of 8 days, and pruritic rash showed the longest at 52 days. Onset times for all PTs are shown in Figure 4.

4 Discussion

AIs, categorized as nonsteroidal and steroidal, are widely used as adjuvant therapy and represent the gold standard for estrogen receptor (ER)+ BC management. Among the nonsteroidal AIs, anastrozole and letrozole significantly benefit ER + BC patients by inhibiting aromatase activity through multiple mechanisms (Fusi et al., 2014; Jameera Begam et al., 2017). For example, a clinical trial involving 3,864 postmenopausal women with BC demonstrated that anastrozole provided greater clinical benefits than placebo, underscoring its therapeutic value (Wollina et al., 2018). Additionally, the combination of ribociclib with letrozole has shown substantial efficacy, with a median PFS of 21.8 months (95% CI, 13.9–25.3) (Fasching et al., 2024). Exemestane, the only third-generation steroidal AI, is also clinically beneficial for postmenopausal BC patients (Jameera Begam et al., 2017). The frequent clinical use of anastrozole, exemestane, and letrozole warrants examination in this study. However, the dermatologic risks associated with AIs cannot be overlooked. For instance, a phase 3b study of ribociclib in BC reported a 35.1% incidence of alopecia with letrozole treatment. Additional dermatologic adverse effects, such as hot flashes, pruritus, and rash, have been noted in the literature (Fasching et al., 2024). These adverse dermatologic events not only impact patients' quality of life but may also lead to interruptions or even discontinuation of cancer therapy (Sussman et al., 2019). While the benefits of AIs generally outweigh the risks, proactive prevention strategies are essential. This study conducts a comprehensive assessment of dermatologic risks associated with the commonly used AIs—exemestane, anastrozole, and letrozole—over the past 2 decades, utilizing real-world data from an AE reporting database.

In our study, the relatively low ROR for dermatologic AEs associated with letrozole (ROR = 0.94) compared to anastrozole and exemestane may be attributed to several pharmacokinetic and pharmacodynamic differences. Letrozole has a longer half-life (approximately 4 days) and reaches steady-state plasma concentrations over a longer period (60 days) (Buzdar et al.,

TABLE 3 Multivariate logistic regression model of dermatologic adverse events.

Characteristic	Number	OR (95%CI)	*P*-value
Anastrozole			
Hospitalization			
No	3,478	Reference	
Yes	1,087	0.46 (0.32–0.65)	<0.001
Age			
<65	2,311	Reference	
≥65	2,254	1.51 (1.18–1.93)	0.001
Weight			
50–100 kg	4,137	Reference	
<50 or >100 kg	428	0.73 (0.44–1.15)	0.200
Exemestane			
Hospitalization			
No	1,399	Reference	
Yes	839	0.35 (0.21–0.55)	<0.001
Age			
<65	1,105		
≥65	1,133	1.56 (1.06–3.00)	0.024
Weight			
50–100 kg	1961	Reference	
<50 or >100 kg	277	0.50 (0.22–0.98)	0.062

Abbreviation: OR, odds ratio; CI, confidence interval; $P < 0.05$ were considered statistically significant.

2002) compared to anastrozole and exemestane, which have shorter half-lives (1–2 days) and quicker peak drug levels (Hamadeh et al., 2018). This steady accumulation may result in fewer fluctuations in drug levels, potentially reducing the incidence of acute skin reactions. Therefore, letrozole's pharmacokinetic profile, with a longer half-life and stable plasma concentrations, might lead to a more gradual onset of adverse effects, including dermatologic reactions. Additionally, each AI is metabolized via different pathways, which can influence the formation of reactive metabolites or drug–drug interactions. Letrozole is primarily cleared by CYP2A6 (with minor involvement of CYP3A4), and it notably inhibits CYP2A6 itself, potentially leading to self-limited metabolism and more stable drug levels over time (De Placido et al., 2018). In contrast, anastrozole is mainly metabolized by CYP3A4 (with contributions from CYP3A5, CYP2C8, and glucuronidation), and it can weakly inhibit several CYP enzymes (e.g., 1A2, 2C8/9, 3A4) (De Placido et al., 2018). Exemestane undergoes oxidation by CYP3A4 and reduction by CYP450 enzymes, including 11β-hydroxylation via CYP4A11 (De Placido et al., 2018). Given this metabolic profile, letrozole's unique CYP2A6 pathway, combined with its steady accumulation and lack of active metabolites, may make it less prone to certain immune-mediated skin reactions or erratic plasma fluctuations that could precipitate rashes. This could partly explain why letrozole has a lower ROR for dermatologic issues relative to anastrozole and exemestane.

Recent clinical publications have highlighted the dermatologic toxicities induced by aromatase inhibitors (AIs) (Wilkinson and Hardman, 2017), Moreover, AIs have been shown to influence humoral immunity and immunoglobulin levels (Cutolo et al., 2012; Aguilar-Pimentel et al., 2020). Increasing evidence suggests that reduced estrogen levels can provoke hyperactive neutrophils, which adhere to vascular endothelium, potentially triggering autoimmune vasculitis and adverse dermatologic responses (Zarkavelis et al., 2016; Woodford et al., 2019). Estrogen thus plays a critical role in preserving skin vasculature and function. Although AIs benefit postmenopausal women with BC by reducing estrogen, excessive estrogen deficiency adversely impacts skin maintenance. Consequently, AIs in clinical use often leads to dermatologic side effects such as hot flushes, sweating, vaginal dryness, nail disorders, onychoclasis, hypopigmentation, and vascular purpura (Pagani et al., 2014; Fasching et al., 2024; Zhang et al., 2024). The prevalence of these adverse effects calls for rigorous dermatologic monitoring to ensure safe AI application.

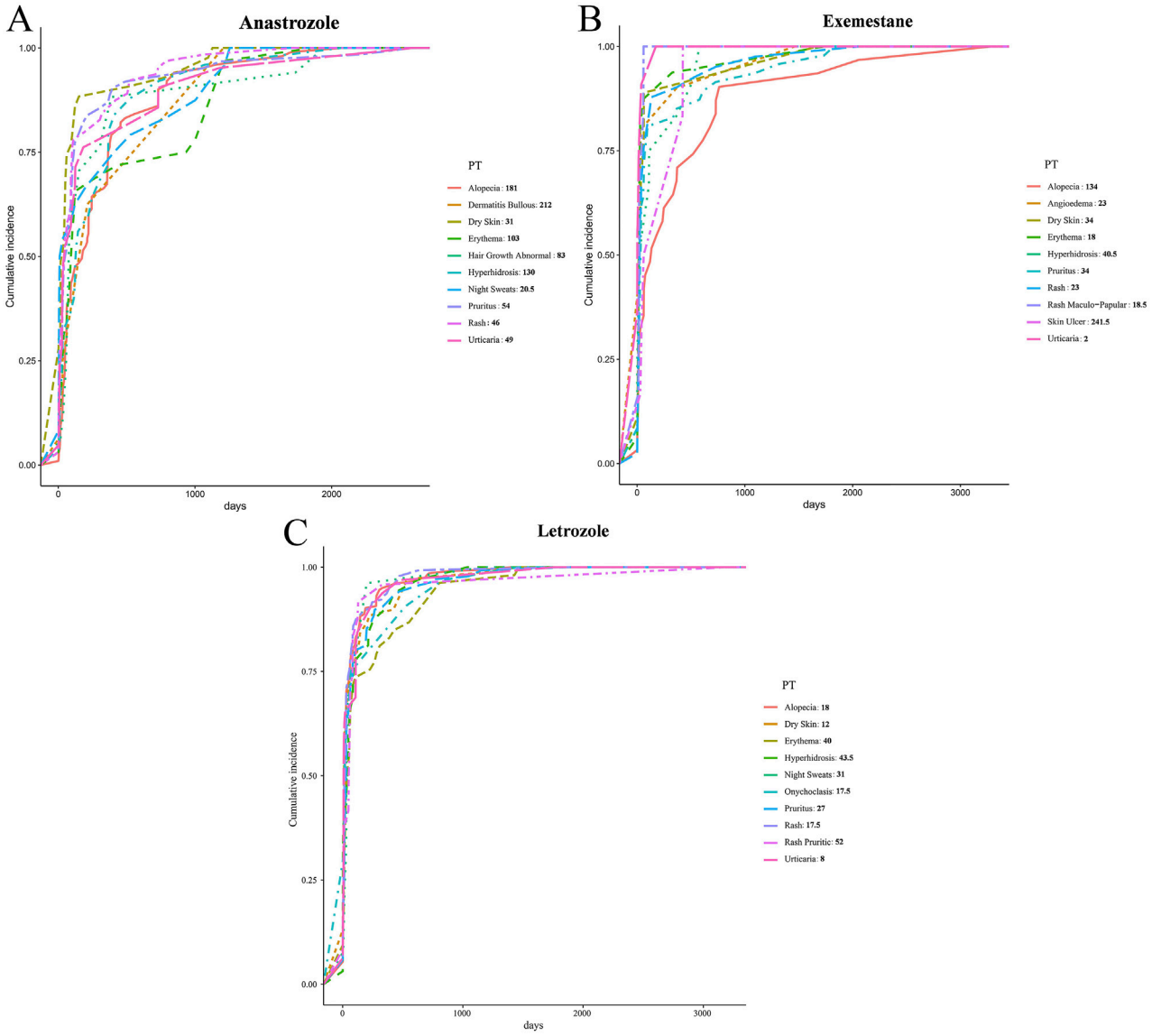


FIGURE 4
Time-to-onset on dermatologic AEs elicited by AIs. **(A)** Anastrozole, **(B)** Exemestane, **(C)** Letrozole.

Alopecia is particularly common in BC patients treated with AIs, with a notable incidence among AEs (Fasching et al., 2024). Alopecia affects approximately 2.5% of BC patients, and about 8% discontinue AI therapy due to this adverse effect (Freites-Martinez et al., 2018; Ferreira et al., 2019; Behbahani et al., 2021). In our retrospective pharmacovigilance analysis, 76.55% of alopecia cases were associated with anastrozole (555 out of 725 reports). All three AIs were linked to hair abnormalities, with alopecia and abnormal hair growth linked to anastrozole, androgenetic alopecia linked to letrozole, and abnormal hair growth linked to exemestane. These findings predict a high risk of alopecia with AIs in BC therapy, suggesting that concurrent use of AIs with minoxidil may help sustain hair follicle health (Freites-Martinez et al., 2018; Ferreira et al., 2019).

Our analysis found positive signals for onychoclasis, vascular responses (e.g., hypersensitivity vasculitis, vascular purpura), hair abnormalities (e.g., alopecia, androgenetic alopecia, hair growth abnormality), and nail toxicity (e.g., nail disorder, discoloration, nail dystrophy) across all three AIs, indicating a need for appropriate patient care. Additionally, dry skin, erythema, hyperhidrosis, pruritus, and rash were frequently associated with AI-related skin impairments, emphasizing the necessity for concurrent protective strategies during AI treatment in BC patients. While letrozole showed a negative association with skin-related AEs (ROR 0.94; 95% CI 0.91–0.98), anastrozole (ROR 1.07; 95% CI 1.03–1.11) and exemestane (ROR 1.1; 95% CI 1.04–1.16) had significant positive associations, underscoring the need for close monitoring of dermatologic adverse effects with these drugs.

Regarding onset time, all three AIs were associated with urticaria, with a median onset of just 2 days for exemestane, indicating a rapid adverse response. Most positive PTs had

onset times of less than 50 days (dry skin, alopecia, erythema, night sweats, onychoclasis, pruritus, rash, urticaria, angioedema, and maculopapular rash), suggesting acute impacts on patient quality of life. These findings highlight the need for proactive intervention, enabling targeted measures based on onset timing.

This pharmacovigilance study has limitations. First, duplicate reports, false information, and missing data in the FAERS database reduce data accuracy. For example, reports with inaccurate dates were excluded, though they may have contained relevant information on AI-related dermatologic AEs. Second, FAERS data are based on voluntary submissions, primarily from healthcare providers, which lack direct causality. This limitation is particularly relevant when interpreting discrepancies between our findings (e.g., the relatively low ROR for letrozole) and prior literature, as FAERS cannot establish a direct causal relationship between AIs and dermatologic AEs. Third, this study reflects only FAERS reports, suggesting an elevated risk of AEs with AIs but not a causal relationship with dermatologic effects. Finally, FAERS is a spontaneous global reporting system that introduces selection bias. Most reports in this study originated from the United States, limiting geographical diversity in the data.

5 Conclusion

Given the high incidence of AI-induced dermatologic toxicity in postmenopausal women with BC treatment, tailored management strategies should be prioritized the specific dermatologic impact of each AI. Our analysis is the first to highlight the global prevalence of dermatologic adverse reactions associated with AIs, emphasizing that these AEs are a critical factor in AI utilization. Addressing drug-induced skin disorders is essential to ensure the broader application of AIs. This chapter calls for further research into AI-related dermatologic damage in BC management to optimize patient care comprehensively. For high-risk patients, especially those with pre-existing dermatologic conditions, close monitoring is recommended to detect skin-related AEs early and allow for timely intervention. Regular assessments for dryness, alopecia, and rashes, combined with patient education on managing these issues, will help maintain quality of life during treatment.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

Author contributions

Y-YW: Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. Q-LH: Formal Analysis, Investigation, Methodology, Resources, Writing – original draft. Z-YL: Validation, Writing – original draft, Writing – review and editing. X-YS: Methodology, Writing – original draft. Y-YS: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review and editing. J-ZZ: Supervision, Conceptualization, Funding acquisition, Writing – review and editing. SL: Conceptualization, Funding acquisition, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China (Grant number: 82205114) Research Grant for Health Science and Technology of Pudong Municipal Commission of Health committee of Shanghai (Grant number: PW2022D-15).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1529342/full#supplementary-material

References

Aguilar-Pimentel, J. A., Cho, Y. L., Gerlini, R., Calzada-Wack, J., Wimmer, M., Mayer-Kuckuk, P., et al. (2020). Increased estrogen to androgen ratio enhances immunoglobulin levels and impairs B cell function in male mice. *Sci. Rep.* 10 (1), 18334. doi:10.1038/s41598-020-75059-9

Almenoff, J. S., Pattishall, E. N., Gibbs, T. G., DuMouchel, W., Evans, S. J., and Yuen, N. (2007). Novel statistical tools for monitoring the safety of marketed drugs. *Clin. Pharmacol. Ther.* 82 (2), 157–166. doi:10.1038/sj.clpt.6100258

Ando, G., Taguchi, K., Enoki, Y., Yokoyama, Y., Kizu, J., and Matsumoto, K. (2019). Evaluation of the expression time of ganciclovir-induced adverse events using JADER and FAERS. *Biol. Pharm. Bull.* 42 (11), 1799–1804. doi:10.1248/bpb.b19-00156

Behbahani, S., Geisler, A., Kolla, A., Dreker, M. R., Kaunitz, G., and Pomeranz, M. K. (2021). Art of prevention: the importance of dermatologic care when using aromatase inhibitors. *Int. J. Womens Dermatol* 7 (5Part B), 769–773. doi:10.1016/j.ijwd.2021.07.002

Buzdar, A., Douma, J., Davidson, N., Elledge, R., Morgan, M., Smith, R., et al. (2001). Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J. Clin. Oncol.* 19 (14), 3357–3366. doi:10.1200/jco.2001.19.14.3357

Buzdar, A. U., Robertson, J. F., Eiermann, W., and Nabholtz, J. M. (2002). An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. *Cancer* 95 (9), 2006–2016. doi:10.1002/cncr.10908

Cutolo, M., Sulli, A., and Straub, R. H. (2012). Estrogen metabolism and autoimmunity. *Autoimmun. Rev.* 11 (6-7), A460–A464. doi:10.1016/j.autrev.2011.11.014

Dellapasqua, S., and Colleoni, M. (2010). Letrozole. *Expert Opin. Drug Metab. Toxicol.* 6 (2), 251–259. doi:10.1517/17425250903540246

De Placido, S., Gallo, C., De Laurentiis, M., Bisagni, G., Arpino, G., Sarobba, M. G., et al. (2018). Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. *Lancet Oncol.* 19 (4), 474–485. doi:10.1016/s1470-2045(18)30116-5

Diamond, M. P., Legro, R. S., Coutifaris, C., Alvero, R., Robinson, R. D., Casson, P., et al. (2015). Letrozole, gonadotropin, or clomiphene for unexplained infertility. *N. Engl. J. Med.* 373 (13), 1230–1240. doi:10.1056/NEJMoa1414827

Evans, S. J., Waller, P. C., and Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* 10 (6), 483–486. doi:10.1002/pds.677

Fasching, P. A., Decker, T., Hartkopf, A., Nusch, A., Heinrich, B. J., Kurbacher, C., et al. (2024). Efficacy, safety, and prognosis prediction in patients treated with ribociclib in combination with letrozole: final results of phase 3b RIBECCA study in hormone receptor positive, human epidermal growth factor receptor-2 negative, locally advanced or metastatic breast cancer. *Eur. J. Cancer* 198, 113480. doi:10.1016/j.ejca.2023.113480

Ferreira, M. N., Ramseier, J. Y., and Leventhal, J. S. (2019). Dermatologic conditions in women receiving systemic cancer therapy. *Int. J. Womens Dermatol* 5 (5), 285–307. doi:10.1016/j.ijwd.2019.10.003

Francis, P. A., Pagani, O., Fleming, G. F., Walley, B. A., Colleoni, M., Láng, I., et al. (2018). Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N. Engl. J. Med.* 379 (2), 122–137. doi:10.1056/NEJMoa1803164

Freites-Martinez, A., Shapiro, J., Chan, D., Fornier, M., Modi, S., Gajria, D., et al. (2018). Endocrine therapy-induced alopecia in patients with breast cancer. *JAMA Dermatol* 154 (6), 670–675. doi:10.1001/jamadermatol.2018.0454

Fusi, C., Materazzi, S., Benemei, S., Coppi, E., Trevisan, G., Marone, I. M., et al. (2014). Steroidal and non-steroidal third-generation aromatase inhibitors induce pain-like symptoms via TRPA1. *Nat. Commun.* 5, 5736. doi:10.1038/ncomms6736

Gu, T., Jiang, A., Zhou, C., Lin, A., Cheng, Q., Liu, Z., et al. (2023). Adverse reactions associated with immune checkpoint inhibitors and bevacizumab: a pharmacovigilance analysis. *Int. J. Cancer* 152 (3), 480–495. doi:10.1002/ijc.34332

Hamadeh, I. S., Patel, J. N., Rusin, S., and Tan, A. R. (2018). Personalizing aromatase inhibitor therapy in patients with breast cancer. *Cancer Treat. Rev.* 70, 47–55. doi:10.1016/j.ctrv.2018.07.014

Jameera Begam, A., Jubie, S., and Nanjan, M. J. (2017). Estrogen receptor agonists/antagonists in breast cancer therapy: a critical review. *Bioorg Chem.* 71, 257–274. doi:10.1016/j.bioorg.2017.02.011

Kharb, R., Haider, K., Neha, K., and Yar, M. S. (2020). Aromatase inhibitors: role in postmenopausal breast cancer. *Arch. Pharm. Weinh.* 353 (8), e2000081. doi:10.1002/ardp.202000081

Pagani, O., Regan, M. M., Walley, B. A., Fleming, G. F., Colleoni, M., Láng, I., et al. (2014). Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N. Engl. J. Med.* 371 (2), 107–118. doi:10.1056/NEJMoa1404037

Patel, S. (2017). Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: a comprehensive review. *J. Steroid Biochem. Mol. Biol.* 168, 19–25. doi:10.1016/j.jsbmb.2017.01.009

Pritchard, K. I., Burris, H. A., 3rd, Ito, Y., Rugo, H. S., Dakhil, S., Hortobagyi, G. N., et al. (2013). Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. *Clin. Breast Cancer* 13 (6), 421–432. doi:10.1016/j.clbc.2013.08.011

Rižner, T. L., and Romano, A. (2023). Targeting the formation of estrogens for treatment of hormone dependent diseases-current status. *Front. Pharmacol.* 14, 1155558. doi:10.3389/fphar.2023.1155558

Robertson, J. F. R., Paridaens, R. J., Lichfield, J., Bradbury, I., and Campbell, C. (2021). Meta-analyses of phase 3 randomised controlled trials of third generation aromatase inhibitors versus tamoxifen as first-line endocrine therapy in postmenopausal women with hormone receptor-positive advanced breast cancer. *Eur. J. Cancer* 145, 19–28. doi:10.1016/j.ejca.2020.11.038

Santoro, S., Santini, M., Pepe, C., Tognetti, E., Cortelazzi, C., Ficarelli, E., et al. (2011). Aromatase inhibitor-induced skin adverse reactions: exemestane-related cutaneous vasculitis. *J. Eur. Acad. Dermatol Venereol.* 25 (5), 596–598. doi:10.1111/j.1468-3083.2010.03803.x

Sauzet, O., Carvajal, A., Escudero, A., Molokhia, M., and Cornelius, V. R. (2013). Illustration of the weibull shape parameter signal detection tool using electronic healthcare record data. *Drug Saf.* 36 (10), 995–1006. doi:10.1007/s40264-013-0061-7

Sonke, G. S., Hart, L. L., Campone, M., Erdkamp, F., Janni, W., Verma, S., et al. (2018). Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res. Treat.* 167 (3), 659–669. doi:10.1007/s10549-017-4523-y

Stocco, C. (2012). Tissue physiology and pathology of aromatase. *Steroids* 77 (1-2), 27–35. doi:10.1016/j.steroids.2011.10.013

Sussman, T. A., Kruse, M. L., Thacker, H. L., and Abraham, J. (2019). Managing genitourinary syndrome of menopause in breast cancer survivors receiving endocrine therapy. *J. Oncol. Pract.* 15 (7), 363–370. doi:10.1200/jop.18.00710

Tregunno, P. M., Fink, D. B., Fernandez-Fernandez, C., Lázaro-Bengoa, E., and Norén, G. N. (2014). Performance of probabilistic method to detect duplicate individual case safety reports. *Drug Saf.* 37 (4), 249–258. doi:10.1007/s40264-014-0146-y

Wilkinson, H. N., and Hardman, M. J. (2017). The role of estrogen in cutaneous ageing and repair. *Maturitas* 103, 60–64. doi:10.1016/j.maturitas.2017.06.026

Wollina, U., Schönlebe, J., Heinig, B., Tchernev, G., França, K., and Lotti, T. (2018). Segmental erythema multiforme-like drug eruption by aromatase inhibitor anastrozole - first case report and another example of an immunocompromised district. *Open Access Maced. J. Med. Sci.* 6 (1), 79–81. doi:10.3889/oamjms.2018.026

Woodford, R. G., Becker, G. J., and Jain, A. (2019). Leukocytoclastic vasculitis associated with use of aromatase inhibitors. *Intern Med. J.* 49 (9), 1162–1167. doi:10.1111/imj.14422

Yang, Z., Yu, M., Mei, M., Chen, C., Lv, Y., Xiang, L., et al. (2022). The association between GLP-1 receptor agonist and diabetic ketoacidosis in the FDA adverse event reporting system. *Nutr. Metab. Cardiovasc Dis.* 32 (2), 504–510. doi:10.1016/j.numecd.2021.10.003

Zarkavelis, G., Kollas, A., Kampletsas, E., Vasiliou, V., Kaltsonoudis, E., Drosos, A., et al. (2016). Aromatase inhibitors induced autoimmune disorders in patients with breast cancer: a review. *J. Adv. Res.* 7 (5), 719–726. doi:10.1016/j.jare.2016.04.001

Zhang, Y., Zhao, L., Liu, Y., Zhang, J., Zheng, L., and Zheng, M. (2024). Adverse event profiles of the third-generation aromatase inhibitors: analysis of spontaneous reports submitted to FAERS. *Biomedicines* 12 (8), 1708. doi:10.3390/biomedicines12081708

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 30 June 2025
DOI 10.3389/fphar.2025.1498814

OPEN ACCESS

EDITED BY
Patricia Moriel,
State University of Campinas, Brazil

REVIEWED BY
Pedro Eduardo Nascimento Silva Vasconcelos,
Universidade Federal de São Paulo, Brazil
Narsis Daftarian,
University of British Columbia, Canada

*CORRESPONDENCE
Nuo Dong,
profeye@163.com

†These authors have contributed equally to this work

RECEIVED 19 September 2024
ACCEPTED 22 May 2025
PUBLISHED 30 June 2025

CITATION
Li X, Zhang S-Q, Wang K-R, Wu S-N, Wang M-Y, Chen C-T and Dong N (2025) Chloroquine and hydroxychloroquine-related ocular adverse events in SLE treatment: a real-world disproportionality analysis based on FDA adverse event reporting system (FAERS). *Front. Pharmacol.* 16:1498814. doi: 10.3389/fphar.2025.1498814

Chloroquine and hydroxychloroquine-related ocular adverse events in SLE treatment: a real-world disproportionality analysis based on FDA adverse event reporting system (FAERS)

Xiang Li[1,2,3,4,5,6,7,8†], Si-Qi Zhang[9†], Ke-Rui Wang[1,2†], Shi-Nan Wu[1,2], Meng-Yuan Wang[1,2], Cui-Ting Chen[1,2] and Nuo Dong[1,2,3,4,5,6,7,8*]

[1]Xiamen Eye Center and Eye Institute of Xiamen University, School of Medicine, Xiamen, China, [2]Xiamen Clinical Research Center for Eye Diseases, Xiamen, Fujian, China, [3]Xiamen Key Laboratory of Ophthalmology, Xiamen, Fujian, China, [4]Fujian Key Laboratory of Corneal & Ocular Surface Diseases, Xiamen, Fujian, China, [5]Xiamen Key Laboratory of Corneal & Ocular Surface Diseases, Xiamen, Fujian, China, [6]Translational Medicine Institute of Xiamen Eye Center of Xiamen University, Xiamen, Fujian, China, [7]Huaxia Eye Hospital of Quanzhou, Quanzhou, Fujian, China, [8]Department of Ophthalmology, Affiliated People's Hospital and Zhenjiang Kangfu Eye Hospital, Zhenjiang College, Zhenjiang, Jiangsu, China, [9]Department of Oncology, Xiang'an Hospital of Xiamen University, Xiamen, Fujian, China

Objective: This study aimed to evaluate the risk of adverse events associated with chloroquine (CQ) and hydroxychloroquine (HCQ) in patients with systemic lupus erythematosus (SLE), using data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: Disproportionality analysis was conducted using the Reporting Odds Ratio (ROR) to detect potential safety signals. Sensitivity analyses were performed to validate these signals, and the time to onset for each Preferred Term (PT) was assessed.

Results: Between 2004 and 2024, a total of 2,575 adverse event reports related to HCQ or CQ use in patients with SLE were identified in the FAERS database, of which 437 involved ocular adverse events. The most frequently reported ocular conditions were cataract, macular degeneration, and glaucoma. Disproportionality analysis demonstrated strong associations between HCQ/CQ use and retinal degeneration (ROR = 28.5, 95%CI: 19.94–40.74), cystoid macular oedema (ROR = 12.46, 95%CI: 8.01–19.37), and optic atrophy (ROR = 6.55, 95%CI: 3.51–12.19). Sensitivity analyses, conducted after excluding SLE cases, indicated that all but one event (vitreous floaters) remained statistically significant, suggesting that these risks are more likely attributable to HCQ/CQ exposure than to the underlying disease. The time-to-onset analysis showed that cataract had the shortest average onset time (125.5 days), whereas retinal degeneration had the longest (937.5 days).

Conclusion: The extensive clinical use of HCQ and CQ raises significant concerns regarding their ocular safety profile. This study provides real-world pharmacovigilance evidence supporting a substantial risk of ocular adverse

events associated with HCQ/CQ use. Further mechanistic and prospective studies are warranted to elucidate the underlying pathophysiological pathways and to confirm these associations.

KEYWORDS

cloroquine, hydroxychloroquine, ocular adverse events, FAERS, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects multiple organs and tissues, including the skin, joints, kidneys, heart, lungs, blood, and nervous system. Its pathogenesis is characterized by immune system abnormalities, wherein the immune response targets normal tissues and organs, leading to inflammation and tissue damage (O'Donnell and Nabel, 2011). In the management of SLE, chloroquine and hydroxychloroquine are extensively employed due to their efficacy in reducing disease activity and preventing disease progression. However, recent in-depth investigations into the safety profiles of these agents have highlighted ocular complications as a significant concern. Notably, systemic administration of these drugs, particularly in the treatment of dermatological conditions, has been associated with a range of serious ocular adverse effects.

Prolonged use of chloroquine and hydroxychloroquine can result in irreversible damage to the retinal pigment epithelium and the photoreceptor complex. This damage typically arises after extended exposure and is associated with the accumulation of melanin within the retinal tissues, particularly when recommended dosages are exceeded or when treatment is prolonged. To facilitate early detection and prevent progression to severe conditions such as bull's eye maculopathy (Pryor et al., 2022), novel diagnostic and imaging techniques—such as optical coherence tomography (OCT) and wide-field fundus autofluorescence (FAF)—have been increasingly employed.

The study conducted by Radun et al. further underscores the importance of monitoring quantitative autofluorescence (QAF) in patients receiving chloroquine or hydroxychloroquine therapy. Their findings demonstrate a significant increase in QAF values over a 1-year follow-up period, suggesting rapid progression of ocular structural changes and the potential development of bull's eye maculopathy (Singh et al., 2023).

The Adverse Event Reporting System (FAERS), managed by the United States Food and Drug Administration (FDA), represents the largest spontaneous reporting database, encompassing over 27 million submissions related to adverse events, medication errors, and product quality issues reported to the FDA. This database provides a comprehensive overview of adverse events observed in real-world clinical settings (Hu et al., 2022). The present study aims to evaluate ocular adverse reactions associated with the use of chloroquine and hydroxychloroquine in the treatment of systemic lupus erythematosus, thereby offering clinicians a more robust basis for risk assessment and monitoring recommendations for these medications (Hu et al., 2022).

Abbreviations: SLE, Systemic Lupus Erythematosus; OCT, Optical Coherence Tomography; FAF, Fundus Autofluorescence; QAF, Quantitative Autofluorescence; FAERS, FDA Adverse Event Reporting System; FDA, The United States Food and Drug Administration; READUS-PV, Recommendations for Evaluation and Analysis of Disproportionality in the Use of Safety Signal Detection Based on Individual Case Safety Reports; AEs, Adverse Events; HCQ, Hydroxychloroquine; CQ, Chloroquine; ROR, Ratio of Odds Ratios; CI, Confidence Interval; PT, Preferred Term; RPE, Retinal Pigment Epithelium; AAO, The American Academy of Ophthalmology.

Materials and methods

Data sources

This study was conducted as a retrospective observational pharmacovigilance analysis based on the publicly accessible FAERS database. All methodologies and procedures strictly adhered to the guidelines and standards outlined in the Recommendations for Evaluation and Analysis of Disproportionality in the Use of Safety Signal Detection Based on Individual Case Safety Reports (READUS-PV) (Li et al., 2025b). Given that the FAERS database is publicly available and contains anonymized patient information, informed consent and ethical approval were not required for this study.

FAERS (accessible at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) is a publicly available pharmacovigilance database that collects reports of adverse events (AEs), medication errors, and product quality complaints from healthcare professionals worldwide (Long et al., 2024). The database is structured into seven interlinked subfiles, each connected through unique identifiers to form the complete FAERS dataset.

To ensure the accuracy and reliability of the data, only cases reported by healthcare professionals—specifically physicians and pharmacists (coded as MD and PH)—were included in the analysis (Li et al., 2025a). Between January 2004 and December 2024, FAERS recorded a total of 22,249,476 initial reports; after deduplication, 18,627,667 valid records were retained for analysis. Detailed information is presented in Figure 1.

Data processing

To obtain reports of adverse events associated with hydroxychloroquine (HCQ) or chloroquine (CQ) treatment, relevant records were identified from the DRUG file using the generic and brand names approved by the FDA. This study specifically focused on adverse events classified under the "Eye Disorders" System Organ Class (SOC code: 10015919) in cases where HCQ or CQ was used for the treatment of systemic lupus erythematosus, with the aim of detecting potential ocular toxicity induced by these drugs. In addition, the onset time of

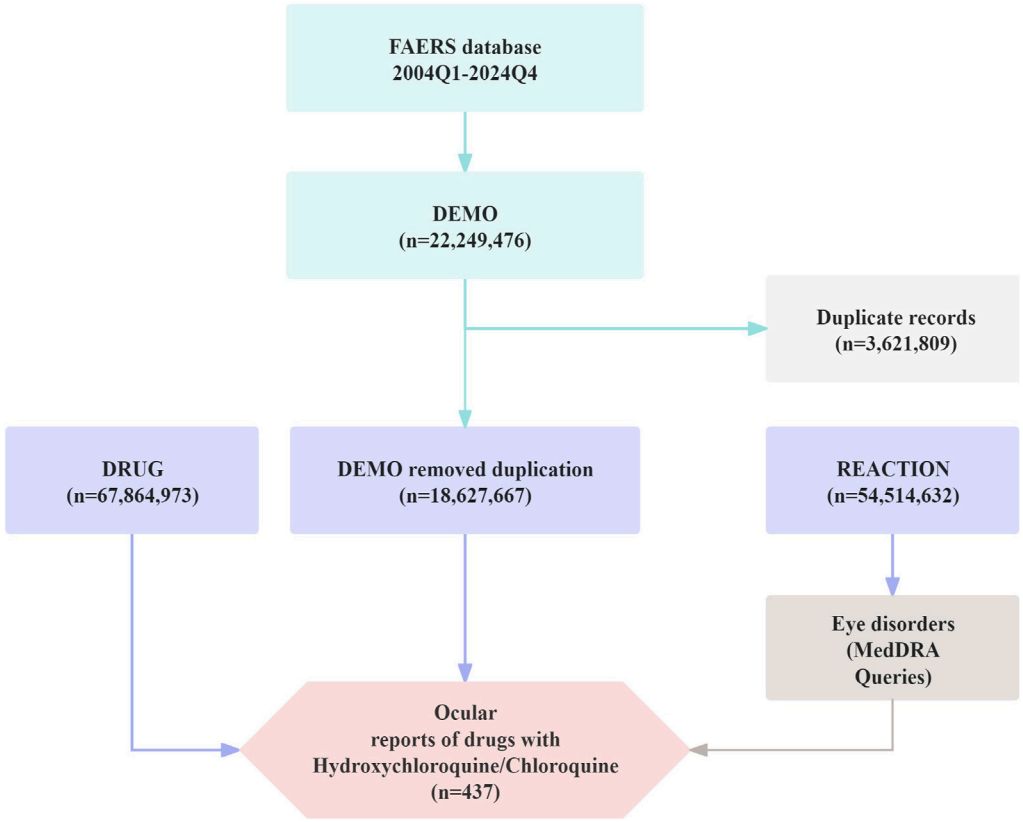


FIGURE 1
Flow diagram illustrating the selection process of ocular adverse events associated with Chloroquine and Hydroxychloroquine from the FAERS database.

TABLE 1 Proportional imbalance method four-grid table.

Item	Reports with the target AEs	All other AEs	Total
Reports with the target drug	a	b	a+b
All other drugs	c	d	c+d
Total	a+c	b+d	a+b+c+d

Abbreviation: AEs, Adverse Events.

ocular adverse events was assessed, defined as the interval between the initiation of HCQ or CQ therapy and the occurrence of the adverse event. Only cases with an onset time greater than 0 days were included in the analysis (Li et al., 2025c); reports containing erroneous dates (e.g., drug initiation after event occurrence) or missing date information were excluded. The control group comprised individuals exposed to non-target drugs, whereas the experimental group consisted of individuals exposed to HCQ or CQ.

Data analysis

Signal detection in this study was performed using the disproportionality analysis method of reporting odds ratio (ROR). This method is based on a 2 × 2 contingency table (see Table 1), and the ROR was calculated using the following formula: ROR = $\frac{a/c}{b/d} = \frac{ad}{bc}$, 95%CI = $e^{\ln(ROR)\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$ (Luo et al., 2025). A positive signal was considered present when the number of co-reported cases (a) between a specific drug and an adverse event was ≥3, and the lower bound of the 95% confidence interval (CI) exceeded 1, indicating a potential association between the drug and the adverse event (Liu et al., 2025). Categorical variables were summarized as frequencies and percentages. All statistical analyses were performed using R software (version 4.3.2) and Microsoft Excel (2021).

Results

Descriptive analysis

From 2004 to 2022, the number of adverse event reports related to HCQ or CQ exhibited a continuous upward trend (Figure 2A). By

10.3389/fphar.2025.1498814

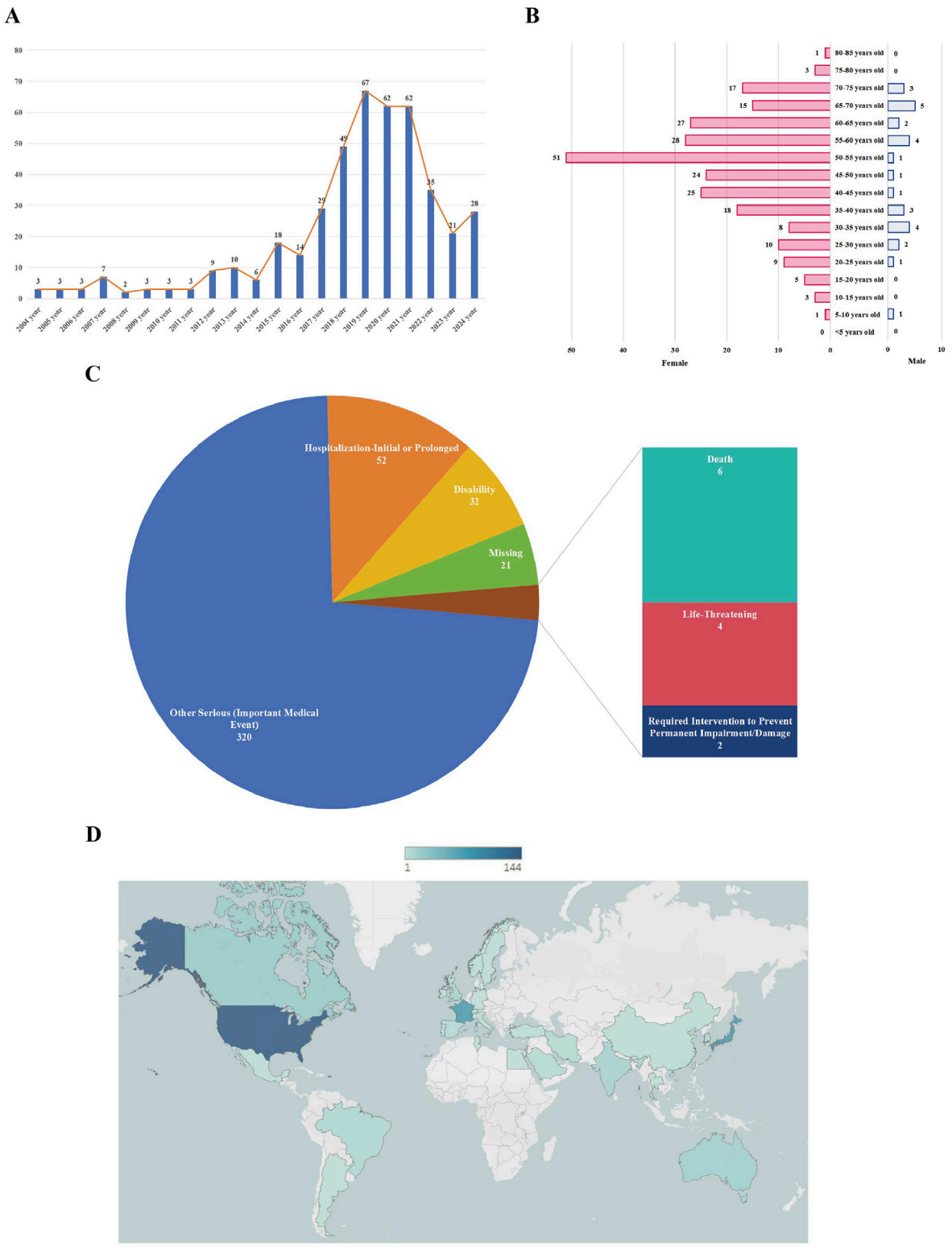


FIGURE 2
The characteristics of chloroquine- and hydroxychloroquine-related ocular adverse events in the treatment of systemic lupus erythematosus. **(A)** Annual distribution of ocular adverse event reports from 2004 to 2022; **(B)** Age and sex distribution of patients with reported ocular adverse events; **(C)** Proportions of different serious outcomes; **(D)** Geographic distribution of reported cases by country.

December 2024, a total of 2,575 patients had reported adverse events associated with HCQ or CQ treatment for systemic lupus erythematosus, among which 437 cases were classified as ocular adverse events. The mean age of these patients was 49.45 ± 15.07 years, as detailed in Table 1. In terms of sex distribution, a higher incidence of ocular adverse events was observed among

PT	N	ROR(95%CI)
Cystoid Macular Oedema	22	235.78 (55.43 - 1002.88)
Retinal Degeneration	23	164.35 (49.34 - 547.49)
Papilloedema	7	29.96 (9.51 - 94.41)
Retinal Vein Occlusion	5	26.74 (7.18 - 99.6)
Macular Degeneration	8	19.02 (7.34 - 49.31)
Optic Atrophy	5	17.83 (5.44 - 58.43)
Vitreous Floaters	7	13.62 (5.28 - 35.13)
Glaucoma	9	7.41 (3.47 - 15.81)
Cataract	30	5.85 (3.9 - 8.76)

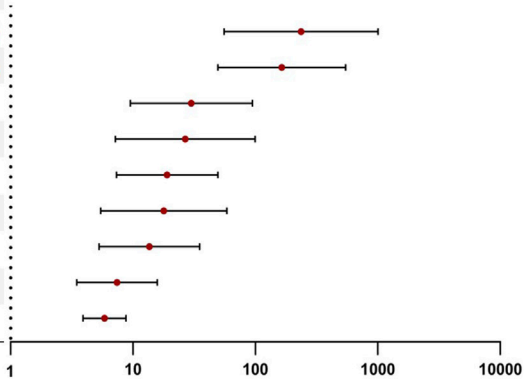


FIGURE 3
Forest plots of PT-level RORs for Chloroquine- and Hydroxychloroquine-related ocular adverse events in SLE therapy.

PT	N	ROR(95%CI)
Retinal Degeneration	31	28.5 (19.94 - 40.74)
Cystoid Macular Oedema	20	12.46 (8.01 - 19.37)
Optic Atrophy	10	6.55 (3.51 - 12.19)
Macular Degeneration	42	3.79 (2.8 - 5.14)
Retinal Vein Occlusion	8	3.04 (1.52 - 6.09)
Glaucoma	33	1.8 (1.28 - 2.53)
Cataract	78	1.42 (1.14 - 1.77)
Vitreous Floaters	7	0.78 (0.37 - 1.64)

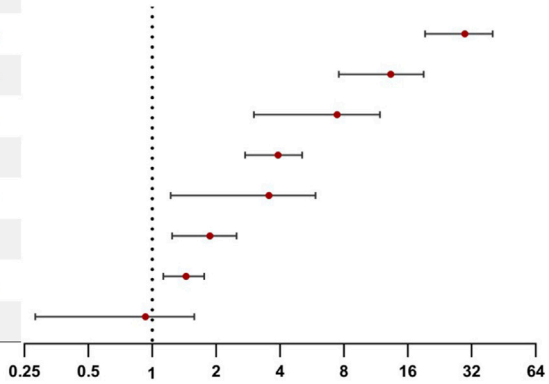


FIGURE 4
PT-level ROR forest plots for Chloroquine- and Hydroxychloroquine-related ocular AEs excluding SLE patients.

female patients (n = 271, 62.01%) compared with male patients (n = 30, 6.86%). Notably, the age distribution of patients approximated a normal curve, characterized by an initial increase followed by a subsequent decline, with the highest number of reports observed in the 50–55-year age group (Figure 2B). Hospitalization (n = 52, 11.90%) and other serious outcomes, such as important medical events (n = 320, 73.23%), were the most frequently reported serious adverse outcomes (Figure 2C). The geographic distribution of reported cases across countries is shown in Figure 2D. Additionally, individual dosage information for each patient was collected and is presented in Supplementary Table S1.

The spectrum of ocular adverse effects at the PT level

An analysis of adverse events associated with HCQ or CQ was conducted at the Preferred Term (PT) level. The three most frequently reported PTs were cataract (n = 78), macular degeneration (n = 42), and glaucoma (n = 33). Disproportionality analysis of these PTs revealed eight signals with positive associations (ROR >1). All PTs listed in Figure 3 demonstrated statistical significance and are ranked in descending order according to their ROR values. The top three adverse events were retinal degeneration (ROR = 28.5), cystoid macular oedema (ROR = 12.46), and optic atrophy (ROR = 6.55), indicating a strong statistical association between HCQ/CQ use and ocular disorders, particularly retinal diseases. Detailed information is presented in Figure 3.

Sensitivity analysis

Given that SLE itself carries an inherent risk of vascular retinal diseases, a sensitivity analysis was performed by excluding all individuals who used HCQ or CQ for the treatment of SLE. This analysis aimed to eliminate the potential confounding effect of SLE on the study outcomes. Upon reanalysis, we found that, in the sensitivity analysis, all PTs—except for vitreous floaters (ROR = 0.78)—still exhibited ROR values greater than 1, indicating that SLE

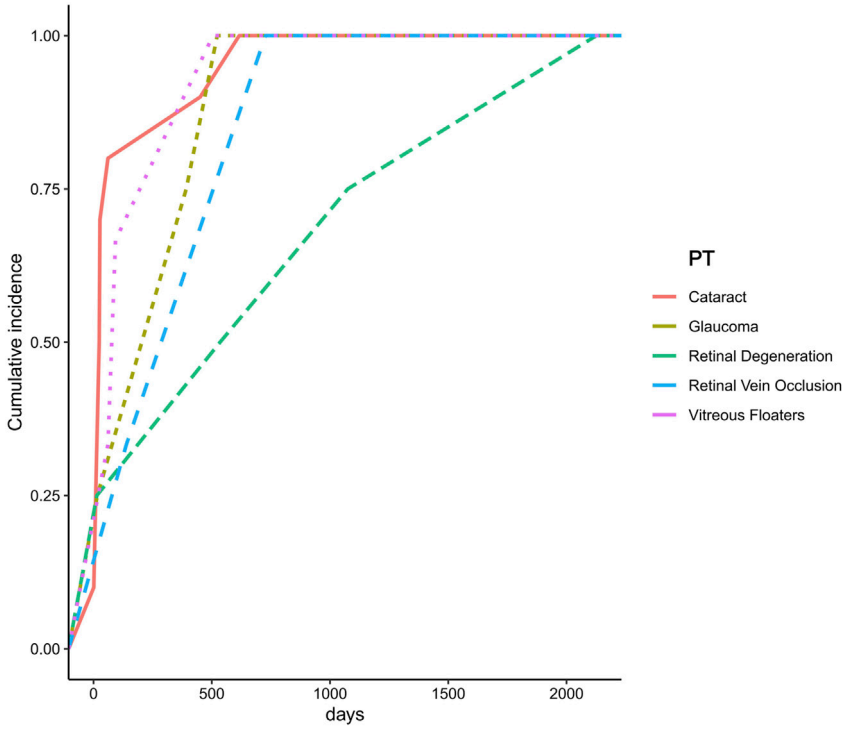


FIGURE 5
Time to onset of ocular adverse events associated with Chloroquine and Hydroxychloroquine.

did not confound the associations observed for the remaining seven PTs. Rather, these risks appeared to be directly attributable to HCQ/CQ exposure. Detailed results are presented in Figure 4.

Time-to-onset analysis

Further analysis was conducted to assess the onset time for individuals corresponding to the seven PTs that remained positive in the sensitivity analysis.

Due to missing data, onset time information was available for only five PTs. The results indicated that cataract had the shortest mean onset time, averaging 125.5 days, whereas retinal degeneration exhibited the longest mean onset time, with an average of 937.5 days (Figure 5).

Discussion

This study, based on real-world data from the FAERS database, comprehensively evaluated the post-marketing safety of HCQ and chloroquine CQ in the treatment of SLE, providing updated insights into ocular adverse events associated with these agents. Previous clinical trials and literature reviews have consistently demonstrated that the use of HCQ or CQ in SLE significantly increases the risk of ocular adverse events. Building upon these findings, the present study systematically identified and characterized the full spectrum of HCQ/CQ-associated ocular adverse events to date, thereby addressing a critical gap in real-world evidence in this field.

SLE is a chronic autoimmune disease characterized by the production of autoantibodies against nuclear and cytoplasmic antigens. It can affect multiple organ systems, presenting with a wide range of clinical manifestations and immunological abnormalities, and typically follows a relapsing–remitting course (Borchers et al., 2010). SLE affects individuals across all races, sexes, and age groups, but it exhibits a higher incidence among African American and Afro-Caribbean populations, with a strong predilection for women between 30 and 40 years of age (Costedoat-Chalumeau et al., 2015). In the present study, baseline demographic characteristics (Table 2) revealed that ocular adverse events were significantly more frequent among female patients than male patients (271 cases vs. 30 cases) and that middle-aged patients (18–64 years, n = 220, 50.34%) were more prone to ocular adverse events compared to elderly patients (>65 years, n = 44, 10.07%). These findings are consistent with the known epidemiological patterns of SLE.

HCQ and CQ are cornerstone therapies for the treatment of SLE. The use of HCQ and CQ in the management of SLE and other rheumatic diseases has spanned more than 5 decades. Generally, these agents are well tolerated, and treatment discontinuation due to systemic adverse events is relatively uncommon. However, both drugs have been associated with irreversible retinal toxicity, and recent studies suggest that such toxicity may not be as rare as previously believed (Rosenthal et al., 1978).

In our database, a total of 224 cases of retinal-related adverse events were identified. The three most frequently reported conditions were retinal degeneration (n = 31, ROR = 28.5), retinal vein occlusion (n = 8, ROR = 3.04), and optic atrophy

TABLE 2 Population baseline information.

Characteristics	HCQ/CQ induced eye AES(N = 437)	HCQ/CQ induced overall AES(N = 2575)
Gender,n (%)		
Female	271 (62.01)	1757 (68.23)
Male	30 (6.86)	228 (8.85)
Unknown	136 (31.12)	590 (22.91)
Weight (kg),n (%)		
<50	25 (5.72)	98 (3.81)
50~100	1 (0.23)	27 (1.05)
>100	82 (18.76)	288 (11.18)
Unknown	329 (75.29)	2162 (83.96)
Age (years),n (%)		
<18	16 (3.66)	119 (4.62)
18~64.9	220 (50.34)	1318 (51.18)
65~85	44 (10.07)	212 (8.23)
>85	0 (0.00)	1 (0.04)
Unknown	157 (35.93)	925 (35.92)
Occupation of reporters,n (%)		
Consumer (CN)	105 (24.03)	367 (14.25)
Physician (MD)	132 (30.21)	814 (31.61)
Pharmacist (PH)	6 (1.37)	60 (2.33)
Health-Professional (HP)	86 (19.68)	700 (27.18)
Other health-professional (OT)	94 (21.51)	540 (20.97)
Unknown	14 (3.20)	94 (3.65)
Reported countries,n(%)		
US	144	1015
Non-US	293	1560
Outcomes,n(%)		
Death (DE)	6 (1.37)	136 (5.28)
Disability (DS)	32 (7.32)	55 (2.14)
Hospitalization (HO)	52 (11.90)	646 (25.09)
Life-Threatening (LT)	4 (0.92)	122 (4.74)
Other serious (Important medical event)(OT)	320 (73.23)	1363 (52.93)
Required intervention to prevent permanent impairment/ damage (RI)	2 (0.46)	6 (0.23)
Congenital Anomaly (CA)	0 (0.00)	16 (0.62)
Unknown	21 (4.81)	231 (8.97)

Notes: Continuous numerical variables are expressed as mean ± standard deviation, and categorical variables are presented as n (%).

(n = 10, ROR = 6.55). Although the precise mechanisms by which HCQ and CQ induce retinal changes remain incompletely understood, it is known that both drugs extensively accumulate in ocular pigmented tissues, particularly within the retinal pigment epithelium (RPE), where they bind tightly to melanin. Importantly, these agents can persist in ocular tissues for extended periods even after discontinuation (Mao et al., 2024).

Histopathological studies of advanced chloroquine retinopathy in humans have demonstrated damage to both rod and cone photoreceptors, with relative preservation of central macular cones (Bernstein and Ginsberg, 1964; Wetterholm and Winter 1964), a finding that explains the clinical manifestation of bull's eye maculopathy observed on fundoscopic examination. Narrowing of the retinal arterioles is thought to represent a secondary phenomenon following widespread retinal injury, while pigmentary changes may result from the migration of RPE cells. This has been confirmed by the presence of pigment-laden cells within the outer nuclear and outer plexiform layers, suggesting that RPE metabolic dysfunction occurs early in the disease process (Wetterholm and Winter 1964). Impairment of the RPE's ability to phagocytose photoreceptor outer segments leads to RPE degeneration and subsequent photoreceptor loss (Bernstein and Ginsberg, 1964). These retinal changes are typically irreversible in clinical settings. Although HCQ and CQ are generally well tolerated, updated 2016 guidelines recommend that the maximum daily dose should not exceed 5 mg/kg of actual body weight, as excessive dosing and long-term therapy are considered major risk factors for retinal toxicity (Marmor et al., 2016).

A considerable number of adverse events involving the macular region were also observed, specifically including macular degeneration (n = 42, ROR = 3.79) and cystoid macular oedema (n = 20, ROR = 12.46). These findings suggest a potential association between HCQ or CQ exposure and the development of macular diseases. Previous studies have demonstrated that treatment of ARPE-19 cells with chloroquine induces lysosomal enlargement and intracellular lipid accumulation, implicating lysosomal dysfunction as a potential pathogenic mechanism in macular injury. Additionally, chloroquine has been reported to promote intracellular vesicle formation and disrupt autophagy pathways. Nevertheless, the exact mechanisms underlying the association between HCQ/CQ use and macular diseases remain incompletely understood and warrant further investigation (Chen et al., 2011).

Some of these adverse events have been previously documented in the drug labeling information. However, through database mining, we also identified several adverse events not explicitly listed in the prescribing information, such as cataract (n = 25, ROR = 4.82) and glaucoma (n = 8, ROR = 7.40). All adverse events selected for analysis demonstrated statistical significance (ROR >1 and a ≥3). Following the sensitivity analysis, vitreous floaters yielded a negative result, suggesting that this outcome may be more attributable to the underlying SLE pathology rather than to HCQ or CQ exposure. The specific impact of HCQ or CQ on these newly identified adverse events, as well as the underlying pathogenic mechanisms, remains incompletely understood and warrants further clinical and basic research.

In this study, an onset time analysis was performed for the seven ocular adverse events (PTs) that remained positive in the sensitivity analysis. Due to missing data, onset time information was available for only five PTs. The results revealed significant differences in the time to onset among different types of ocular adverse events following initial drug exposure. Cataract exhibited the shortest mean onset time, averaging 125.5 days, suggesting that the lens may be particularly sensitive to the pharmacological effects of chloroquine and HCQ, with damage manifesting within a relatively short period. However, the current evidence regarding the association between HCQ use and cataract development remains inconclusive. A retrospective cohort study conducted in patients with rheumatoid arthritis found no significant association between HCQ use and cataract formation (adjusted hazard ratio, 1.17; 95% CI: 0.86–1.59; P > 0.05) (Zhang et al., 2023). Therefore, the rapid onset of cataracts observed in this study may be influenced by underlying disease conditions, concomitant medication use (e.g., corticosteroids), or other environmental factors, and warrants further investigation. In contrast, retinal degeneration exhibited the longest mean onset time, averaging 937.5 days, suggesting that retinal damage represents a slow and progressive accumulation process. This finding is consistent with previous reports characterizing hydroxychloroquine-induced retinal toxicity. Studies have shown that HCQ accumulates over time within RPE cells, leading to cellular dysfunction and subsequent photoreceptor damage (Jorge et al., 2018). Moreover, the risk of HCQ-induced retinal toxicity is closely associated with cumulative dose and duration of therapy. The American Academy of Ophthalmology (AAO) recommends initiating retinal toxicity screening after 5 years of HCQ use in patients without additional risk factors (Marmor et al., 2016).

Limitations

Although this study leveraged a real-world data mining approach based on the FAERS database, several inherent limitations common to all pharmacovigilance databases must be acknowledged. First, issues such as false reports, underreporting, reporting errors, incomplete information, and reporting delays may occur, introducing unavoidable biases. Second, the FAERS database includes only reported adverse event cases (Sakaeda et al., 2013); due to the lack of denominator data (i.e., the total number of patients exposed to HCQ or CQ), the true incidence of HCQ/CQ-related ocular adverse events could not be determined. Third, the association analyses conducted in this study provide only statistical correlations and do not establish definitive causal relationships (Godfrey et al., 2025). Fourth, many adverse event reports within the FAERS database are submitted by non-medical personnel, potentially resulting in improper use of medical terminology or inconsistencies with established medical definitions. For example, retinal vascular occlusion or retinal vein occlusion (RVO) is generally associated with SLE itself (Hsu et al., 2020). Although our database analysis revealed differing trends, it is possible that some of these events were incorrectly reported as adverse reactions related to CQ/HCQ by non-professionals. Additionally, the onset timing of retinal lesions observed in our study differs from the timing of CQ/HCQ-associated retinopathy previously reported in the literature (Dammacco, 2018). This discrepancy may similarly stem from incomplete or inaccurate documentation by non-medical reporters in the FAERS database. Therefore, the interpretation of our findings should be approached with caution.

To address the aforementioned limitations, a more comprehensive approach is required. First, rigorous validation and verification of reported cases through cross-referencing with other medical records should be conducted to ensure data accuracy and reliability. Second, the integration of multiple data sources—including international pharmacovigilance databases, hospital records, and individual health records—would provide a broader and more diversified perspective. Furthermore, combining prospective clinical studies with retrospective data analyses could enable a more balanced and comprehensive assessment of drug-related adverse effects and their epidemiological characteristics. This multilayered strategy would enhance research quality and objectivity, thereby allowing for a more accurate evaluation of the risk–benefit profile of the drugs.

Conclusion

The widespread use of HCQ and CQ has raised concerns regarding their safety, particularly the risk of ocular AEs. Although spontaneous reporting systems have certain inherent limitations, they remain an important tool for identifying rare adverse events. Based on real-world data from the FAERS database, this study systematically evaluated the risk of ocular

adverse events associated with HCQ and CQ. The results demonstrated that most findings were consistent with previous clinical studies and information provided in the prescribing information. In addition, several potential new and unexpected adverse event signals were identified, offering valuable insights for clinical risk monitoring and management.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. S-QZ: Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review and editing. K-RW: Data curation, Methodology, Writing – review and editing. S-NW: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review and editing. M-YW: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. C-TC: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – review and editing. ND: Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. The study described was supported by grants from the Project supported by the General Plan Project of Quanzhou, Fujian Province, China [Grant. 2024NS009 (to ND)].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1498814/full#supplementary-material

References

Bernstein, H. N., and Ginsberg, J. (1964). The pathology of chloroquine retinopathy. *Arch. Ophthalmol.* 71, 238–245. doi:10.1001/archopht.1964.00970010254019

Borchers, A. T., Naguwa, S. M., Shoenfeld, Y., and Gershwin, M. E. (2010). The geoepidemiology of systemic lupus erythematosus. *Autoimmun. Rev.* 9, A277–A287. doi:10.1016/j.autrev.2009.12.008

Chen, P. M., Gombart, Z. J., and Chen, J. W. (2011). Chloroquine treatment of ARPE-19 cells leads to lysosome dilation and intracellular lipid accumulation: possible implications of lysosomal dysfunction in macular degeneration. *Cell. Biosci.* 1, 10. doi:10.1186/2045-3701-1-10

Costedoat-Chalumeau, N., Dunogué, B., Leroux, G., Morel, N., Jallouli, M., Le Guern, V., et al. (2015). A critical review of the effects of hydroxychloroquine and chloroquine on the eye. *Clin. Rev. Allergy Immunol.* 49, 317–326. doi:10.1007/s12016-015-8469-8

Dammacco, R. (2018). Systemic lupus erythematosus and ocular involvement: an overview. *Clin. Exp. Med.* 18, 135–149. doi:10.1007/s10238-017-0479-9

Godfrey, H., Leibovit-Reiben, Z., Jedlowski, P., and Thiede, R. (2025). Alopecia associated with the use of semaglutide and tirzepatide: a disproportionality analysis using the FDA adverse event reporting system (FAERS) from 2022 to 2023. *J. Eur. Acad. Dermatol Venereol.* 39, e153–e154. doi:10.1111/jdv.20197

Hsu, C.-S., Hsu, C.-W., Lu, M.-C., and Koo, M. (2020). Risks of ophthalmic disorders in patients with systemic lupus erythematosus - a secondary cohort analysis of population-based claims data. *BMC Ophthalmol.* 20, 96. doi:10.1186/s12886-020-01360-w

Hu, W., Chen, L., Li, H., and Liu, J. (2022). Eye disorders associated with newer antiepileptic drugs: a real-world disproportionality analysis of FDA adverse event reporting system. *Seizure* 96, 66–73. doi:10.1016/j.seizure.2022.01.011

Jorge, A., Ung, C., Young, L. H., Melles, R. B., and Choi, H. K. (2018). Hydroxychloroquine retinopathy - implications of research advances for rheumatology care. *Nat. Rev. Rheumatol.* 14, 693–703. doi:10.1038/s41584-018-0111-8

Li, X., Sun, Y.-Q., Huang, Q.-L., Zhang, Z.-J., Shi, L.-Q., Tang, J.-F., et al. (2025a). Drug-related macular edema: a real-world FDA adverse event reporting system database study. *BMC Pharmacol. Toxicol.* 26, 23. doi:10.1186/s40360-025-00856-9

Li, X., Sun, Y.-Q., Liu, M.-M., and Tang, J.-F. (2025b). Real-world pharmacovigilance analysis of drug-related conjunctivitis using the FDA adverse event reporting system database. *Sci. Rep.* 15, 13407. doi:10.1038/s41598-025-92796-x

Li, X., Wang, S. W., Zhang, Z.-J., Luo, Z. Y., Tang, J. F., and Tao, T. (2025c). Real-world pharmacovigilance analysis of drug-related cataracts using the FDA adverse event reporting system database. *Front. Pharmacol.* 16, 1498191. doi:10.3389/fphar.2025.1498191

Liu, H., Yang, Q., Li, Z., Yan, S., and Ming, S. (2025). Systematic analysis of sugammadex-related adverse drug reaction signals using FAERS database. *Int. J. Surg.* 111, 1988–1994. doi:10.1097/JS9.0000000000002194

Long, P., Li, S., Pan, L., Wang, Y., Chen, W., and Wang, X. (2024). Cardiovascular adverse events associated with antibody-drug conjugates (ADCs): a pharmacovigilance study based on the FAERS database. *Front. Pharmacol.* 15, 1378010. doi:10.3389/fphar.2024.1378010

Luo, Z.-Y., Li, X., Chen, C.-T., Kang, H.-H., Zhang, Z.-J., Wang, D., et al. (2025). Ocular adverse events associated with GLP-1 receptor agonists: a real-world study based on the FAERS database and network pharmacology. *Expert Opin. Drug Saf.* 24, 287–296. doi:10.1080/14740338.2024.2419989

Mao, K., Li, J., Zhu, X., Sun, H., Zhong, S., and Mao, W. (2024). Signal mining study of severe cutaneous adverse events of valaciclovir or acyclovir based on the FAERS database. *Expert Rev. Clin. Pharmacol.* 17, 101–110. doi:10.1080/17512433.2023.2294002

Marmor, M. F., Kellner, U., Lai, T. Y. Y., Melles, R. B., Mieler, W. F., and American Academy of Ophthalmology (2016). Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 123, 1386–1394. doi:10.1016/j.ophtha.2016.01.058

O'Donnell, C. J., and Nabel, E. G. (2011). Genomics of cardiovascular disease. *N. Engl. J. Med.* 365, 2098–2109. doi:10.1056/NEJMra1105239

Pryor, K. P., Xu, C., Collins, J. E., Costenbader, K. H., and Feldman, C. H. (2022). Predictors of initial hydroxychloroquine receipt among medicaid beneficiaries with incident systemic lupus erythematosus. *Arthritis Care Res. Hob.* 74, 1263–1268. doi:10.1002/acr.24572

Rosenthal, A. R., Kolb, H., Bergsma, D., Huxsoll, D., and Hopkins, J. L. (1978). Chloroquine retinopathy in the rhesus monkey. *Investig. Ophthalmol. Vis. Sci.* 17, 1158–1175.

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* 10, 796–803. doi:10.7150/ijms.6048

Singh, R., Singuri, S., Batoki, J., Lin, K., Luo, S., Hatipoglu, D., et al. (2023). Deep learning algorithm detects presence of disorganization of retinal inner layers (DRIL)-an early imaging biomarker in diabetic retinopathy. *Transl. Vis. Sci. Technol.* 12, 6. doi:10.1167/tvst.12.7.6

Wetterholm, D. H., and Winter, F. C. (1964). Histopathology of chloroquine retinal toxicity. *Arch. Ophthalmol.* 71, 82–87. doi:10.1001/archopht.1964.00970010098016

Zhang, Z., Ma, X., Wang, Y.-H., Shi, X., and Wei, J. C.-C. (2023). Hydroxychloroquine is neutral on incidental cataracts in patients with rheumatoid arthritis. *Sci. Rep.* 13, 5576. doi:10.1038/s41598-023-32297-x

Frontiers in Pharmacology

Explores the interactions between chemicals and living beings

The most cited journal in its field, which advances access to pharmacological discoveries to prevent and treat human disease.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact