frontiers | Research Topics

Emerging trends in real-world pharmacoepidemiology 2023

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Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-6265-9
DOI 10.3389/978-2-8325-6265-9

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Emerging trends in real-world pharmacoepidemiology: 2023

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Citation

Salahudeen, M., Kao, L.-T., Da Silva Dal Pizzol, T., Peterson, G., eds. (2025). *Emerging trends in real-world pharmacoepidemiology: 2023*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6265-9

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frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 15 April 2025
DOI 10.3389/fphar.2025.1601477

OPEN ACCESS

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RECEIVED 28 March 2025
ACCEPTED 08 April 2025
PUBLISHED 15 April 2025

CITATION
Salahudeen MS, Da Silva Dal Pizzol T, Kao L-T and Peterson GM (2025) Editorial: Emerging trends in real-world pharmacoepidemiology: 2023.
Front. Pharmacol. 16:1601477.
doi: 10.3389/fphar.2025.1601477

Editorial: Emerging trends in real-world pharmacoepidemiology: 2023

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KEYWORDS

pharmacoepidemiology (MeSH), real-world, medication safety, real-world data (RWD), big data, population-level, patient safety, electronic health records

Editorial on the Research Topic
Emerging trends in real-world pharmacoepidemiology: 2023

It is our great pleasure to introduce the Research Topic "*Emerging Trends in Real-World Pharmacoepidemiology: 2023*," published in Frontiers in Pharmacology. This special Research Topic showcases innovative, real-world studies that advance our understanding of medication safety, efficacy, and utilisation across diverse clinical settings and patient populations.

Pharmacoepidemiology continues to evolve rapidly, integrating complex real-world data and sophisticated analytical techniques (Pazzagli et al., 2018; Dimakos and Douros, 2024) designed to assess effectiveness and patterns of medication use (Sabaté and Montané, 2023). The contributions in this Research Topic reflect these advancements and underscore the interdisciplinary and global scope of contemporary pharmacoepidemiologic research.

Several studies in this Research Topic provide valuable insights into the effectiveness and safety of medications in clinical practice. For instance, it was demonstrated that therapeutic drug monitoring of vancomycin blood concentrations was associated with a significantly reduced mortality risk in critically ill patients (Peng et al.). Similarly, a systematic qualitative review elucidated key barriers and facilitators influencing medication self-management in polypharmacy, offering practical strategies for improving adherence and patient outcomes (Jin et al.).

A number of articles in this Research Topic utilised large pharmacovigilance databases, such as the FDA Adverse Event Reporting System (FAERS), to identify new safety signals. For example, novel adverse events were reported for dexmedetomidine (Liu et al.), and strong signals of drug-induced liver injury were associated with certain CDK4/6 inhibitors (She et al.). Studies also highlighted serious adverse reactions, including pulmonary haemorrhage and haemoptysis, associated with bevacizumab regimens (Hu et al.), safety concerns with transthyretin inhibitors (Liu et al.), and potential risks of tumor lysis syndrome with melanoma treatments involving encorafenib and binimetinib (Xia et al.). Further, analysis of real-world safety profiles of cenobamate underscored the importance of pharmacovigilance in clinical decision-making (Chen et al.). Such pharmacovigilance studies emphasise the necessity of heightened clinical awareness and proactive patient monitoring.

Some of the limitations of the pharmacovigilance databases should be acknowledged. In particualr, while FAERS is a valuable tool for hypothesis generation in medication safety research, it is important to recognise critical limitations inherent in such analyses, including voluntary reporting biases, lack of causality assessments, incomplete demographic data, inability to determine the prevalence of adverse reactions, and potential false-positive signals (Sakaeda et al., 2013; Chedid et al., 2018). As recommended by current best practice guidelines, such as the READUS-PV guideline (Fusaroli et al., 2024), robust pharmacovigilance research requires comprehensive methodologies, including systematic reviews, individual case assessments, and sensitivity analyses to validate these findings further.

This Research Topic also includes significant clinical insights, such as identifying patterns of antimicrobial prescribing in surgical units, revealing opportunities for stewardship interventions to improve antibiotic use (Jamaluddin et al.). Further, the retrospective analysis of spontaneous adverse drug reactions in a tertiary hospital illustrated the importance of local pharmacovigilance efforts to enhance patient safety through targeted interventions (Montané et al.).

Additionally, novel findings around dosing strategies emerged, highlighting therapeutic anti-Xa targets for enoxaparin and underscoring sex-based differences in achieving therapeutic anticoagulation (Tinchon et al.). These real-world insights challenge conventional dosing paradigms and suggest the need for more individualised therapeutic approaches.

Collectively, the 11 studies (Chen et al.; Hu et al.; Jamaluddin et al.; Jin et al.; Liu et al.; Liu et al.; Montané et al.; Peng et al.; She et al.; Tinchon et al.; Xia et al.) make significant contributions to the field of pharmacoepidemiology, highlighting both the complexities and potential of real-world medication safety and effectiveness research. The continued integration of real-world data and evidence has been promoted for being better, bigger, brisker, broader, and bolder, positioning pharmacoepidemiology to embrace new challenges and opportunities.

Data-adaptive techniques, such as machine learning, coupled with expert human interpretation, are increasingly essential to fully leverage electronic health records and advance analytical methodologies (Alowais et al., 2023; Javaid et al., 2024; Chaabene et al., 2025). The development of robust and practical methodologies to manage complex and integrated datasets will further advance the field. Building upon its strong foundation, pharmacoepidemiology is well-positioned to advance significantly across several domains and thrive in this exciting era of real-world data and evidence.

We invite readers to explore these insightful articles, hoping they will inspire further research and innovation in pharmacoepidemiology.

Author contributions

MS: Writing – review and editing, Writing – original draft. TD: Writing – review and editing. L-TK: Writing – review and editing. GP: Writing – review and editing.

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.

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 authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 15 March 2024
DOI 10.3389/fphar.2024.1369384

OPEN ACCESS

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RECEIVED 12 January 2024
ACCEPTED 06 March 2024
PUBLISHED 15 March 2024

CITATION
Chen S, Fang W, Zhao L and Xu H (2024), Safety assessment of cenobamate: real-world adverse event analysis from the FAERS database. *Front. Pharmacol.* 15:1369384. doi: 10.3389/fphar.2024.1369384

Safety assessment of cenobamate: real-world adverse event analysis from the FAERS database

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Objective: This study aims to analyze adverse drug events (ADEs) associated with cenobamate from the FAERS database, covering the third quarter of 2020 to the second quarter of 2023.

Methods: Data related to cenobamate-associated ADEs from the third quarter of 2020 to the second quarter of 2023 were collected. After standardizing the data, various signal quantification techniques, including ROR, MHRA, BCPNN, and MGPS, were employed for analysis.

Results: Among 2535 ADE reports where cenobamate was the primary suspected drug, 94 adverse reactions involving 11 different System Organ Class (SOC) categories were identified through the application of four signal quantification techniques. More specifically, neurological disorders and injuries resultant from complications are frequent adverse reactions associated with cenobamate.

Conclusion: Our research findings align with established results, affirming the favorable safety profile of cenobamate. Effective prevention of adverse reactions induced by cenobamate can be achieved through the establishment of efficient blood concentration monitoring and dose adjustments.

KEYWORDS

FAERS database, cenobamate, adverse drug events, epilepsy, real-world study

1 Introduction

Epilepsy, as a prevalent neurological disorder, is characterized by sudden abnormal discharges of brain neurons, leading to transient cerebral dysfunction and significantly impacting the physical and mental wellbeing as well as daily life of affected individuals. According to the 2019 Global Burden of Disease (GBD) study, epilepsy affects over 50 million people worldwide (Shu et al., 2023). Despite the fact that the majority of epilepsy patients can achieve seizure control through pharmacological intervention, a subset of patients exhibits poor responsiveness to existing antiepileptic drugs (Panebianco et al., 2023). Hence, the urgent need to identify more effective and less adverse-reactive antiepileptic drugs persists.

The third-generation antiepileptic drug, cenobamate, received approval from the U.S. FDA in November 2019. Its primary mechanisms involve blocking sodium ion channels and positively modulating GABA receptor activity, exhibiting antiepileptic effects. Currently, both the FDA and EMA have sanctioned its use for the treatment of focal epilepsy. Clinical studies demonstrate that, compared to other antiepileptic drugs, cenobamate significantly excels in reducing focal epilepsy seizures (Makridis and

Kaindl, 2023). Furthermore, several real-world studies substantiate its significant benefits in treating many drug-resistant epilepsy patients (Beltran-Corbellini et al., 2023; Schmitz et al., 2023). Despite the broad therapeutic potential of cenobamate in managing epilepsy, attention should be directed towards its safety.

The FDA Adverse Event Reporting System (FAERS) serves as a platform for collecting and analyzing drug adverse events (ADEs) related to drug utilization (Iyer et al., 2014). These data represent a crucial resource for evaluating drug safety and effectiveness. The purpose of this article is to analyze adverse event signals related to cenobamate in the real-world using data mining techniques, providing insights for the clinical use of the drug.

2 Methods

Using the trade name "XCOPRI" as the search term in the U.S. FAERS database, we retrieved ADEs reports related to cenobamate from the third quarter of 2020 to the second quarter of 2023. Descriptions and classifications of ADE reports were based on the Preferred Term (PT) and System Organ Class (SOC) concentrated in the Medical Dictionary for Regulatory Activities (MedDRA) terminology set (version 24.0) released by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ADE reports primarily implicating cenobamate were selected, and duplicates were excluded to minimize bias in ADE risk signal identification. This study employed four methods for ADEs signal mining, including the Reporting Odds Ratio (ROR) method, the Medicines Healthcare Products Regulatory Agency (MHRA) method, Bayesian Confidence Propagation Neural Network (BCPNN) method, and Multi-Item Gamma Poisson Shrinker (MGPS) method (Sakaeda et al., 2013). The ROR method originated from the Lareb laboratory of the Dutch Pharmacovigilance Centre, characterized by less bias and higher sensitivity, hence it is widely applied (Moore et al., 2005). The MHRA method is an extension of the PRR method, combining the PRR value, absolute report numbers, and chi-square values on the premise of ensuring a minimum combination of cases. It is known for its high sensitivity and stability of results and is currently extensively used by the Medicines and MHRA of the United Kingdom (Rothman et al., 2004; Hou et al., 2014). However, studies have shown that the sensitivity of this method decreases as the number of reports increases (Zhang et al., 2017). At present, the BCPNN method is a mature signal detection technique applied both domestically and internationally. It is capable of early signal detection even with fewer data or in case of missing data, and its detection results become more stable as the number of reports increases (van Puijenbroek et al., 2000), but the method is computationally complex and lacks transparency. Additionally, the MGPS method has the advantage of detecting signals for rare events (Jiang et al., 2024). Although there is no gold standard for signal detection methods, each method has its characteristics, with respective advantages and disadvantages in terms of applicability and feasibility in the database. Consequently, this study employed a combination of four methods to obtain signals with strong associations. These four methods compare the ratio of target AEs for the target drug to the ratio of target AEs for all other drugs. If this ratio exceeds a set threshold, it is deemed imbalanced, indicating the generation of potential AEs signals. In this study, a positive signal for drug-related AEs is considered when at least one of the four algorithms meets the criteria; when all four algorithms meet the criteria, it suggests a strong association of AEs, thereby avoiding potential false-positive signals. The parameters required for the ROR and other formulas are calculated based on a 2 × 2 contingency table, which is specifically available in Table 1. Specific formulas and signal detection criteria for the four algorithms can be found in Table 2 (Bate et al., 1998; Evans et al., 2001; van Puijenbroek et al., 2002; Sakaeda et al., 2013).

We used SPSS software version 26.0 (IBM, United States), Microsoft Excel 2019, and R software version 4.3.1 for statistical analysis. The creation of figures relied on the "ggplot2" package in the R language.

3 Results

3.1 Descriptive analysis

Following the exclusion of duplicates, data from reports logged between the third quarter of 2020 and the second quarter of 2023 were extracted from the FAERS database. Among 2,535 reports, cenobamate was identified as the primary drug used. The specific relevant information and calculated figures are provided in Supplementary Material S1. The majority of these reports originated from the United States (n = 2,378), with the United Kingdom contributing the second-highest number (n = 29). Within the pool of reports, a cumulative total of 770 serious ADEs were recorded, encompassing instances of fatalities, life-threatening outcomes, disability, and permanent damage. Of these, 315 reports indicated ADEs necessitating hospital admission, 375 reports noted other significant medical events of severity, and there were 36 reports marked with fatalities.

3.2 Signal detection

Using four distinct algorithms, including the ROR method and BCPNN method, 139 PTs were found using the ROR method, 131 PTs were separated using the MHRA method, 323 PTs were separated using the EBGM method, and 295 PTs were separated using the BCPNN method. Ultimately, a total of 94 effective PTs were identified, as detailed in Figure 1A. The most prevalent PTs included Seizure (n = 648), Product Dose Omission Issue (n = 446), and Fatigue (n = 340). The top 30 PTs with the strongest associations is displayed in Table 3, according to the frequency of occurrence, while the detailed information for all positive signals is available in Supplementary Table S2. Furthermore, we probed the onset times of each PTs, as depicted in Figure 1B. It was observed that the PTs predominantly clustered within the first month post-medication (n = 1,129), thereafter exhibiting a decremental pattern over time. This insight could hasten the recognition and governance of safety issues related to cenobamate, thereby enabling prompt modifications in therapy to mitigate adverse reactions and augment the effectiveness of the treatment.

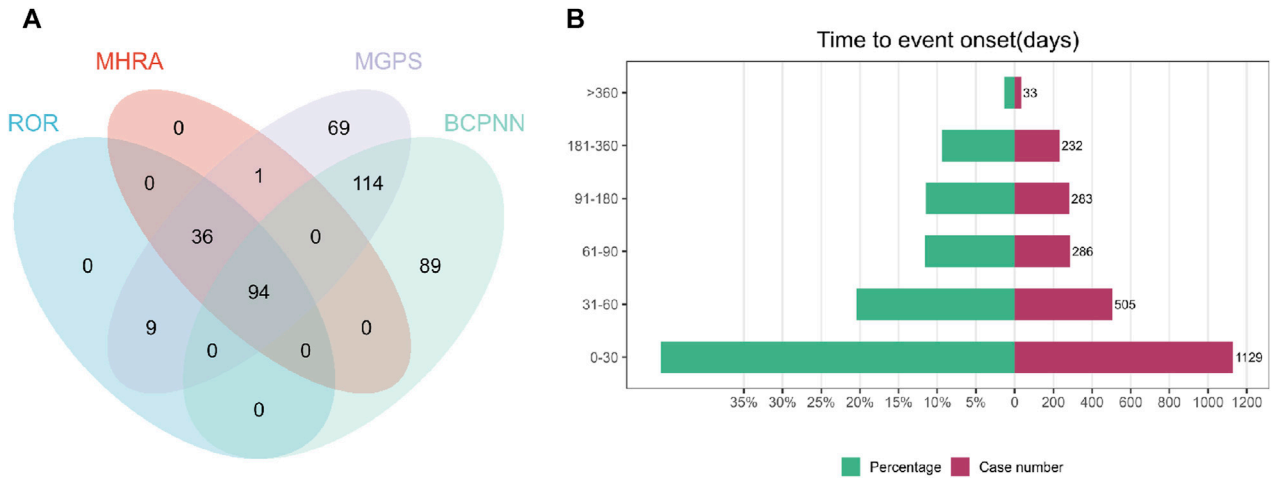

FIGURE 1
(A) The meticulous application of four distinct methodologies culminated in the identification of 94 efficacious PTs. Out of an assemblage of 882 signals, the ROR method surfaced 139 relevant signals, the MHRA method segregated 131, the EBGM method segregated 323, and the BCPNN method segregated 295 effective signals. **(B)** Onset Time of Adverse Reactions Related to Cenobamate.

TABLE 1 Fourfold table for calculation, used for comparing the association between a specific drug and the occurrence of a specific adverse event.

	Cenobamate-related ADEs	Non-cenobamate-related ADEs	Total
Cenobamate	a	b	a + b
Non-cenobamate	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

ADE, adverse drug events. a is the number of cases where a specific adverse event occurred after using cenobamate, b is the number of cases where cenobamate was used but the specific adverse event did not occur, c is the number of cases where the specific adverse event occurred without the use of cenobamate, d is the number of cases where neither cenobamate was used nor the specific adverse event occurred.

3.3 Signals of system organ class

The 94 positive signals of PTs were classified according to the MedDRA 24.0 version SOC, revealing that 11 organ systems are impacted by AEs associated with cenobamate. Table 4 elucidates the signal intensities of the cenobamate-linked AEs stratified by SOCs. The positive signals predominantly clustered within three SOCs, namely: Nervous System Disorders (n = 2069), Injury, Poisoning and Procedural Complications (n = 865), and General Disorders and Administration Site Conditions (n = 705), with the comprehensive details of the remaining SOCs available in Table 4. Specifically, neurological disorders along with injuries due to complications such as falls or cranial impacts are noted as common adverse reactions to cenobamate.

4 Discussion

Cenobamate, as one of the latest antiepileptic drugs, is commonly employed for the treatment of focal seizures in adult patients, offering advantages such as lower cost and improved tolerability (Specchio et al., 2021; Laskier et al., 2023). Functioning not only as a blocker of voltage-gated sodium channels and a positive modulator of GABA receptors, cenobamate also activates the PI3K/Akt-CREB-BDNF pathway, leading to elevated anti-apoptotic factor levels and reduced pro-apoptotic factor levels. This induction inhibits apoptosis, thereby enhancing neuronal survival (Wicinski et al., 2021).

In terms of pharmacokinetic studies on cenobamate, research by Roberti et al. indicates its nonlinear pharmacokinetics. The recommended initial dose of cenobamate is 12.5 mg/day, titrated gradually to the target daily dose of 200 mg, with the possibility of increasing to a maximum of 400 mg/day based on clinical response (Roberti et al., 2021). Some central nervous system-related side effects are more prevalent, including drowsiness, dizziness, diplopia, and gait and coordination disturbances, particularly when the daily dose exceeds 300 mg (Roberti et al., 2021).

Concurrently, studies support the significant improvement in seizure control among adults with uncontrolled focal seizures when cenobamate is used as adjunctive therapy at a dose of 200 mg/day, with good tolerability (Chung et al., 2020; Smith et al., 2022).

Based on clinical trial experience, cenobamate exhibits minor side effects, primarily consisting of dizziness and drowsiness (Catalan-Aguilar et al., 2023; Villanueva et al., 2023). Considering that various neurological and psychiatric conditions are common ADEs) associated with antiepileptic drugs, our study results corroborate this conclusion. Additionally, in patients treated with cenobamate, our study identified high-frequency and strong-signal ADEs such as Seizure (n = 648, ROR = 52.52, IC025 = 3.92) and generalized tonic-clonic seizure (n = 55, ROR = 28.86, IC025 = 3.17), which may be linked to treatment failure with cenobamate. Past research has established a close correlation between

TABLE 2 Four main algorithms are used to evaluate the correlation between cenobamate and AEDs. This includes ROR, MHRA, BCPNN, and EBGM methods, formulas, and thresholds.

Method	Formula	Threshold
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	a>3 and 95% CI (lower limit) > 1
	$SE(\ln ROR) = \sqrt{(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d})}$	
	$95\%CI = e^{\ln(ROR) \pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	
MHRA	$PRR = \frac{a/(a+b)}{c/(c+d)}$	a>3, PRR>2 and $\chi^2 > 4$
	$x^2 = \frac{(\lvert ab-cd\rvert - \frac{N}{2})^2 \times N}{(a+b)(c+d)(a+c)(b+d)}$	
BCPNN	$IC = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025 > 0
	$\gamma = \gamma ij \frac{(N+\alpha)(N+\beta)}{(a+b+\alpha i)(a+c+\beta j)}$	
	$E(IC) = log_2 \frac{(a+\gamma ij)(N+\alpha)(N+\beta)}{(N+\gamma)(a+b+\alpha i)(a+c+\beta j)}$	
	$SD = \sqrt{V(IC)}$	
	$IC025 = E(IC) - 2SD$	
MGPS	$EBGM = \frac{a/(a+b+c+d)}{(a+c)(a+b)}$	EBGM05 > 2
	$95\%CI = e^{\ln(EBGM) \pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	

N, the number of reports; a is the number of cases where a specific adverse event occurred after using cenobamate, b is the number of cases where cenobamate was used but the specific adverse event did not occur, c is the number of cases where the specific adverse event occurred without the use of cenobamate, d is the number of cases where neither cenobamate was used nor the specific adverse event occurred; ROR, reporting odds ratio; γ, γ_{ij} represent the parameters of the Dirichlet distribution; α, α_i, β, β_j represent the parameters of the Beta distribution; SD, standard deviation; MHRA, healthcare products regulatory agency; BCPNN, bayesian confidence propagation neural network; MGPS, Multi-Item Gamma Poisson Shrinker; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; χ2, chi-squared; IC, information component; IC025, the lower limit of 95% CI, for the IC; E(IC), the IC, expectations; V(IC), the variance of IC; EEBGM05, the lower limit of the 95% CI, for EBGM.

antiepileptic drug efficacy and blood drug concentration: elevated concentrations increase toxicity and the likelihood of ADEs, while insufficient concentrations fail to control seizures (Alldredge, 1999).

Furthermore, we observed adverse signals such as Fall (n = 155, ROR = 3.66, IC025 = 0.19) and Head banging (n = 4, ROR = 53.16, IC025 = 4.05). Although some falls may be attributed to poorly controlled seizure symptoms (Jung et al., 2023), numerous studies indicate that less than half of falls and fractures are directly associated with seizures. Falls are also frequent among patients taking antiepileptic drugs (Leppik et al., 2017), posing greater risks and severe consequences, particularly in elderly individuals. However, in another literature on falls in the elderly from the FAERS database, we found that the ROR value for cenobamate is lower than that for common antiepileptic drugs (Zhou et al., 2022), suggesting a favorable effect of cenobamate. Additionally, antiepileptic medications may impinge upon the functionality of the nervous system, encompassing balance and coordination capabilities, thereby elevating the risk of cranial impacts. Although the incidence of head collisions under cenobamate therapy appears to be infrequent, we must nevertheless maintain vigilance regarding this adverse reaction. In summary, monitoring blood drug concentrations during clinical use of antiepileptic drugs is necessary and holds significance for dose adjustments in epilepsy patients. Additionally, our observations revealed that cenobamate may trigger certain skin conditions, such as pruritic rash, possibly due to drug-induced allergic reactions. While generally mild, these skin reactions may serve as precursors to severe allergic reactions (Zgolli et al., 2023). Thus, seeking timely help and advice from healthcare professionals for appropriate diagnosis and treatment is crucial.

The adverse effects of antiepileptic drugs can significantly encroach upon a patient's quality of life, precipitating physical discomforts such as fatigue, dizziness, and visual disturbances; psychological health issues, including mood fluctuations and depression; as well as cognitive impairments characterized by diminished memory and attention. These detriments may lead to reduced medication adherence, a decline in quality of life, increased economic strain, limited vocational choices, and an intensified sensation of social isolation, as reported in the literature (Kowski et al., 2016; Lin et al., 2016). Furthermore, patients who reduce or discontinue medication due to adverse reactions may experience escalated risks of epilepsy symptom recurrence (Shinnar and Berg, 1995; Ramos-Lizana et al., 2010). This scenario can result in a pernicious cycle that severely compromises the quality of life for many individuals living with epilepsy. To break this cycle, it is imperative to identify antiepileptic medications with fewer adverse reactions and minimal impact on quality of life. Our research observed that severe outcomes comprised 30.4% of the total reports, which signifies that cenobamate has achieved commendable results in clinical therapy, suggesting it might be a preferable treatment option.

Overall, this study, based on the FAERS database and utilizing the ROR method and PRR, among other algorithms, comprehensively presents the safety signal spectrum of cenobamate. It further substantiates cenobamate as a well-tolerated antiepileptic drug.

There are still some limitations in this study. Firstly, while the FAERS database boasts substantial volume and broad coverage, it is marred by incomplete data, with some reports lacking critical information such as age and gender. Additionally, as reporting is voluntary, there is an inherent risk of underreporting, delayed reporting, and misreporting of incomplete information, which introduces potential bias. Secondly, the utilization of analytical methods such as the ROR and PRR can only elucidate the association strength between the medication and ADEs, and

TABLE 3 The top 30 signal strength of adverse events of cenobamate ranked by number of incidence cases at the PTs level in FAERS database.

PTs	SOC	Case reports	ROR (95% CI)	PRR	EBGM	EBGM05	IC025
Seizure	Nervous system disorders	648	52.52 (48.45–56.93)	48.27	29,817.45	27,871.31	3.92
Product dose omission issue	Injury, poisoning and procedural complications	446	20.89 (18.99–22.99)	19.76	7,943.02	7,331.75	2.63
Fatigue	General disorders and administration site conditions	340	3.58 (3.22–4.00)	3.47	605.79	553.13	0.13
Somnolence	Nervous system disorders	334	13.39 (12.00–14.94)	12.86	3,659.10	3,338.16	2.02
Dizziness	Nervous system disorders	268	4.27 (3.78–4.82)	4.16	647.31	584.56	0.39
Fall	Injury, poisoning and procedural complications	155	3.66 (18.99–22.99)	3.61	293.89	257.27	0.19
Feeling abnormal	General disorders and administration site conditions	130	4.03 (3.39–4.79)	3.98	291.21	251.88	0.33
Gait disturbance	General disorders and administration site conditions	121	4.86 (4.06–5.82)	4.80	364.89	313.97	0.60
Wrong technique in product usage process	Injury, poisoning and procedural complications	110	4.70 (3.89–5.67)	4.65	315.39	269.42	0.55
Balance disorder	Nervous system disorders	109	9.65 (7.98–11.66)	9.53	831.92	710.12	1.58
Memory impairment	Nervous system disorders	85	4.78 (3.86–5.92)	4.74	251.26	210.10	0.58
Hypersomnia	Nervous system disorders	76	21.08 (16.81–26.43)	20.88	1,434.68	1,187.19	2.71
Product use issue	Injury, poisoning and procedural complications	74	3.28 (2.61–4.12)	3.26	115.96	95.74	0.04
Vision blurred	Eye disorders	70	4.07 (3.22–5.15)	4.04	160.44	131.76	0.35
Diplopia	Eye disorders	69	21.24 (16.75–26.93)	21.06	1,314.43	1,077.64	2.73
Lethargy	Nervous system disorders	57	7.54 (5.81–9.78)	7.49	320.51	257.69	1.24
Generalised tonic-clonic seizure	Nervous system disorders	55	28.86 (22.13–37.65)	28.67	1,462.33	1,170.72	3.17
Product availability issue	Product issues	51	28.41 (21.56–37.44)	28.23	1,334.12	1,059.04	3.15
Dysarthria	Nervous system disorders	46	9.32 (6.97–12.46)	9.27	339.16	266.07	1.54
Adverse event	General disorders and administration site conditions	46	3.89 (2.91–5.20)	3.88	98.26	77.09	0.29
Therapy interrupted	Surgical and medical procedures	43	8.47 (6.27–11.43)	8.43	281.20	218.79	1.41
Aura	Nervous system disorders	33	141.87 (100.41–200.46)	141.28	4,496.20	3,366.85	5.44
Disturbance in attention	Nervous system disorders	33	4.57 (3.25–6.44)	4.56	91.73	68.90	0.52
Feeling drunk	General disorders and administration site conditions	32	32.01 (22.60–45.33)	31.88	952.52	711.86	3.32
Irritability	Psychiatric disorders	31	3.82 (2.68–5.43)	3.81	64.18	47.77	0.26
Amnesia	Nervous system disorders	30	3.42 (2.39–4.89)	3.41	51.11	37.86	0.10
Speech disorder	Nervous system disorders	29	4.20 (2.92–6.05)	4.19	70.37	51.86	0.40
Anger	Psychiatric disorders	28	6.06 (4.18–8.79)	6.04	117.79	86.34	0.93
Abnormal behaviour	Psychiatric disorders	27	4.81 (3.29–7.01)	4.79	81.04	59.07	0.59
Partial seizures	Nervous system disorders	26	40.56 (27.56–59.68)	40.43	993.43	45.59	3.66

PT, preferred term; SOC, system organ class; ROR, reporting odds ratio; PRR, proportional reporting ratio; CI, confidence interval; IC, information component; IC025, the lower limit of the 95% CI, for IC; EBGM, empirical bayes geometric mean; EBGM05, the lower limit of the 95% CI, for EBGM.

TABLE 4 The signal strength of ADEs of cenobamate at the SOC level in FAERS database.

System organ class	SOC code	Case reports
Nervous system disorders	10,029,205	2069
Injury, poisoning and procedural complications	10,022,117	865
General disorders and administration site conditions	10,018,065	705
Psychiatric disorders	10,037,175	199
Eye disorders	10,015,919	155
Surgical and medical procedures	10,042,613	78
Product issues	10,077,536	62
Musculoskeletal and connective tissue disorders	10,028,395	16
Investigations	10,022,891	15
Respiratory, thoracic and mediastinal disorders	10,038,738	11
Social circumstances	10,041,244	6

SOC, system organ class; ADE, adverse drug events.

cannot directly confirm causality. The actual relationship requires corroboration with existing literature and clinical application. Furthermore, our current study investigated only one limited safety dataset, with all reports predominantly originating from European and American countries. Given regional and ethnic variabilities, these findings may not be extrapolated to other populations, such as those in Asia. Lastly, given cenobamate's relatively recent introduction to the market, larger-scale clinical trials in the future may unearth additional potential adverse signals. Hence, clinicians should remain vigilant regarding drug safety and promote the judicious use of cenobamate.

5 Conclusion

Our study, predicated upon the data derived from the FAERS database, indicates that cenobamate exhibits a commendable safety profile. We have deliberated on the preventive potential of adverse reactions associated with cenobamate, which can be effectively actualized through the establishment of vigilant therapeutic drug monitoring and meticulous dosage titration. These insights proffer substantive guidance for the clinical utilization of cenobamate in the treatment of epilepsy, further buttressing the assurance of patient safety and therapeutic efficacy during the administration of cenobamate.

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

SC: Conceptualization, Formal Analysis, Writing–original draft, Writing–review and editing. WF: Formal Analysis, Visualization, Writing–original draft. LZ: Formal Analysis, Writing–original draft. HX: Funding acquisition, Writing–original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank everyone who participated 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1369384/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 03 April 2024
DOI 10.3389/fphar.2024.1378090

OPEN ACCESS

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RECEIVED 29 January 2024
ACCEPTED 20 March 2024
PUBLISHED 03 April 2024

CITATION
She Y, Guo Z, Zhai Q, Liu J, Du Q and Zhang Z (2024), CDK4/6 inhibitors in drug-induced liver injury: a pharmacovigilance study of the FAERS database and analysis of the drug–gene interaction network.
Front. Pharmacol. 15:1378090.
doi: 10.3389/fphar.2024.1378090

CDK4/6 inhibitors in drug-induced liver injury: a pharmacovigilance study of the FAERS database and analysis of the drug–gene interaction network

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Objective: The aim of this study was to investigate the potential risk of drug-induced liver injury (DILI) caused by the CDK4/6 inhibitors (CDK4/6is abemaciclib, ribociclib, and palbociclib by comprehensively analyzing the FDA Adverse Event Reporting System (FAERS) database. Moreover, potential toxicological mechanisms of CDK4/6is-related liver injury were explored via drug–gene network analysis.

Methods: In this retrospective observational study, we collected reports of DILI associated with CDK4/6i use from the FAERS dated January 2014 to March 2023. We conducted disproportionality analyses using the reporting odds ratio (ROR) with a 95% confidence interval (CI). Pathway enrichment analysis and drug-gene network analyses were subsequently performed to determine the potential mechanisms underlying CDK4/6i-induced liver injury.

Results: We found positive signals for DILI with ribociclib (ROR = 2.60) and abemaciclib (ROR = 2.37). DILIs associated with liver-related investigations, signs, and symptoms were confirmed in all three reports of CDK4/6is. Moreover, ascites was identified as an unlisted hepatic adverse effect of palbociclib. We isolated 189 interactive target genes linking CDK4/6 inhibitors to hepatic injury. Several key genes, such as STAT3, HSP90AA1, and EP300, were revealed via protein-protein analysis, emphasizing their central roles within the network. KEGG pathway enrichment of these genes highlighted multiple pathways.

Conclusion: Our study revealed variations in hepatobiliary toxicity among the different CDK4/6 inhibitors, with ribociclib showing the highest risk of liver injury, followed by abemaciclib, while palbociclib appeared relatively safe. Our findings emphasize the need for cautious use of CDK4/6 inhibitors, and regular liver function monitoring is recommended for long-term CDK4/6 inhibitor use.

KEYWORDS

cyclin-dependent kinase 4/6 inhibitors, drug-induced liver injuries, pharmacovigilance, FAERS, disproportionality analyses, protein-protein interaction

1 Introduction

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), such as palbociclib, ribociclib, and abemaciclib, have been approved for treating patients with hormone receptor-positive and human epidermal growth factor receptor 2-negative breast cancer (Finn et al., 2015; Cristofanilli et al., 2016; Finn et al., 2016; Hortobagyi et al., 2016; Dickler et al., 2017; Goetz et al., 2017; Sledge et al., 2017; Slamon et al., 2018; Tripathy et al., 2018; Turner et al., 2018; Johnston et al., 2020; Royce et al., 2022). With a median progression-free survival (PFS) exceeding 2 years in first-line metastatic patients, indicating long-term use, evaluating the enduring safety of CDK4/6is in breast cancer treatment is imperative (Gao et al., 2020; Harbeck et al., 2021).

While these drugs exhibit similar clinical efficacy, their adverse event (AE) spectra differ markedly (Asghar et al., 2015; Desnoyers et al., 2020; George et al., 2021). To assess the safety of CDK4/6is, it is essential to evaluate their risk for rare adverse effects, such as drug-induced liver injuries (DILIs), which can range from mild test result abnormalities to severe liver failure (David and Hamilton, 2010; Bøttcher et al., 2019; Desnoyers et al., 2020). Despite the low incidence of DILI, the severity of this disease is concerning. Current adverse drug reaction (ADR) data for CDK4/6is are predominantly from short-term clinical trials and cohort studies and may not capture rare DILI events (Bøttcher et al., 2019; Desnoyers et al., 2020). Therefore, collecting additional data from real-world settings and extending the follow-up duration are necessary to accurately measure DILI risk.

Spontaneous adverse event reporting, a valuable source of real-world evidence, is facilitated by databases such as the Food and Drug Administration Adverse Event Reporting System (FAERS) (Goldman, 1998; Toki and Ono, 2018). Disproportionality methods are often used to automatically obtain signals about drug safety from large databases (Montastruc et al., 2011). To determine whether DILI is associated with CDK4/6is, we analyzed the FAERS database using disproportionality analysis. To inform clinical practice, we compared signals for hepatic injuries caused by different CDK4/6is.

The exploration of drug–gene interactions has advanced our understanding of drug toxicity (Hahn and Roll, 2021). Recent studies have proposed combined analyses using FAERS and drug–gene interaction data to enhance our knowledge of adverse events (AEs) (Tanaka et al., 2021). However, the mechanisms underlying CDK4/6i-induced liver injury are unclear. To address this gap, we constructed a drug–gene interaction network utilizing datasets of human genes interacting with CDK4/6 inhibitors and genes associated with liver injury. Functional enrichment analyses were subsequently applied to determine the potential toxicological mechanisms of CDK4/6 inhibitor-associated liver injury.

2 Materials and methods

2.1 FAERS data extraction and mining

We executed a retrospective observational pharmacovigilance study using OpenVigil 2.1-MedDRA (http://openvigil.sourceforge.net), a publicly available tool for pharmacovigilance analysis on the FAERS database that does not require any special licenses or statistical programs (Böhm et al., 2016). Our study collected adverse reaction data from January 2014 to March 2023 and categorized the patients according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system. We analyzed preferred terminology (PT), high-level terminology (HLT), and standardized MedDRA queries (SMQs) to comprehensively identify and classify ADRs (Pearson et al., 2009; Vogel et al., 2020; MedDRA, 2022).

To improve signal detection, we applied eight SMQs (as shown in Table 1) in the "Drug-related hepatic disorders - comprehensive search" and 324 PTs at lower SMQs to classify adverse events related to liver disorders.

2.2 Disproportionality analysis and signal detection

Disproportionality analysis is a statistical method used in pharmacovigilance to identify possible AEs (Montastruc et al., 2011). For this study, it compares the frequency of reporting of a specific liver-related AE associated with a CDK4/6 inhibitor with the frequency of that event for all other drugs in the database. To determine whether CDK4/6 inhibitors have a higher-than-expected rate of reported adverse events, statistical metrics such as the reporting odds ratio (ROR) were calculated, indicating a potential safety signal (Bate and Evans, 2009).

The analysis focused on reports that were marked as "major suspicious" for the drugs "palbociclib," "ribociclib," and "abemaciclib" in the FAERS database. To ensure accuracy, duplicate reports were removed (as shown in Figure 1). The ROR method was applied using OpenVigil 2.1-MedDRA-v24. To identify liver-related AE signals associated with CDK4/6 inhibitors compared to other drugs in the FAERS database. The criteria for positive AE signals included at least three AE reports and a lower limit of the 95% confidence interval (CI) of the ROR greater than 1 to minimize false positive signals (Rothman et al., 2004; Bate and Evans, 2009; Montastruc et al., 2011).

2.3 Network analysis of CDK4/6is-hepatic injury gene interactions

Network analysis is an interdisciplinary approach that delves into the interactions between drugs and biological systems at the network level. It integrates various types of biological data, including drug-target interactions, protein–protein interactions, gene expression profiles, and disease associations, into comprehensive network models (see Table 2 for definitions). In this study, biological entities such as CDK4/6is, targets, genes, and proteins associated with liver injury are depicted as nodes in the network, while their interactions are represented as edges. By employing graph theory and network analysis techniques to scrutinize the properties of these networks, we aimed to predict the potential targets and pathways involved in liver injury induced by CDK4/6is.

2.3.1 CDK4/6is- hepatic injury gene interaction network dataset

We utilized SwissTargetPrediction (http://www.swisstargetprediction.ch) and SuperPred (https://prediction.charite.de) databases to identify genes linked with CDK4/6is (abemaciclib, ribociclib, palbociclib). Genes associated with liver injury were extracted from (https://www.genecards.org) and OMIM (https://www.omim.org) databases using "liver injury" as the keyword.

TABLE 1 Standardized MedDRA query (SMQ) terms for performing liver injury signal evaluation.

Code	SMQ terms
20000008	Liver related investigations, signs and symptoms (SMQ)
20000013	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
20000009	Liver tumors of unspecified malignancy (SMQ)
20000010	Hepatitis, noninfectious (SMQ)
20000209	Liver tumors of unspecified malignancy (SMQ)
20000208	Liver malignant tumors (SMQ)
20000015	Liver-related coagulation and bleeding disturbances (SMQ)
20000012	Liver neoplasms, benign (incl cysts and polyps) (SMQ)

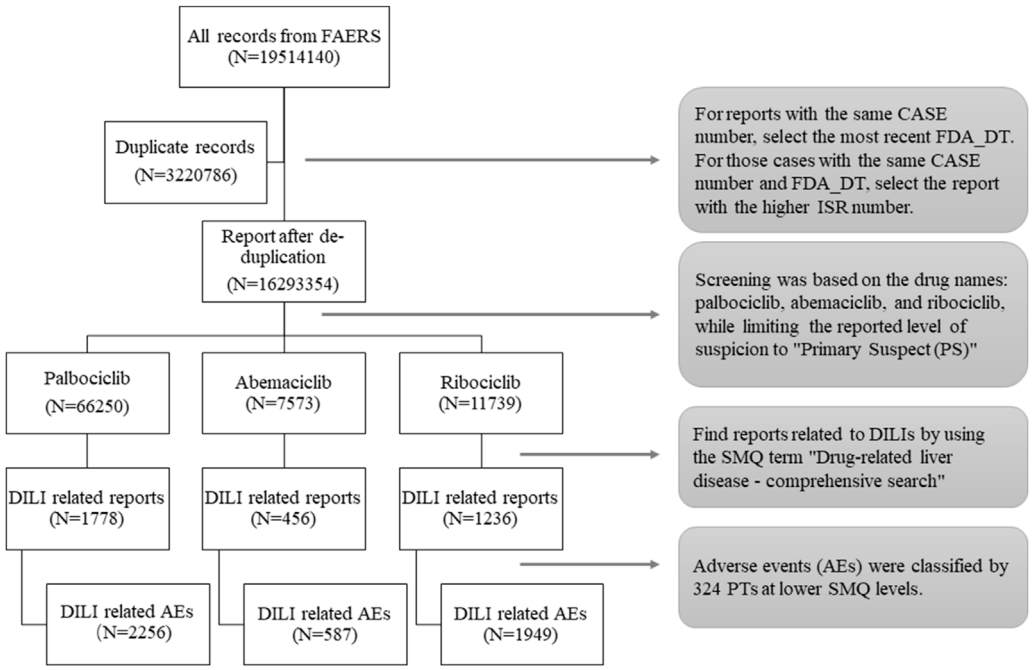

FIGURE 1
Flow chart of data extraction. A detailed description of the data extraction process for drug-induced liver injury (DILI) adverse events for CDK4/6 inhibitors in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

TABLE 2 Definition of pharmacovigilance and pharmacogenetic terms.

Term	Defination
FAERS	FDA Adverse Event Reporting System, a database maintained by the U.S. Food and Drug Administration (FDA) that contains reports of medication errors and adverse events
ROR	Reporting Odds Ratio, a statistical tool frequently utilized in pharmacovigilance to detect signals in databases of reported adverse events. It measures the degree of correlation between a specific drug and a particular adverse event in comparison to all other drugs present in the database
Drug-gene interactions	Interactions between drugs and specific genetic variants (polymorphisms) that influence drug metabolism, efficacy, or toxicity
Protein-protein interactions (PPI)	Protein-protein interactions occur when two or more proteins physically bind within a biological system. Proteins rarely act independently, but rather participate in complex networks of protein interactions
KEGG pathway analysis	KEGG pathway analysis involves the use of the KEGG database to computationally analyze biological data and identify important biological pathways

10.3389/fphar.2024.1378090

TABLE 3 Characteristics of reports on CDK4/6i-associated DILIs in the FAERS database (January 2014 to March 2023).

	Palbociclib	Abemaciclib	Ribociclib
Gender			
Female (%)	1,625 (91.39)	401 (87.94)	1,156 (93.53)
Male (%)	29 (1.63)	4 (0.88)	16 (1.29)
Missing (%)	124 (6.97)	51 (11.18)	64 (5.18)
Age			
N (Missing)	1,475 (303)	273 (183)	710 (526)
Median (q1, q3)	63 (54.70)	62 (54.70)	59 (50.68)
Year of report			
Before 2019 (%)	922 (51.84)	85 (18.64)	290 (23.46)
2020 (%)	223 (12.54)	97 (21.27)	214 (17.31)
2021 (%)	247 (13.89)	95 (20.83)	259 (20.95)
2022 (%)	292 (16.42)	134 (29.39)	340 (27.51)
2023 (%)	94 (5.29)	45 (9.87)	133 (10.76)
Reported by			
Consumers (%)	606 (34.08)	234 (51.32)	505 (40.86)
Health Professionals (%)	1,148 (64.57)	210 (46.05)	719 (58.17)
Unknown (%)	24 (1.35)	12 (2.63)	12 (0.97)
Outcome, n (%)			
Life-Threatening	38 (2.14)	24 (5.26)	86 (6.96)
Hospitalization	430 (24.18)	141 (30.92)	371 (30.02)
Disability	8 (0.45)	6 (1.32)	18 (1.46)
Death	320 (18.00)	55 (12.06)	205 (16.59)
Other	596 (33.52)	139 (30.48)	373 (30.16)
Missing	386 (21.71)	91 (19.96)	183 (14.81)
Time-to-onset, days			
N (Missing)	509 (1,269)	159 (297)	491 (745)
Median (q1, q3)	48 (14.146)	32 (13.63)	42 (14.120)

Gene data underwent curation via the UniProt database. The intersection of drug-associated genes and those related to liver injury formed the basis for constructing the drug-gene network using Cytoscape 3.7.2.

2.3.2 Protein-protein interaction network dataset

Protein-protein interactions were analyzed using the String (https://string-db.org) database focusing on *Homo sapiens* species with a 0.7 interaction score threshold. KEGG pathway analysis through the R package "clusterProfiler (version 1.4.0)" provided insights into biological pathways influenced by gene interactions, visualized using "ggplot2."

This analysis aims to clarify the interaction between CDK4/6 inhibitors and genes associated with hepatic injury, revealing potential mechanisms underlying drug-induced liver damage.

3 Results

3.1 Descriptive analysis

A total of 84,462 records associated with CDK4/6is were extracted, revealing 3,470 records (4.1%) linked to DILI AEs. Table 3 outlines patient characteristics relevant to CDK4/6i-induced DILI. The table demonstrates that palbociclib exhibited the highest number of DILI-associated reports, followed by ribociclib and abemaciclib. Notably, hospitalization was the primary outcome among patients affected by DILI. The median onset of DILI occurred approximately 30 days after treatment initiation, with distinct median onset durations observed: 48 days for palbociclib, 32 days for abemaciclib, and 42 days for ribociclib. Intriguingly, during the data deduplication process, 101 patients experienced DILI due to various CDK4/6 inhibitors.

3.2 Signal detection of DILI-related AEs in the FAERS database

Signal detection at the SMQ and PT levels revealed associations between CDK4/6 inhibitors and DILI (as shown in Table 4). A comprehensive search was performed using the SMQ term "Drug-related hepatic disorders." Abemaciclib (ROR = 2.37) and ribociclib (ROR = 2.60) were shown to be associated with increased incidences of DILI, while palbociclib (ROR = 0.70) did not significantly affect the incidence of DILI.

After identifying signals in 8 lower-level SMQ terms (Table 1; Figure 2), all the CDK4/6 inhibitors were found to be associated with liver-related signs and symptoms. Abemaciclib and ribociclib were specifically correlated with hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions, while ribociclib was associated with unspecified liver tumors.

The results of AE signal detection under PT conditions are shown in Table 5. Ribociclib had positive signals in 36 PT terms, including 196 patients with elevated alanine aminotransferase (ROR = 3.70) and 183 patients with increased aspartate aminotransferase (ROR = 3.99). Abemaciclib had 19 positive signals, primarily related to hepatic function abnormalities (ROR = 8.29). Conversely, palbociclib exhibited seven positive signals, including ascites (ROR = 1.94) in 202 patients and hypertransaminasemia (ROR = 2.58). Moreover, through data mining, several previously unreported adverse events have been discovered that are not mentioned in the CDK4/6 inhibitor labels. These included ascites (N = 323, 6.74%), jaundice (N = 79, 1.65%), hepatomegaly (N = 28, 0.58%), hepatic neoplasm (N = 21, 0.43%), hepatic cytolysis (N = 12, 0.25%), hepatic cirrhosis (N = 11, 0.22%), and hepatic cysts (N = 8, 0.17%).

3.3 Drug–hepatic injury–related gene interaction network analysis

After deduplicating the database, we identified 395 target genes associated with abemaciclib, ribociclib, and palbociclib, as well as 2,697 genes linked to liver injury. By intersecting these gene sets, we isolated 189 interactive target genes representing the intersection of CDK4/6 inhibitor targets and genes involved in hepatic injury. The

TABLE 4 Disproportionality analyses for CDK4/6i-related DILIs.

CDK4/6 inhibitor	Number of DILIs reports	ROR (95%CI)
Palbociclib	2,256	0.70 (0.67, 0.73)
Abemaciclib	587	2.37 (2.18, 2.58)
Ribociclib	1949	2.60 (2.48, 2.72)

ROR, reporting odds ratio; 95% CI, 95% confidence interval.

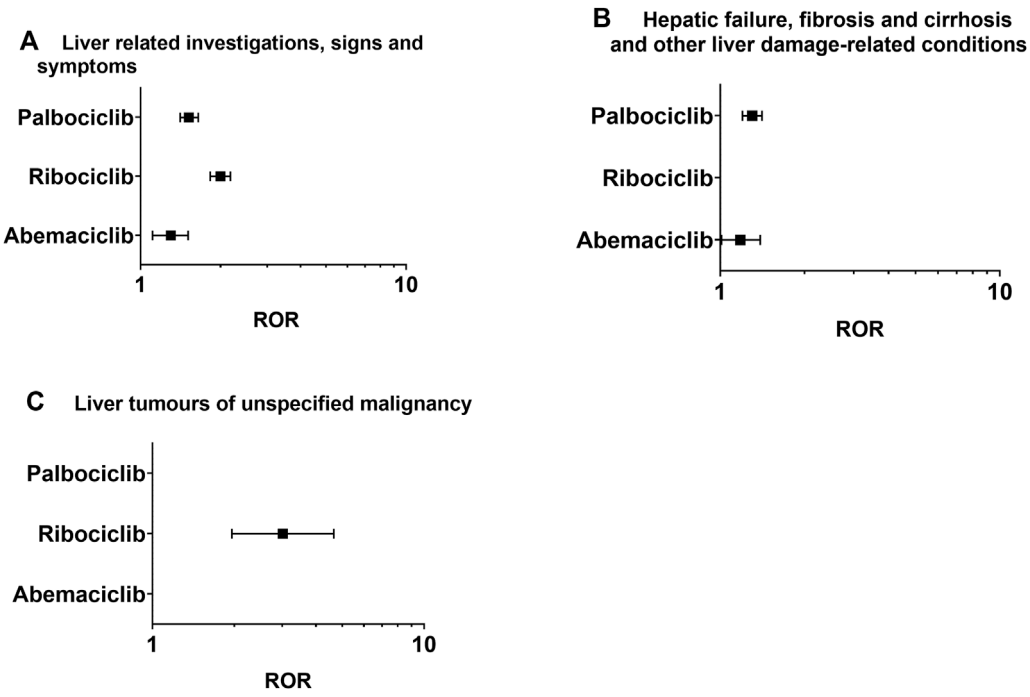

FIGURE 2
Positive signal distribution for CDK4/6 inhibitors using the standardized MedDRA queries (SMQs). **(A)** Liver-related investigations, signs and symptoms (SMQ); **(B)** hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ); **(C)** liver tumors of unspecified malignancy (SMQ). ROR = Reporting odds ratio, statistically positive signals with a lower limit of the 95% confidence interval of ROR greater than 1. Negative signals are not displayed in the figure.

intersecting genes were subjected to protein–protein interaction (PPI) prediction via the String database (https://string-db.org), facilitating the construction of a protein interaction network using Cytoscape 3.7.2 software. The results are shown in Figure 3. Upon topological analysis, key targets (the centermost circle of nodes) of the interaction were revealed, including STAT3, HSP90AA1, EP300, HIF1A, ESR1, PIK3CA, NFKB1, STAT1, PIK3R1, and CREBBP, revealing their centrality within the network. In addition, we found that CCND1, SIRT1, and PPARG are potential targets for interaction.

To better understand the involvement of CDK4/6 inhibitor-induced liver injury target genes in biological signaling pathways, we conducted KEGG pathway enrichment analysis. We focused on the top 20 pathways for comprehensive mapping, as illustrated in Figure 4. The analysis revealed enrichment of genes interacting with CDK4/6is in various pathways, notably, central carbon metabolism in cancer, the FoxO signaling pathway, insulin resistance, the HIF-1 signaling pathway, cellular senescence, microRNAs in cancer, PD-L1 expression and the PD-1 checkpoint pathway in cancer, the Toll-like receptor signaling pathway, apoptosis, small cell lung cancer, and the PI3K-Akt signaling pathway. These findings strongly suggest the potential association of CDK4/6 inhibitors with the development of liver injury through modulation of these pathways.

4 Discussion

With the expansion of CDK4/6is for the treatment of breast cancer, the balance between efficacy and safety has become critical. Our study revealed the safety of ribociclib, abemaciclib and palbociclib, emphasizing the differences in the relative risk of DILI. Ribociclib and abemaciclib demonstrated significant signs of hepatobiliary toxicity, whereas palbociclib appeared relatively safe. Our findings are consistent with previous randomized controlled trials in which hepatobiliary toxicity was more prominent in patients treated with ribociclib and abemaciclib

TABLE 5 Positive signal strength for liver injuries associated with CDK4/6is based on PT levels of FAERS.

High-level terminology (HLT)	Preferred terminology (PT)	Palbociclib		Abemaciclib		Ribociclib	
		N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
Cholestasis and jaundice	Hyperbilirubinaemia	—	—	—	—	16	1.91 (1.17, 3.13)
	Jaundice	—	—	20	2.51 (1.62, 3.90)	59	2.44 (1.89, 3.15)
Hepatic and hepatobiliary disorders NEC	Hepatic cyst	—	—	—	—	8	2.78 (1.39, 5.57)
	Hepatic lesion	30	2.06 (1.44, 2.95)	—	—	42	12.13 (8.95, 16.45)
	Hepatic mass	—	—	—	—	26	17.44 (11.83, 25.71)
	Hepatobiliary disease	—	—	—	—	7	15.01 (7.12, 31.68)
	Liver disorder	192	1.28 (1.11, 1.48)	43	3.65 (2.71, 4.93)	107	2.99 (2.47, 3.61)
Hepatic enzymes and function abnormalities	Hepatic function abnormal	—	—	79	8.29 (6.65, 10.35)	—	—
	Hypertransaminasaemia	39	2.58 (1.88, 3.54)	7	5.85 (2.79, 12.29)	14	3.85 (2.28, 6.51)
Hepatic failure and associated disorders	Hepatic failure	—	—	30	3.50 (2.44, 5.00)	52	1.99 (1.52, 2.61)
Hepatic fibrosis and cirrhosis	Hepatic cirrhosis	—	—	11	2.28 (1.26, 4.11)	—	—
Hepatobiliary function diagnostic procedures	Alanine aminotransferase abnormal	—	—	—	—	9	5.82 (3.02, 11.20)
	Alanine aminotransferase increased	—	—	38	2.18 (1.58, 2.99)	196	3.70 (3.22, 4.26)
	Aspartate aminotransferase abnormal	—	—	—	—	4	3.78 (1.42, 10.09)
	Aspartate aminotransferase increased	—	—	36	2.38 (1.71, 3.30)	183	3.99 (3.45, 4.61)
	Bilirubin conjugated increased	—	—	—	—	5	2.47 (1.03, 5.95)
	Blood bilirubin abnormal	—	—	—	—	8	8.25 (4.11, 16.54)
	Blood bilirubin increased	—	—	23	2.95 (1.96, 4.45)	74	3.13 (2.49, 3.93)
	Gamma-glutamyltransferase abnormal	—	—	—	—	4	9.13 (3.41, 24.45)
	Gamma-glutamyltransferase increased	—	—	17	2.58 (1.60, 4.15)	81	4.05 (3.25, 5.04)
	Hepatic enzyme abnormal	39	2.33 (1.70, 3.20)	4	3.03 (1.13, 8.07)	21	5.24 (3.41, 8.05)
	Hepatic enzyme increased	—	—	38	2.21 (1.61, 3.04)	177	3.40 (2.93, 3.94)
	Liver function test abnormal	—	—	—	—	61	2.25 (1.75, 2.90)
	Liver function test decreased	—	—	—	—	3	11.73 (3.76, 36.64)
	Liver function test increased	119	1.91 (1.59, 2.29)	34	6.93 (4.95, 9.70)	119	8.01 (6.69, 9.60)
	Transaminases abnormal	—	—	—	—	3	6.57 (2.11, 20.44)
	Transaminases increased	—	—	12	1.93 (1.09, 3.40)	78	4.13 (3.31, 5.16)
Hepatobiliary neoplasms benign	Haemangioma of liver	—	—	—	—	3	3.25 (1.05, 10.10)
Hepatobiliary neoplasms malignancy unspecified	Hepatic neoplasm	—	—	—	—	21	7.57 (4.93, 11.63)
Hepatobiliary signs and symptoms	Hepatic pain	27	1.81 (1.24, 2.64)	—	—	19	5.31 (3.39, 8.34)
	Hepatomegaly	—	—	—	—	28	3.15 (2.18, 4.57)
Hepatocellular damage and hepatitis NEC	Drug-induced liver injury	—	—	31	4.68 (3.29, 6.66)	34	1.68 (1.20, 2.36)
	Hepatic cytolysis	—	—	12	4.79 (2.72, 8.45)	—	—
	Hepatitis	—	—	—	—	42	1.98 (1.46, 2.68)
	Hepatitis acute	—	—	—	—	12	2.20 (1.25, 3.87)

(Continued on following page)

TABLE 5 (*Continued*) Positive signal strength for liver injuries associated with CDK4/6is based on PT levels of FAERS.

High-level terminology (HLT)	Preferred terminology (PT)	Palbociclib		Abemaciclib		Ribociclib	
		N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
	Hepatitis toxic	—	—	—	—	9	3.88 (2.01, 7.46)
	Hepatotoxicity	—	—	35	6.08 (4.36, 8.47)	95	5.43 (4.44, 6.65)
	Liver injury	—	—	15	2.98 (1.79, 4.94)	40	2.61 (1.91, 3.56)
Peritoneal and retroperitoneal disorders	Ascites	202	1.94 (1.69, 2.22)	17	2.06 (1.28, 3.32)	104	4.16 (3.43, 5.05)

NEC, not elsewhere classified; ROR, reporting odds ratio; CI, confidence interval; N, number of reports; statistically significant (lower limit of the 95% CI>1 and N>3).

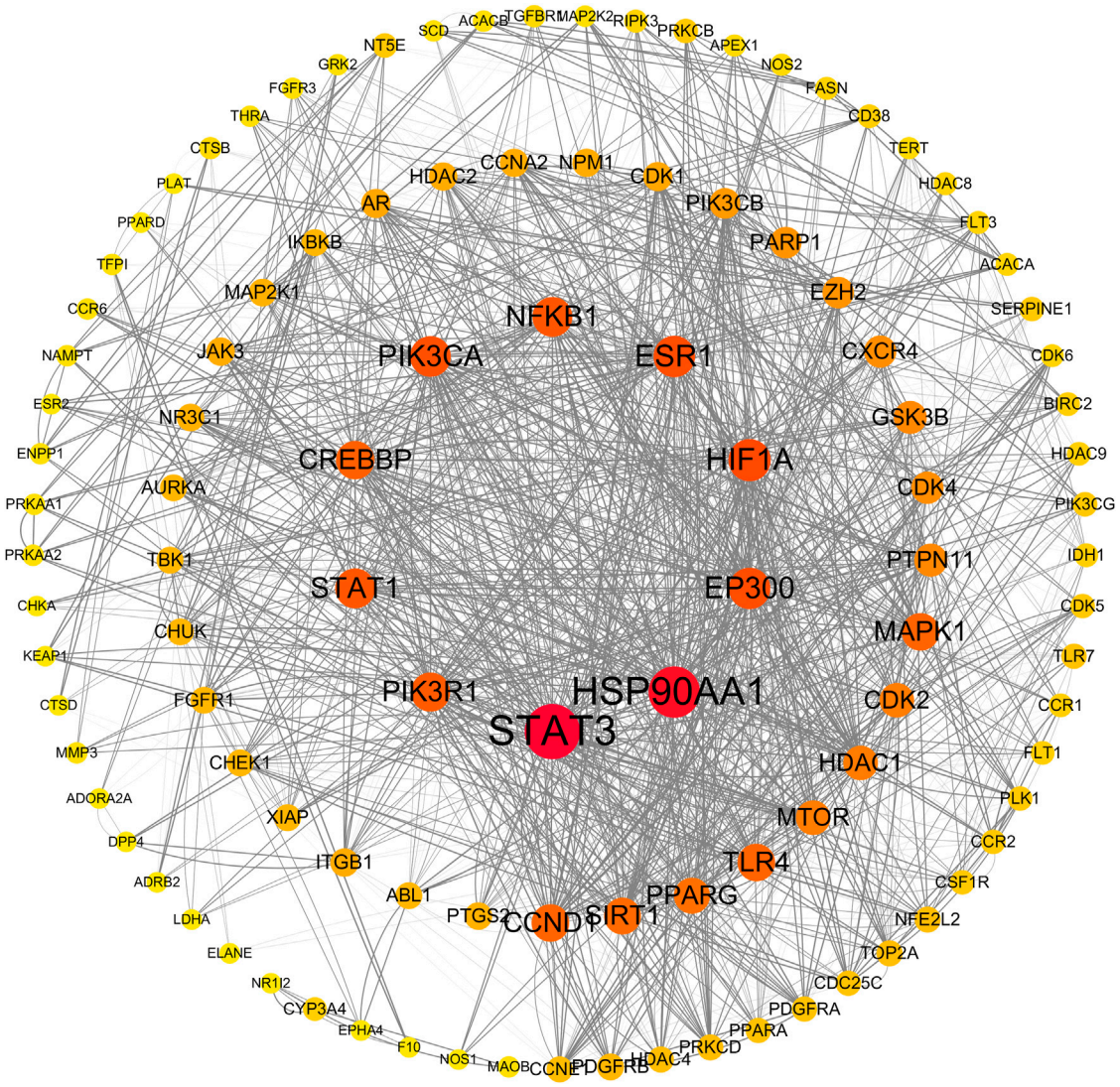

FIGURE 3
Protein-protein interaction network by Cytoscape. The size and color of nodes in the network represent the degree value, indicating the number of interactions each protein has with other proteins. Larger nodes indicate higher degrees, suggesting greater centrality in biological processes. Edge thickness reflects the magnitude of the combined score, with thicker edges indicating higher combined scores. A higher combined score suggests a stronger likelihood of genuine interactions between proteins, providing insights into the network's overall connectivity and functional relevance.

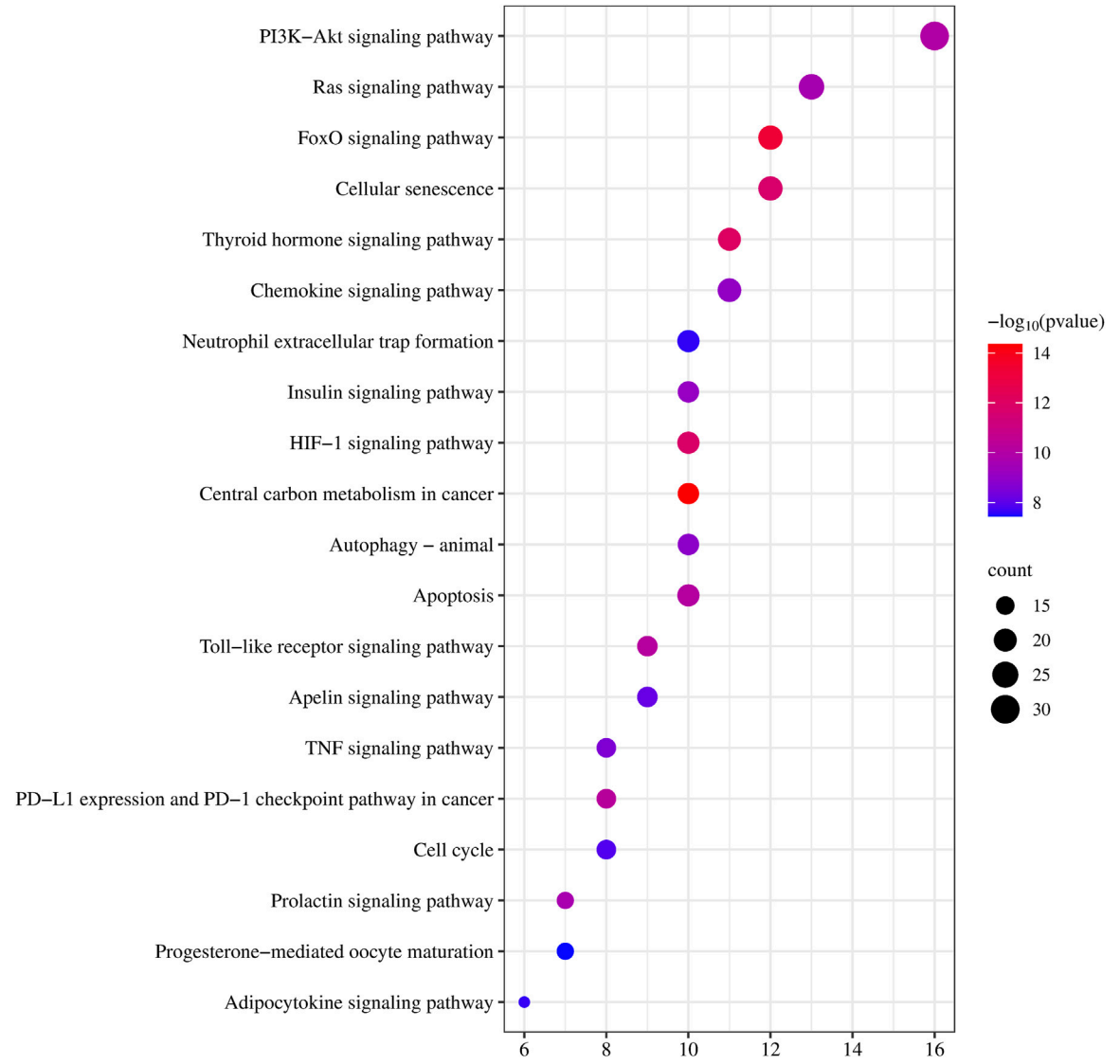

FIGURE 4
KEGG pathway enrichment analysis. Each bubble represents a specific pathway. The horizontal axis represents the number of genes enriched in each pathway, while the size of the bubbles indicates the extent of enrichment for the corresponding pathway. Color indicates significance, with a gradient from blue to red representing decreasing *p*-values.

than in controls, making our study the first to comprehensively compare the risk of liver injury with that of these CDK4/6is (Johnston et al., 2020; Onesti and Jerusalem, 2021; Lu et al., 2022).

There is a potential association between hepatic and biliary toxicity and factors such as lipolysis, mitochondrial injury, metabolism and hepatic transporters (Gu and Manautou, 2012). The high lipophilicity of abemaciclib may be the factor responsible for its association with more hepatic adverse effects than palbociclib (Chen et al., 2016). Ribociclib inhibits hepatic transporters, such as bile salt efflux pumps (BSEPs), and the basal outflow system and may therefore induce additional DILI signals (Rana et al., 2019; Jetter and Kullak-Ublick, 2020). Moreover, palbociclib lacks BSEP inhibition and mitochondrial toxicity and therefore has a relatively low hepatotoxicity signal (Rana et al., 2019; Raschi and De Ponti, 2019).

Notably, our study revealed previously undetected hepatotoxic adverse events associated with CDK4/6is. While clinical trials have focused on laboratory-sensitive AEs, spontaneous reporting data have provided essential real-world insights, emphasizing the significance of vigilant pharmacovigilance for identifying rare adverse reactions (FDA, 2009; Lucas et al., 2022). AE analysis of palbociclib revealed liver-related signals (ascites, liver disorders, increased liver function), consistent with increased risk in new and long-term users (Beachler et al., 2021; Finn et al., 2021). However, palbociclib labels lack specific liver risk warnings, and no recommended liver function tests may pose safety risks during prolonged use. Healthcare providers should consider regular liver function monitoring for long-term palbociclib patients.

The integration of pharmacogenetic network analysis revealed important insights into the underlying molecular mechanisms involved in CDK4/6is-induced DILI. The constructed protein interaction network highlighted STAT3, HSP90AA1 and EP300 as key players, suggesting that they play important roles

in mediating the interaction between CDK4/6is and liver injury pathways (Gao et al., 2012; Jiao et al., 2023). The association of STAT3 with hepatic inflammation and fibrosis is particularly noteworthy, providing a further avenue for exploring the effects of CDK4/6is on these processes. It is known that activating hepatic STAT3 can prevent inflammation by inhibiting the proinflammatory signaling of STAT1 (Gao et al., 2012). However, it may also promote inflammation by inducing hepatocyte-derived acute-phase proteins. In terms of fibrosis, inhibiting components of hepatic STAT3 activation has shown promise in attenuating hepatic fibrosis, suggesting a complex interplay in liver pathophysiology (Zhao et al., 2021; Lee and Hoe, 2023).

HSP90AA1, a molecular chaperone involved in protein folding and stabilization, is potentially implicated in alcoholic hepatitis and cirrhosis (Choudhury et al., 2020; Costa et al., 2020). EP300, a histone acetyltransferase, has been linked to multiorgan fibrosis through the TGFβ pathway, suggesting epigenetic regulation of fibrogenesis and progression (Rubio et al., 2023). These findings provide avenues for future studies of the precise mechanisms by which CDK4/6 inhibitors influence these key molecular players in liver pathophysiology.

SIRT1 (Sirtuin 1) is a member of the Sirtuin family and acts as a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase. It plays an important role in various physiological processes, including metabolism and aging (Rahman and Islam, 2011; Martins, 2016; Martins, 2017a; Martins, 2017b). Our investigation revealed that SIRT1 could be one of the proteins that interact with CDK4/6 inhibitors leading to liver injury. Given its integral role in liver function, prior studies have linked the downregulation of SIRT1 to the onset and progression of non-alcoholic fatty liver disease (NAFLD) (Colak et al., 2011; Martins, 2017c). Consequently, we posited that hepatic SIRT1 activity might be attenuated by CDK4/6 inhibitors, potentially precipitating hepatotoxicity. However, no empirical study has yet confirmed the impact of CDK4/6 inhibitors on SIRT1 activity. As a result, further empirical investigations are required to validate this assumption.

Understanding the differential risks and underlying mechanisms of CDK4/6 inhibitor-induced liver injury has pivotal clinical implications for treatment decisions and drug development. Our findings pave the way for targeted interventions, biomarker discoveries, and personalized treatment strategies aimed at mitigating hepatotoxicity risks associated with CDK4/6 inhibitors.

Despite the advantages of utilizing the FAERS database and data mining techniques in our study, there are inherent limitations (self-reporting nature of the database, incomplete data and bias) (Alomar, 2014). Second, the database included only reported cases of AEs, and the denominator for the incidence of AEs was unknown. Finally, FAERS-based disproportionality analyses cannot indicate causality or quantify risk; rather, they can only show signal strength and statistical associations without pharmacological mechanism studies. Although our study investigated the potential mechanisms of liver injury caused by CDK4/6is through the examination of drug–gene networks, further research is necessary to validate and expand upon our findings.

5 Conclusion

In conclusion, our study sheds light on the differential risk of drug-induced liver injury among CDK4/6 inhibitors, unravels potential mechanistic insights through drug–gene network analysis, and highlights central molecular targets. These findings hold significant clinical implications and pave the way for further investigations, potentially guiding the development of safer and more effective therapies for breast cancer 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.

Author contributions

YS: Data curation, Investigation, Methodology, Writing–original draft, Writing–review and editing. ZG: Data curation, Formal Analysis, Methodology, Writing–review and editing. QZ: Conceptualization, Formal Analysis, Supervision, Writing–review and editing. JL: Conceptualization, Formal Analysis, Supervision, Writing–review and editing. QD: Conceptualization, Formal Analysis, Methodology, Supervision, Writing–review and editing. ZZ: Conceptualization, 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 research was funded by the Shanghai “Rising Stars of Medical Talent” Youth Development Program-Youth Medical Talents-Clinical Pharmacist Program (SHWRS (2020) 087).

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

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 April 2024
DOI 10.3389/fphar.2024.1381843

OPEN ACCESS

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RECEIVED 04 February 2024
ACCEPTED 28 March 2024
PUBLISHED 24 April 2024

CITATION
Jamaluddin NAH, Periyasamy P, Lau CL, Ponnampalavanar S, Lai PSM, Loong LS, Tg Abu Bakar Sidik TMI, Ramli R, Tan TL, Kori N, Yin MK, Azman NJ, James R, Thursky K and Naina Mohamed I (2024), Assessment of antimicrobial prescribing patterns, guidelines compliance, and appropriateness of antimicrobial prescribing in surgical-practice units: point prevalence survey in Malaysian teaching hospitals.
Front. Pharmacol. 15:1381843.
doi: 10.3389/fphar.2024.1381843

Assessment of antimicrobial prescribing patterns, guidelines compliance, and appropriateness of antimicrobial prescribing in surgical-practice units: point prevalence survey in Malaysian teaching hospitals

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Objectives: This study sought to investigate the quality of antimicrobial prescribing among adult surgical inpatients besides exploring the determinants of non-compliance and inappropriate prescribing to inform stewardship activities.

Methods: A cross-sectional point prevalence study employing Hospital National Antimicrobial Prescribing Survey (Hospital NAPS) was conducted in April 2019 at two teaching hospitals in Malaysia.

Results: Among 566 surgical inpatients, 44.2% were receiving at least one antimicrobial, for a total of 339 prescriptions. Antimicrobials belonging to the World Health Organization's Watch group were observed in 57.8% of cases. Both hospitals exhibited similar types of antimicrobial treatments prescribed and administration routes. A significant difference in antimicrobial choice was observed between hospitals ($p < 0.001$). Hospital with electronic prescribing demonstrated better documentation practice ($p < 0.001$). Guidelines compliance,

32.8% (p = 0.952) and appropriateness, 55.2% (p = 0.561) did not significantly differ. The major contributors of inappropriateness were incorrect duration, (15%) and unnecessary broad-spectrum coverage, (15.6%). Non-compliance and inappropriate prescribing were found to be 2 to 4 times significantly higher with antimicrobial prophylaxis prescription compared to empirical therapy.

Conclusion: Antimicrobial stewardship efforts to improve appropriate surgical prescribing are essential. These initiatives should prioritize surgical prophylaxis prescribing, focusing on reducing unnecessarily prolonged use and broad-spectrum antimicrobials, raising awareness among prescribers and promoting proper documentation.

KEYWORDS

point prevalence, guidelines compliance, appropriateness, surgical, antimicrobial prophylaxis, antimicrobial stewardship

1 Introduction

Rapid development of antimicrobial resistance (AMR) has become a serious healthcare issue in recent decades (Rice, 2009; Murray et al., 2022). Unchecked use of antimicrobials resulting in their overuse and misuse is driving the acceleration of this issue, which has a direct impact on the healthcare system (Laxminarayan et al., 2013; Allcock et al., 2017). Hence, identifying and stopping inappropriate antimicrobial prescribing is essential to slow the emergence and spread of AMR organisms. In response to the World Health Organization (WHO) Global Action Plan to combat AMR, Malaysia has formulated the Malaysian Action Plan on Antimicrobial Resistance (MyAP-AMR), under a One Health approach targeting to reduce inappropriate antimicrobial use in human and animal health (Ministry of Health Malaysia, 2017; Ministry of Health Malaysia, 2022a). Similarly, the United States' National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) include a target of reducing inappropriate prescribing by 20% in hospital settings (National Action Plan for combating antibiotic-resistant bacteria, 2015). In line with these goals, point prevalence surveys (PPS) of antimicrobial utilization and audit on compliance with national or local guidelines were integrated into the antimicrobial stewardship (AMS) program as part of this national strategy (Ministry of Health Malaysia, 2022b).

A 3-year observation study in a Malaysian hospital from 2018 to 2020 identified a concerning correlation between the increased consumption of broad-spectrum antibiotics and the rise of multidrug resistant organisms, underscoring the urgency of addressing this growing trend in Malaysia (Tan et al., 2022). Although resistance patterns of certain pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae* remained stable over 5-year period, *Methicillin-resistant Staphyloccocus aureus* (MRSA) showed a downward trend. Conversely, *Acinetobacter baumannii* demonstrated a worrisome increase in resistance to various antibiotics, with rates as high as 68.8% for imipenem and meropenem in 2021. Similarly, *Pseudomonas aeruginosa* exhibited an upward trend in resistance, while *Klebsiella pneumonia* and *Escherichia coli* displayed a doubling in resistance to carbapenems over the same period (Ministry of Health Malaysia, 2022a).

Furthermore, antimicrobial consumption rates in this country remain high despite efforts to curb their discriminate use. Total antibiotic utilization has shown an upward trend in all areas, particularly in intensive care units (ICUs), suggesting the need for targeted interventions in hospital settings (Ministry of Health Malaysia, 2022a; Pharmacy Practice and Development Division and Ministry of Health, 2022). In 2018, while low- and middle-income countries (LMICs) recorded an antibiotic consumption rate of 13.1 DDD per population 1,000 per day, Malaysia reported a lower rate of 9.9 DDD per 1,000 per day, ranking behind Vietnam (30 DDD per 1,000 per day) and Thailand (12.4 DDD per 1,000 per day) (Browne et al., 2021). Comparatively, the country demonstrated a concerning high antibiotic usage of 79%, surpassing larger neighboring countries such as Philippines (42%) and Indonesia (43%) (Browne et al., 2021).

In surgical practice, antimicrobials are used widely for both prophylactic and medical treatment. Evidence-based national and local antimicrobial guidelines for surgical practices, including surgical prophylactic use have been published and constantly updated. Despite evidence suggesting that good practice is sufficient, hospitals are still struggling to comply (Gul et al., 2005; Ng and Chong, 2012; Oh et al., 2014; Lim et al., 2015; Bardia et al., 2021; Cabral et al., 2023). While studies have assessed the appropriateness of antimicrobial prescribing across various specialties (Charani et al., 2019; Sheng et al., 2019; Vandael et al., 2020; de Guzman Betito et al., 2021; Macera et al., 2021), it is important to recognize that the conditions for which antimicrobials are prescribed can differ in surgical practices, even though the principles of infection diagnosis and management remain the same. Data from National Antibiotic Utilisation survey in 2015 and 2016 revealed that only a small percentage of in-patient prescriptions (5.7%) were for surgical prophylaxis, 2.6% for non-surgical prophylaxis, and the remaining majority were for therapeutic indications (Ministry of Health Malaysia, 2020). A study in surgical wards found 86% of antibiotics were prescribed for therapeutics, and highlighted significant inappropriate prescribing practices in the wards, indicating a need for improved compliance with guidelines (Lim et al., 2015). Notably, most literature on antimicrobial prescribing in surgical practices in the country focuses on surgical antimicrobial prophylaxis (SAP) (Gul et al., 2005; Oh et al., 2014; Fadzwani et al., 2020; Zammari et al., 2022), leaving the gap in understanding broader antimicrobial prescribing patterns in surgical units.

To assess antimicrobial use and prescribing quality, the Royal Melbourne Hospital developed the Hospital National Antimicrobial Prescribing Survey (Hospital NAPS) (National Centre for Antimicrobial Stewardship, 2023), a validated web-based auditing

platform, delivered by the National Centre for Antimicrobial Stewardship (NCAS) in collaboration with the Australian Government Department of Health and Aged Care, to monitor the performance of AMS program in hospitals. The platform enables multidisciplinary healthcare professionals across various healthcare institutions to identify focus areas and benchmark the performance indicators among participating hospitals in a standardized manner. The anonymized aggregate survey data from Hospital NAPS has facilitated the establishment of the Antimicrobial Use and Resistance in Australia (AURA) surveillance system, which informs national AMS strategies and assists in the regular review and updating of prescribing guidelines (Australian Commission on Safety and Quality in Health, 2021). Since its successful implementation in Australia, Hospital NAPS has been adopted by other countries with varied healthcare systems, including Canada and Bhutan; demonstrating the feasible, generalizable, with potential to optimize antimicrobial use (James et al., 2022).

Limited information regarding antimicrobial prescribing for different infection diagnoses in surgical settings suggesting a clear need for more comprehensive data in these contexts to guide tailored AMS initiatives and approaches. Such knowledge is vital to shift from a one-size-fits-all model to one that addresses the specific challenges faced by prescribers in surgical units. Using the Hospital NAPS protocol, this study sets out to investigate and report an in-depth picture of antimicrobial prescribing patterns among surgical inpatients and evaluates the prescribing quality in surgical-practice units in two teaching hospitals in Malaysia, including compliance with guidelines and reasons for inappropriate prescribing. The findings from this study can facilitate comparative studies with other surgical populations, and inform more specific investigations.

2 Materials and methods

2.1 Study design and settings

A hospital-wide cross-sectional point prevalence survey (PPS) of antimicrobial prescribing was performed in two teaching hospitals in Klang Valley, Malaysia (Jamaluddin et al., 2021). Hospital Canselor Tuanku Muhriz or HCTM (1,054 beds, 63 wards) and University Malaya Medical Centre or UMMC (1,617 beds, 44 wards) are university-affiliated hospitals with multidisciplinary AMS teams. PPS was conducted for each facility on designated days between 16 April to 30 April 2019. Auditors were assigned a specific day to complete a standard Hospital NAPS protocol, completing a data collection form for each patient prescribed with an antimicrobial on the designated audit day (Supplementary Material). A detailed description of the Hospital NAPS antimicrobial prescribing surveys is described in previous publications (James et al., 2014; James et al., 2022). Survey and assessment were executed by fourteen pharmacists and two infectious disease (ID) physicians in HCTM, while one pharmacist and four ID physicians undertook the exercises in UMMC. The Australian NAPS support team provided training, technical and clinical support throughout the survey period. All surveyors received online webinar training on the audit protocol before the survey day. Data collected during the survey were compiled and submitted through a secure web-based online platform. Data on antimicrobial prescribing among patients admitted to surgical-practice units were analyzed for this report. The study was approved and ethics approval from each institution was obtained before the commencement of this study.

2.2 Eligibility criteria/patient selection

All adult patients admitted to the obstetrics and gynecology (OBGYN), trauma and orthopedic and surgical specialties, before or at 8 a.m. on the day of the survey were audited once (denominator). Patients admitted after 8 a.m., outpatients, as well as patients undergoing same-day treatment and surgery in daycare or at emergency unit, were excluded. The following information were retrieved from medical records and associated documents for patients who were prescribed with at least an antimicrobial (numerator) regardless of route of administration: demographics, diagnosis, antimicrobial data (including indications, dose, route, frequency, duration, start and review/stop date) and any additional clinical variables (cultures, biomarkers) relevant for the assessment. The survey also included patients who were prescribed a stat dose of antimicrobial or SAP since 8 a.m. the previous day. A unique, non-identifiable survey number was assigned to every de-identified patient data. Aligning with established protocols by Hospital NAPS (James et al., 2014; James et al., 2022) and WHO (World Health Organization, 2018), setting 8 a.m. as the cut-off time for patient inclusion ensures comprehensive representation of all admitted patients while minimizing variability of different time points and the capture of diverse sample encompassing individuals who have undergone consultations and received treatment. Additionally, corresponding with the facilities' operational day, this timing facilitates efficient data collection by the survey team. This method strikes a balance between practical considerations and the imperative to obtain a representative patient group, plus ensuring consistency and comparability with existing literature. The calculated minimum sample size, determined by the Krejcie and Morgan formula, was 256 subjects. This estimation was based on a preliminary survey conducted in the hospital, which reported a prevalence of antimicrobial use at 78.9%, considering type 1 error rate of 5% and a precision of 5% (Krejcie and Morgan, 1970).

2.3 Assessment

2.3.1 Compliance with guidelines

To meet "guideline compliant" assessment criteria, the prescription must be the first-line or preferred recommendations outlined in the primary guidelines. Doses were also evaluated using the hospital renal dose adjustment protocol, if necessary. HCTM followed the Malaysian National Antibiotic Guideline 2014 (Ministry of Health, 2014) and the hospital surgical prophylaxis guide as the main prescribing guidelines; while UMMC adhered to the UMMC antibiotic guideline (University Malaya Medical Center, 2020) available at the time of assessment. The evaluation was based on the

information documented in the patient records. When clear recommendations were lacking in the primary references, a consensus was reached among the experts; including ID physicians and clinical pharmacists. The consensus was achieved either with or without consulting additional sources, such as international guidelines or ward protocols. Categories in accordance to the Hospital NAPS were compliant, non-compliant, directed therapy (prescribing guided by microbiology and susceptibility results), non-assessable due to insufficient reports or unclear diagnosis, or no guidelines available.

2.3.2 Appropriateness

The Hospital NAPS defines appropriateness as the degree to which antimicrobial prescribing aligns with the primary references or best practices endorsed by experts (optimal); or considered reasonable alternative (adequate). Prescriptions that deviate from these standards are deemed inappropriate, either suboptimal or inadequate. Suboptimal prescribing encompasses prescription where antimicrobial choice is unreasonably broad in spectrum, dosage is excessively high, or duration is prolonged, including failure to de-escalate empirical to targeted therapy. This category also includes cases where the prescribed antimicrobial does not match the patient's allergy profile, potentially resulting in mild adverse reactions. Inadequate prescriptions are those unlikely to effectively treat the infection, or unnecessary for the given indication. These prescriptions may pose severe or life-threatening toxicity risks, or when SAP is unnecessarily prolonged beyond 24 h (Supplementary Material).

2.4 Data analysis

Antibiotics were classified as "Access," "Watch" and "Reserve" (AWaRe) according to the 2021 WHO AWaRe classification (World Health Organization, 2021). Antimicrobials not included in the AWaRe classification were listed as "unclassified." Details on AWaRe classification for the type of treatment are shown in Supplementary Material. Continuous data were presented as the mean and standard deviation (SD) for normally distributed data. If the distribution was not normal, continuous data were presented as the median and interquartile range (IQR). Other descriptive statistics, such as minimum and maximum values were reported when necessary. Normality of the data was examined using histogram (approximately bell-shaped), skewness (within −1 to 1) and kurtosis (within −3 to 3). The difference between hospitals was analyzed using the Chi-square test or Fisher's exact test (if minimum expected count was less than 5) for categorical variables. For continuous age variables, independent *t*-test was used to analyze the mean difference between hospitals. Compliance with guidelines and appropriateness were treated as dichotomous variables. The associations of each potential factor with compliance and appropriateness were examined through the Chi-square test or Fisher's exact test. Multiple logistic regressions were used to evaluate significant factors. Odds ratio and 95% confidence interval for each potential factor were calculated, where a *p*-value of less than 0.05 was considered significant. All analyses were carried out using SPSS (IBM Corp. released 2011 IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3 Results

3.1 Demographics and prevalence

A total of 229 admissions in HCTM from twenty wards plus one burn unit, and 337 in UMMC from thirteen wards were identified. Admissions to the surgical and burn units accounted for 51.1% (289) of patients, followed by OBGYN with 24.4% (138), trauma and orthopedic with 22.6% (128) and mix ward with 1.9% (Browne et al., 2021). Among 566 patients, 250 (44.2%) received at least one antimicrobial prescription at the time of the survey, for a total of 339 prescriptions (median 1 per patient, range 1–5), with 171 (68.4%) receiving one antimicrobial agent, 71 (28.4%) receiving two and 8 (3.2%) receiving three or more. Demographic data is presented in Table 1.

3.2 Antimicrobial prescribing patterns

Common types of treatment and route of antimicrobials administration were seen to be prescribed in both hospitals ($p > 0.05$), but UMMC demonstrated better rates (>95%) for documentation practice ($p < 0.001$) (Table 2). Of all agents prescribed empirically, 51.2% (86/168) were in the Watch group [piperacillin/tazobactam (31.4%) and cefuroxime (29%)], while Access antibiotics accounted for 42% (74/168) of prescriptions. More than half (59.6%; 62/104) of all antimicrobials prescribed prophylactically were Watch antibiotics constituted mainly by cefuroxime (54.8%). Directed therapy was largely entailing antibiotics of Watch by 71.6% (48/67), where meropenem (19%, 13), cefepime (13%, 9) and vancomycin (13%, 9) were prescribed. Access antibiotics were higher in HCTM (49.6%, 59), while the use of Watch antibiotics was found to be higher in UMMC (64.1%, 141) ($p = 0.005$).

Antimicrobial were mostly prescribed for surgical prophylaxis (27.1%, 92), followed by cystitis (4.7%, 16), necrotizing fasciitis (4.4%, 15) and acute cholecystitis (4.1%, 14). There was a significant difference in the choice of antimicrobial between hospitals ($p < 0.001$). Cefuroxime (25.5%, 56) and metronidazole (12.3%, 27) were the most commonly used antimicrobials at UMMC, while HCTM recorded the most frequent use of amoxicillin/clavulanic acid (23.5%, 28). From 92 antimicrobial prescriptions for surgical prophylaxis, cephalosporins (53.3%, 49) accounted for predominant choices. The five most used SAP in both hospitals were cefuroxime (37%, 34), metronidazole (18.5%, 17), amoxicillin/clavulanic acid (12.0%, 11), ceftriaxone (7.6%, 7) and vancomycin (5.4%, 5). UMMC mainly utilized cefuroxime (48.5%, 33/68), metronidazole (23.5%, 16/68) and vancomycin (7.4%, 5/68), while HCTM's preferred choice was amoxicillin/clavulanic acid (41.7%, 10/24). A remarkable use of ceftriaxone (29.2%, 7/24) for SAP in HCTM was observed.

3.3 Compliance with guidelines and appropriateness

The study revealed a compliance rate with guidelines was at 32.8% and an appropriateness level at 55.2%. Both indicators displayed no statistically significant difference between the two hospitals (Table 2). Of 146 (44.8%) prescriptions that were assessed as inappropriate, 72 (22.1%) were classified as suboptimal while the remaining 74 (22.7%) were

TABLE 1 Total admissions (n = 566) and the general characteristics of patients on antimicrobials in surgical wards (n = 250).

Characteristics, n	Total	HCTM, *n* (%)	UMMC, *n* (%)	*p*-value[a]
No. of surgical patients	566	229	337	
No. of patients on antimicrobials, *n* (%)	250 (44.2)	88 (38.4)	162 (48.1)	0.023
Surgical-practice specialties, *n* (%)				
General surgery[d]	68 (27.2)	27 (30.7)	41 (25.3)	0.217[c]
Cardiothoracic	12 (4.8)	3 (3.4)	9 (5.6)	
Neurosurgery	16 (6.4)	4 (4.5)	12 (7.4)	
Urology	22 (8.8)	9 (10.2)	13 (8)	
Ophthalmology	6 (2.4)	5 (5.7)	1 (0.6)	
OBGYN	33 (13.2)	8 (9.1)	25 (15.4)	
Trauma and orthopedic	84 (33.6)	29 (33)	55 (34)	
Others[e]	9 (3.6)	3 (3.4)	6 (3.7)	
Mean (SD) age of patients (years)		56.06 (18.17)	54.80 (18.18)	0.601[b]
Age Group, *n* (%)				
<30 years	29 (11.6)	10 (11)	19 (12)	0.717
30–49 years	58 (23.2)	16 (18)	42 (26)	
50–64 years	73 (29.2)	28 (32)	45 (28)	
65–79 years	75 (30.0)	28 (32)	47 (29)	
≥80 years	15 (6.0)	6 (7)	9 (6)	
Gender, *n* (%)				
Male	130 (52)	52 (59)	78 (48)	0.098
No. of prescriptions per patient, *n* (%)				
1	171 (68.4)	64 (72.7)	107 (66)	0.081[c]
2	71 (28.4)	19 (21.6)	52 (32.1)	
≥3	8 (3.2)	5 (5.7)	3 (1.9)	

[a]Chi-squared test.
[b]Independent *t*-test.
[c]Fisher Exact test.
[d]General surgery: inclusive of general surgery, breast and endocrine surgery, colorectal surgery, gastrointestinal and bariatric, hepatobiliary and pancreatic, and vascular surgery.
[e]Others: inclusive of plastic surgery, oral and maxillofacial surgery, and ENT.
HCTM, Hospital Canselor Tuanku Muhriz; UMMC, University Malaya Medical Centre; OBGYN, obstetrics and gynecology.

classified as inadequate. The percentage of prescriptions judged suboptimal and inadequate did not differ between hospitals with p = 0.219 and p = 0.056, respectively. Inappropriate prescribing varied by subspecialties, overall ranging from 40.9% to 58.3%. A group of units inclusive of plastic surgery, oral and maxillofacial surgery and ENT (others) had the highest percentage of inappropriate orders at 58.3% (7/12), along with cardiothoracic at 57.1% (8/14), ophthalmology at 52.9% (9/17) and OBGYN at 46.9% (23/49). HCTM recorded inappropriateness ranging from 30.8% to 100%, with high rates in cardiothoracic, neurosurgery and others. Meanwhile, the tabulation in UMMC revealed ophthalmology, urology and others as among the units with a high percentage of inappropriate orders ranging from 35.3% to 100%.

Prophylaxis (medical and surgical) prescriptions had the highest inappropriateness (n = 69/146, 47.3%) compared to empirical and directional therapy. The greatest percentage of inappropriate prescriptions was SAP with 40 (43.5%) of 92 prescriptions classified as inadequate and 27 (29.3%) as suboptimal. Both hospitals recorded a high number of inappropriate SAP orders presenting 83% (20/24) in HCTM and 69% (47/68) in UMMC. Unnecessary prolongation ≥24 h was the most common reason for inappropriate prescribing of SAP prescriptions, respectively; 50% (12/24) in HCTM and 38.2% (26/68) in UMMC.

A sub-analysis of 146 inappropriate prescriptions is shown in Figure 1. Total rates of SAP ≥24 h (41.3%, 38/92) contributed mainly to the incorrect duration of antimicrobials in overall prescriptions (15%, 49/326). The extensive use of broad-spectrum antimicrobials in the overall prescribing was depicted at 15.6% (51/326). A higher rate of a broader spectrum of antimicrobials was noted in UMMC (17.1%, 36/211), while incorrect dosage/frequency (13.9%, 16/115) was more commonly seen in HCTM.

3.4 Factors associated with non-compliance and inappropriateness

The results of univariate and multivariate models for both hospitals are presented in Tables 3, 4. Non-compliance and inappropriate antimicrobial prescriptions were more frequently associated with prophylaxis indications compared to empirical and directed therapy.

TABLE 2 Antimicrobial prescription details (n = 339).

Characteristics	Total	HCTM, n (%)	UMMC, n (%)	p-value[a]
Number of prescriptions	339	119	220	
Type of treatment				
Empiric	168 (49.6)	64 (53.8)	104 (47.3)	0.179
Directed therapy	67 (19.8)	26 (21.8)	41 (18.6)	
Prophylaxis	104 (30.7)	29 (24.4)	75 (34.1)	
Route of administration				
Intravenous	252 (74.3)	86 (72.3)	166 (75.5)	0.039
Oral/enteral	63 (18.6)	19 (16.0)	44 (20.0)	
Others[c]	24 (7.1)	14 (11.8)	10 (4.5)	
Reason for antimicrobials documented				
Yes	292 (86.1)	81 (68.1)	211 (95.9)	<0.001
No	47 (13.9)	38 (31.9)	9 (4.1)	
Stop/review date documented				
Yes	241 (71.1)	26 (21.8)	215 (97.7)	<0.001
No	98 (28.9)	93 (78.2)	5 (2.3)	
AWaRe category				
Access prescription	133 (39.2)	59 (49.6)	74 (33.6)	0.005[b]
Watch prescription	196 (57.8)	55 (46.2)	141 (64.1)	
Reserve prescription	1 (0.3)	1 (0.8)	0	
Unclassified	9 (2.7)	4 (3.4)	5 (2.3)	
Antimicrobial pharmacological group				
Penicillin	112 (33.0)	60 (50.4)	52 (23.6)	<0.001
Cephalosporin	104 (30.7)	23 (19.3)	81 (36.8)	
Nitroimidazole	34 (10.0)	7 (5.9)	27 (12.3)	
Carbapenem	20 (5.9)	2 (1.7)	18 (8.2)	
Quinolone	17 (5.0)	11 (9.2)	6 (2.7)	
Others[d]	52 (15.3)	16 (13.4)	36 (16.4)	
Compliance with guideline[e]				
Compliance	83 (32.8)	28 (32.6)	55 (32.9)	0.952
Non-compliance	170 (67.2)	58 (67.4)	112 (67.1)	
Appropriateness[f]				
Appropriate (optimal, adequate)	180 (55.2)	61 (53)	119 (56.4)	0.561
Inappropriate (suboptimal, inadequate)	146 (44.8)	54 (47.0)	92 (43.6)	

[a]Chi-squared test.
[b]Fisher-Exact test.
[c]Others: inclusive of vaginal, inhalation and topical routes.
[d]Others: inclusive of aminoglycosides, amphenicol, carboxylic acid, Fusidane, Glycopeptide, Lincomycin, Macrolide, Nitrofuran, Sulfonamide, antituberculosis, antifungal.
[e]Exclude directed therapy, no guidelines available for the specific indication, and not assessable compliance, n = 253.
[f]Exclude prescriptions with no guidelines available for the specific indication, and not assessable appropriateness, n = 326.
HCTM, Hospital Canselor Tuanku Muhriz; UMMC, University Malaya Medical Centre; OBGYN, obstetrics and gynecology.

The likelihood of antimicrobial prophylaxis prescriptions being non-compliant was 4.5 times higher (OR 4.55, 95% CI 1.40–14.78, p = 0.012), and 4.2 times more likely to be found as deemed inappropriate (OR 4.22, 95% CI 1.61–11.10, p = 0.003) in HCTM. Conversely, UMMC showed 2.4 times (OR 2.37, 95% CI 1.21–4.65, p = 0.012) higher likelihood of inappropriateness in prescribing antimicrobial prophylaxis. General surgery (OR 12.56, 95% CI 1.82–86.48, p = 0.010), OBGYN (OR 29.89, 95% CI 3.78–236.49, p = 0.001) as well as trauma and orthopedic (OR 8.06, 95% CI 1.25–52.11, p = 0.028) had significantly higher odds of non-compliance with guidelines compared to cardiothoracic unit. Additionally, prescribing cephalosporins was significantly associated with higher likelihood of non-compliance with guidelines (OR 8.57, 95% CI 2.89–25.39, p < 0.001) compared to penicillins.

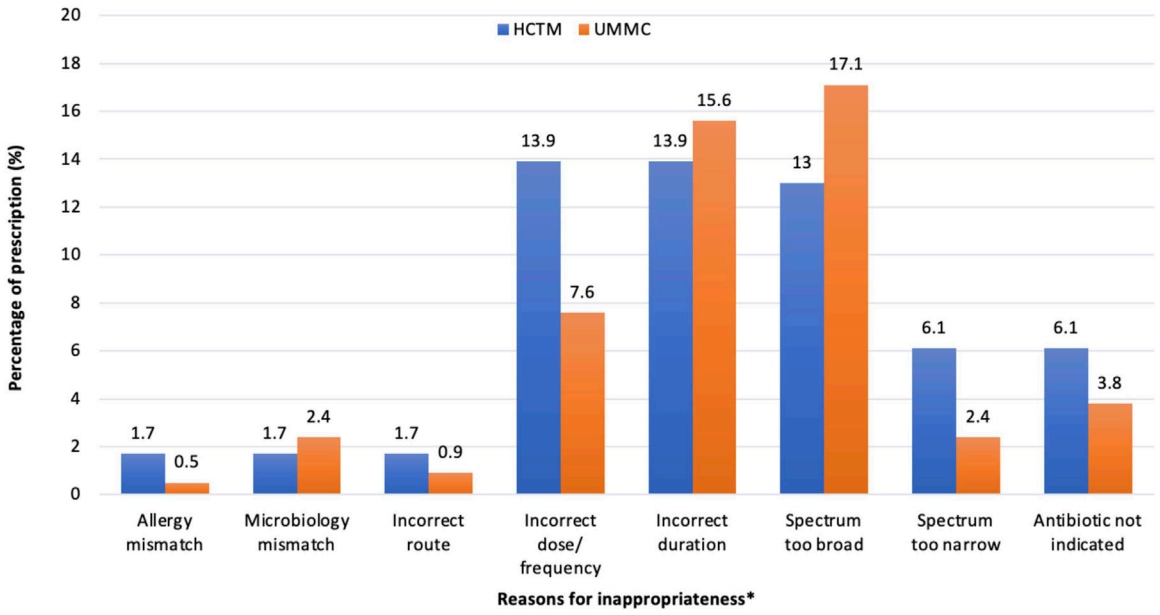

FIGURE 1
Reasons for a prescription being assessed as inappropriateness in HCTM and UMMC (n = 146). *A prescription may have more than one reason of inappropriateness. Spectrum too broad: Antimicrobials that have a spectrum of activity that exceeds the requirements for the specific clinical indication, as outlined by the recommended guidelines or microbiological susceptibility results. This may include prescribing broad-spectrum antimicrobial without de-escalating to a narrower spectrum based on microbiological results or prescribing multiple antimicrobials with unnecessary overlap in spectrum. Spectrum too narrow: Antimicrobials that do not adequately cover the likely causative or cultured pathogens for the given condition.

4 Discussion

This study constitutes a vital component of our ongoing AMS program, which utilizes PPS to delve into various facets of antimicrobial prescribing within our healthcare facilities. We seek to gain an understanding of these practices and to identify areas for enhancing the quality of care in surgical-practice units. This initiative represents an enduring commitment to fostering prudent antimicrobial usage and addressing the ever-pressing issue of antibiotic resistance.

4.1 Prevalence of antimicrobial prescribing in surgical-practice units

The overall usage of antimicrobials in our surgical-practice units at 44.2% was relatively lower compared to rates reported in African hospitals (Bediako-Bowan et al., 2019; Nnadozie et al., 2020), Asia (Limato et al., 2021; Sheng et al., 2019; de Guzman Betito et al., 2021), Italy (Macera et al., 2021), and Serbian hospitals (Šuljagić et al., 2021) (ranged 55.7%–97.6%). Conversely, other surveys, such as PPS in German (Aghdassi et al., 2018) and Belgian hospitals (Vandael et al., 2020), observed a lower prevalence of antimicrobial use, at approximately 30%. The variability in antimicrobial prescribing prevalence, both between our two hospitals, and in comparison to previous reports could be related to differences in the surgical-based case-mix, or structural characteristics unique to each hospital, including the type and proportion of surgical-based specialties. Moreover, significant differences were observed in the patterns of antimicrobial prescribing between the two hospitals, indicating the nature of using local guidelines, which provide various recommendations in accordance with each hospital policy, as well as considerations related to institutional antibiograms and costs, including administrative expenses. Our data also showed a higher usage of antibiotics classified as Watch antibiotics, particularly in UMMC. In response to the global concern of AMR, the AWaRe classification was developed as a general guide to antibiotic prescribing patterns aimed at promoting rational prescribing (World Health Organization, 2021). The WHO recommends at least 60% of all antibiotics prescribed nationwide to be from the Access group. Access antibiotics exhibit a wider range of activity against commonly susceptible pathogens, while sustaining lower resistance potential compared to antibiotics in the other groups. Watch group contain generally broader spectrum antibiotics, pose a higher risk of selecting antimicrobial resistance and are primarily used in patients with more severe conditions. Their use should be vigilantly monitored to prevent overuse. Integrating AWaRe index into our hospital policies shall be an essential measure, as it has been associated with improved usage of Access antibiotics (Budd et al., 2019), highlighting its potential benefits in promoting responsible antimicrobial use and combating AMR.

4.2 Compliance with guidelines and appropriateness

In this study, we identified appropriateness as the key measure of antimicrobial prescribing quality, moving beyond mere guideline compliance. This approach allowed us to consider various contexts in which non-compliance with the guidelines may not necessarily be deemed as inappropriate prescribing, but rather a case-specific approach that may still be adequately appropriate (Ierano et al., 2019a). However, it is important to note that due to variations in

TABLE 3 Factors associated with non-compliance with guidelines in HCTM and UMMC.

Characteristics	HCTM					UMMC				
	Non-compliance (n = 58)	Compliance (n = 28)	p-value[a]	Crude odd ratio (95% CI)	[c]p-value[a]	Non-compliance (n = 112)	Compliance (n = 55)	p-value[a]	Adjusted odd ratio (95% CI)	[c]p-value[a]
Type of treatment, n (%)					0.012					0.076
Empiric	33 (57.9)	24 (42.1)	0.014	1.00 (Reference)		53 (57.0)	40 (43.0)	0.003	1.00 (Reference)	
Prophylaxis	25 (86.2)	4 (13.8)		4.55 (1.40–14.78)	0.012	59 (79.7)	15 (20.3)		2.43 (0.91–6.47)	0.076
Subspecialties Group, n (%)										0.043
Cardiothoracic	2 (100.0)	0 (0.0)	0.198[b]			3 (33.3)	6 (66.7)	0.001[b]	1.00 (Reference)	
General surgery	13 (54.2)	11 (45.8)				31 (70.5)	13 (29.5)		12.56 (1.82–86.48)	0.010
Neurosurgery	2 (40.0)	3 (60.0)				4 (36.4)	7 (63.6)		5.15 (0.47–56.16)	0.179
OBGYN	9 (90.0)	1 (10.0)				30 (88.2)	4 (11.8)		29.89 (3.78–236.49)	0.001
Ophthalmology[d]	7 (53.8)	6 (46.2)				1 (100.0)	0 (0.0)		NA	NA
Trauma and orthopedic	18 (75.0)	6 (25.0)				30 (60.0)	20 (40.0)		8.06 (1.25–52.11)	0.028
Urology	5 (83.3)	1 (16.7)				7 (58.3)	5 (41.7)		7.92 (0.88–70.89)	0.064
Others[d]	2 (100.0)	0 (0.0)				6 (100.0)	0 (0.0)		NA	NA
Antimicrobial group, n (%)										< 0.001
Penicillin	32 (66.7)	16 (33.3)	0.234[b]			17 (40.5)	25 (59.5)	< 0.001[b]	1.00 (Reference)	
Cephalosporin	12 (80.0)	3 (20.0)				62 (88.6)	8 (11.4)		8.57 (2.89–25.39)	< 0.001
Carbapenem	0 (0.0)	1 (100.0)				3 (75.0)	1 (25.0)		10.56 (0.65–171.44)	0.097
Nitroimidazole	2 (33.3)	4 (66.7)				21 (84.0)	4 (16.0)		2.78 (0.68–11.41)	0.155
Quinolone	7 (70.0)	3 (30.0)				2 (40.0)	3 (60.0)		0.64 (0.05–8.04)	0.731
Other	5 (83.3)	1 (16.7)				7 (33.3)	14 (66.7)		0.65 (0.19–2.25)	0.493

[a]Chi-Squared test.

[b]Fisher Exact test. Odd ratio based on non-compliance group (non-compliance/compliance).

[c]p-value for Adjusted Odd Ratio.

[d]Excluded in the multivariate analysis due to small number.

HCTM, Hospital Canselor Tuanku Muhriz; UMMC, University Malaya Medical Centre; OBGYN, obstetrics and gynecology.

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TABLE 4 Factors associated with inappropriate prescribing in HCTM and UMMC.

Hospital	HCTM					UMMC				
Characteristics	Inappropriate (n = 54)	Appropriate (n = 61)	p-value[a]	Crude odd ratio (95% CI)	[c]p-value[a]	Inappropriate (n = 92)	Appropriate (n = 119)	p-value[a]	Adjusted odd ratio (95% CI)	[c]p-value[a]
Type of treatment, n (%)					< 0.001					< 0.001
Empiric treatment	23 (38.3)	37 (61.7)	0.006	1.00 (Reference)		39 (40.6)	57 (59.4)	< 0.001	1.00 (Reference)	
Prophylaxis	21 (72.4)	8 (27.6)		4.22 (1.61–11.10)	0.003	48 (64.9)	26 (35.1)		2.37 (1.21–4.65)	0.012
Directed therapy	10 (38.5)	16 (61.5)		1.01 (0.39–2.59)	0.991	5 (12.2)	36 (87.8)		0.15 (0.05–0.52)	0.003
Reason for use documented, n (%)[d]										
Yes	39 (48.1)	42 (51.9)	0.838			88 (42.5)	119 (57.5)	0.035[b]	NA	NA
No	15 (44.1)	19 (55.9)				4 (100.0)	0 (0.0)		NA	NA
Antimicrobial group, n (%)										0.474
Penicillin	24 (40.7)	35 (59.3)	0.357[b]			16 (33.3)	32 (66.7)	0.029[b]	1.00 (Reference)	
Cephalosporin	13 (59.1)	9 (40.9)				40 (50.0)	40 (50.0)		1.50 (0.66–3.40)	0.335
Carbapenem	0 (0.0)	2 (100.0)				5 (27.8)	13 (72.2)		2.86 (0.65–12.70)	0.166
Nitroimidazole	3 (42.9)	4 (57.1)				18 (66.7)	9 (33.3)		2.38 (0.83–6.82)	0.108
Quinolone	5 (45.5)	6 (54.5)				2 (33.3)	4 (66.7)		1.01 (0.15–6.61)	0.995
Other	9 (64.3)	5 (35.7)				11 (34.4)	21 (65.6)		1.05 (0.38–2.90)	0.922

HCTM, Hospital Canselor Tuanku Muhriz; UMMC, University Malaya Medical Centre; OBGYN, obstetrics and gynecology.

[a]Chi-Squared test.

[b]Fisher Exact test. Odd ratio based on inappropriate group (inappropriate/appropriate).

[c]p-value for Adjusted Odd Ratio.

[d]Excluded in the multivariate analysis due to small number.

10.3389/fphar.2024.1381843

definitions of appropriateness and compliance across the literature, comparisons can be challenging and should be interpreted with caution. Ideally, the target for appropriate antimicrobial prescribing rates in surgical-based units should be above 90%, aligning with general goals for hospital-wide antimicrobial prescribing and SAP prescribing (Vandael et al., 2020; National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care, 2021). Alarmingly, our study revealed that both the rates of compliance with guidelines and appropriateness fell below this recommended threshold in the surveyed population. Only a small number of PPS studies reported the findings on surgical-practice units specifically, demonstrating compliance with guidelines that ranged from 70% to 92.7% (Elhajji et al., 2018; Singh et al., 2019; Vandael et al., 2020; Macera et al., 2021).

One of the main reasons for inappropriate prescribing in this study was the incorrect duration of antimicrobial prescriptions (15%), predominantly reflecting the extended use of SAP following surgery (41.3%). Best practice guidelines typically recommend a total SAP duration of less than 24 h for most procedures (Bratzler et al., 2013) and NAPS setting targets for this quality indicator at less than 5% (National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care, 2018). Unfortunately, there has been a persistent pattern of non-compliance and inappropriate prescribing for SAP documented in the literature (Kaya et al., 2016; Mousavi et al., 2017; Alemkere, 2018; Satti et al., 2019; Vicentini et al., 2019; Alahmadi et al., 2020; Bunduki et al., 2020; Khan et al., 2020; Prévost et al., 2020; Bardia et al., 2021; Cabral et al., 2023) ranging from a complete non-compliant to the national guideline (Alemkere, 2018) to 64% compliant (Prévost et al., 2020), while other reports varied from 40.9% inappropriate (Kaya et al., 2016) to 9.5% appropriate SAP use (Khan et al., 2020). Notably, Australian hospitals have monitored the key indicators of antimicrobial appropriateness using NAPS since 2013. While improvements have been observed in certain indicators (i.e., documentation), the proportion of SAP prescriptions exceeding 24 h has remained consistently high, at approximately 30% and has been static since 2015 (Australian Commission on Safety and Quality in Health, 2021). This persistence underscores the challenges of addressing this widespread issue. A comprehensive systematic review across various surgical subspecialties has also highlighted that extending prophylaxis duration does not confer additional reduction on the risk of surgical site infection when best practice (appropriate timing, dosage and re-dosing) is applied (de Jonge et al., 2020). In addition, prolonged SAP duration has been linked to increased risk of adverse events, including acute kidney injury and *Clostridiodes difficile* infection, contributing to the risk of acquired AMR (Harbarth et al., 2000; Bell et al., 2014; Bernatz et al., 2017; Branch-Elliman et al., 2019).

The proportion of SAP prescriptions in the study (27.1%) was higher compared to Australian Hospital NAPS reports for 2018 and 2019, ranging from 13.9% to 12.6% (National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care, 2021). Surveys conducted in Europe, Canada, Belgium and Thailand have reported a common preference of cefazolin for SAP (Versporten et al., 2018; Vandael et al., 2020; German et al., 2021; Anugulruengkitt et al., 2022). In contrast, our study observed a high usage of cefuroxime, which depicted similar therapeutic efficacy to cefazolin in preventing surgical site infections (Ahmed et al., 2022). This unconventional choice was influenced by local guidelines recommending cefuroxime, with or without metronidazole, and amoxicillin/clavulanic acid for most procedures due to the unavailability of cefazolin in our centers during the audit period, resulting in non-standard cefazolin use among prescribers. Similar antimicrobials were commonly employed in several lower-middle-income countries (LMIC) (Labi et al., 2018; Saleem et al., 2019; Umeokonkwo et al., 2019; de Guzman Betito et al., 2021), in accordance with their standard treatment guidelines (Bediako-Bowan et al., 2019). In line with global standards and recommendations, our recent guidelines have designated cefazolin as the first-line agent for the majority of procedures (Ministry of Health Malaysia, 2019; University Malaya Medical Center, 2020). While narrow-spectrum antimicrobial is recommended for SAP, inappropriate broad-spectrum antimicrobials were observed, with a dominance of third-generation cephalosporins (ceftriaxone and cefoperazone) and unnecessary anaerobe coverage with metronidazole. Ceftriaxone, a WHO Watch group antibiotic, is not recommended for SAP in our settings due to its lack of significant advantages over the first and second-generation cephalosporins, and its potential for resistance selection. Its usage is limited to cases of contamination or treatment for infection (Bratzler et al., 2013; Ministry of Health Malaysia, 2019). The preference for ceftriaxone in SAP can be attributed to its easy availability and long half-life, which eliminates the need for additional intra-operative doses. An extensive use of ceftriaxone as SAP in this study and various studies globally (Alemkere, 2018; Satti et al., 2019; Rachina et al., 2020; Limato et al., 2021; Fentie et al., 2022) ranging from 26.4% to 84%, poses another significant challenge for AMS.

Both hospitals also displayed a tendency to choose broader-spectrum coverage antimicrobials across all types of treatment (empiric, prophylaxis and directed therapy). In general, the antimicrobial sensitivity testing (AST) results serve as a valuable tool in determining the optimum antimicrobial therapeutic option, highlighting narrow-spectrum agents whenever possible and keeping in check broad-spectrum antimicrobials that exert higher selective pressure for AMR (Gajic et al., 2022). However, the accurate and timely AST performance is challenged by several factors in our hospitals. Proper interpretation of AST results with regard to efficacy and sensitivity among susceptible categories should be counselled by experts to provide individualized or personalized targeted treatment, as selecting antimicrobials based upon a direct comparison of susceptibility values obtained through *in vitro* testing could be misleading and inaccurate (Gajic et al., 2022). The absence or delay of laboratory data and AST in empiric therapy decisions often leads to the use of broad-spectrum antimicrobials, and at times, polypharmacy, inadvertently encouraging drug resistance (Chokshi et al., 2019).

In UMMC, a noteworthy pattern of non-compliance was identified, with significantly higher occurrence observed in general surgery, OBGYN and trauma and orthopedic units. Evidence of guideline compliance has yielded diverse outcomes in various prospective observational studies. NAPS reports on antimicrobial use in Canada indicated a commendable rate of appropriate prescription, notably in gynecology unit at 86.2% (CARSS, 2022). Conversely in Nigeria, an audit in OBGYN wards painted a different picture, highlighting excessive and inappropriate antimicrobial usage,

with similar output including high incidence of redundant anaerobic coverage with metronidazole (Abubakar et al., 2018). Meanwhile, Thomas et al. (2022) found higher compliance in both gynecology (88.6%) and orthopedic (86.3%) compared to surgery (67.9%). Our study also highlighted that although documentation practices were significantly higher in UMMC, which utilizes electronic medical records (EMR) and electronic prescribing (e-prescribing), compared to HCTM, where paper-based health records are used, this criterion did not significantly influence the rates of compliance and appropriateness. However, King et al. (2017) and Hand et al. (2017) have outlined the potential of digital platforms and electronic health information technology in aiding prescribers throughout the antimicrobial lifecycle encompassing initiation, review, stopping and supplying of discharge medications. The technology is anticipated to have a positive impact on documentation and compliance in the surgical unit (Charani et al., 2017).

Despite these observations, the precise causes of the high non-compliant of prescribers in this study were uncertain and unexplored; thus, the explanation for this finding warrants further investigation. Insights drawn from an ethnographic study shed light on surgeons' priorities, which primarily revolve around surgical procedures, surgical care and patient outcomes. Surgeons often place a strong emphasis on starting antimicrobials than on reviewing or stopping them, while rarely discussing the choice of antimicrobial (Charani et al., 2018). This potentially leading to prolonged and unnecessary use of these drugs. A review by Hassan et al. identified a common barrier to compliance with guidelines stemming from prescribers' inadequate knowledge and unfamiliarity of guideline content (Hassan et al., 2021). However, Ierano et al. (2019b) highlighted that prescriber preferences and autonomy are often considered more important than strict compliance with guidelines, even when prescribers are well-informed about the guidelines. Moreover, guidelines are often viewed as general recommendations that lack the necessary details to address the diverse array of surgical procedures and various patient characteristics and environmental factors that complicate decision-making in complex situations. A recent survey conducted among Surgical Infection Society (SIS) members, experts in surgical infections, revealed that surgeons hold varying opinions regarding the appropriate duration of prophylaxis and therapeutic antimicrobials for inpatients across common indications (Delaplain et al., 2022). It is evident that heightened prescribers' awareness regarding their prescribing practices is a crucial component of AMS efforts.

5 Limitations

While the PPS is capable of presenting the overview of antimicrobial usage in surgical-practice units, we believe the widespread use of the extended duration of antimicrobial post-surgery is underestimated, given that the survey methodology does not capture the intricacy of preoperative, intraoperative and post-operative antimicrobial use. Second, the results from two tertiary teaching hospitals may not be generalized to all surgical-practice units across hospitals in the country but still they are required to set direction and targets for AMS interventions. It is also an important contribution to drive a change in prescribing and policy development. Third, a variable degree in assessment is possible, as interpretations may differ from one another. However, an assessment tool and support from the Australian NAPS were available to assist with any disagreement throughout the study. Another limitation is the absence of quantitative measures such as defined daily doses (DDD) to quantify antimicrobial consumption, as this study focused primarily on qualitative assessment of antimicrobial practices. Future study may benefit from incorporating quantitative measures to complement qualitative assessment of antimicrobial prescribing practices.

6 Conclusion

This study provides valuable insights into the antimicrobial usage, indications and determinants of non-compliance and inappropriateness within the surgical-practice units of two teaching hospitals in Malaysia. The findings emphasized the urgent need for a strong commitment of AMS initiatives that focus on reducing unnecessary prolongation of SAP and unnecessary use of broad-spectrum antimicrobials to enhance rational prescribing in the surgical field. It is recommended that the WHO AWaRe classification be incorporated into the national and local antimicrobial guidelines, as well as embedded in the AMS quality improvement program to facilitate monitoring and restriction of Watch antibiotics, which carry higher risk of resistance potential. A collective work by actively involving and raising awareness among prescribers is crucial to promote proper documentation, encouraging guidelines compliance and favoring overall appropriateness to ensure responsible use of antimicrobial in surgical settings.

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 Research Ethics Committee of Universiti Kebangsaan Malaysia, and University of Malaya Medical Centre-Medical Research Ethics Committee (UMMC-MREC). 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.

Author contributions

NJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing–original draft, Writing–review and editing. PP: Conceptualization, Data curation,

Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–original draft, Writing–review and editing. CL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–original draft, Writing–review and editing. SP: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–review and editing. PL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing–review and editing. LL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing–review and editing. TgT: Formal Analysis, Writing–review and editing. RR: Conceptualization, Data curation, Formal Analysis, Investigation, Writing–review and editing. ToT: Conceptualization, Data curation, Formal Analysis, Investigation, Writing–review and editing. NK: Data curation, Formal Analysis, Investigation, Conceptualization, Writing–review and editing. MY: Data curation, Formal Analysis, Investigation, Resources, Writing–review and editing. NA: Resources, Writing–review and editing, Data curation, Formal Analysis, Investigation. RJ: Conceptualization, Methodology, Resources, Writing–review and editing. KT: Conceptualization, Methodology, Resources, Writing–review and editing. IN: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, 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 study was funded by Pfizer Independent Grants for Learning and Change (IGCL), grant ID number 40867041, and The Joint Commission provides administrative oversight for the programme.

Acknowledgments

We would like to thank all auditors, antimicrobial stewardship team, pharmacy department and Infection Control Unit from both hospitals for their valuable contributions. The authors acknowledge the assistance and support provided by Australian NAPS in assessment and web data management, including Ron Cheah (National Centre for Antimicrobial Stewardship, Department of Infectious Diseases, University of Melbourne) for his attendance and support. The study would not have been possible without assistance, support and effort from Malaysian NAPS working group at the University of Malaya–Adeeba Kamarulzaman, Sharifah Faridah Syed Omar, Asma Sohail, Pui Li Wong, Bushra Megat Johari, Hang Cheng Ong, Rong Xiang Ng, Anjanna Kukreja, Mia Tuang Koh, Lay Teng Tan, Chiang Hooi Tan, Chuey Ee Lee, Ka Yin Lim.

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.2024.1381843/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 30 May 2024
DOI 10.3389/fphar.2024.1368244

OPEN ACCESS

EDITED BY
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RECEIVED 10 January 2024
ACCEPTED 13 May 2024
PUBLISHED 30 May 2024

CITATION
Liu Y, Li H, Hu C, Tan L, Yin P, Li Z, Zhou S and Su L (2024), A real-world pharmacovigilance analysis for transthyretin inhibitors: findings from the FDA adverse event reporting database. *Front. Pharmacol.* 15:1368244. doi: 10.3389/fphar.2024.1368244

A real-world pharmacovigilance analysis for transthyretin inhibitors: findings from the FDA adverse event reporting database

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Objective: The purpose of this study is to investigate the drug safety of three Transthyretin (TTR) inhibitors in the real world using the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: This study extracted reports received by the FAERS database from the first quarter of 2018 to the third quarter of 2023 for descriptive analysis and disproportionality analysis. Safety signal mining was conducted at the Preferred Term (PT) level and the System Organ Class (SOC) level using reporting odds ratio (ROR). The characteristics of the time-to-onset curves were analyzed using the Weibull Shape Parameter (WSP). The cumulative incidence of TTR inhibitors was evaluated using the Kaplan-Meier method. Subgroup analyses were conducted based on whether the reporter was a medical professional.

Results: A total of 3,459 reports of adverse events (AEs) caused by TTR inhibitors as the primary suspect (PS) drug were extracted. The top three reported AEs for patisiran were fatigue, asthenia, and fall, with the most unexpectedly strong association being nonspecific reaction. The top three reported AEs for vutrisiran were fall, pain in extremity and malaise, with the most unexpectedly strong association being subdural haematoma. The top three reported AEs for inotersen were platelet count decreased, blood creatinine increased, and fatigue, with the most unexpectedly strong association being blood albumin decreased. Vitamin A decreased, arthralgia, and dyspnea were the same AEs mentioned in the drug labels of all three drugs, while malaise and asthenia were the same unexpected significant signals. This study offers evidence of the variability in the onset time characteristics of AEs associated with TTR inhibitors, as well as evidence of differences in adverse event reporting between medical professionals and non-medical professionals.

Conclusion: In summary, we compared the similarities and differences in drug safety of three TTR inhibitors in the real world using the FAERS database. The results indicate that not only do these three drugs share common AEs, but they also exhibit differences in drug safety profiles. This study contributes to enhancing the understanding of medical professionals regarding the safety of TTR inhibitors.

KEYWORDS

patisiran, vutrisiran, inotersen, FAERS, pharmacovigilance analysis

Introduction

Transthyretin amyloidosis (ATTR) is a disease characterized by the abnormal deposition of transthyretin in multiple tissues and organs due to misfolding (Castaño et al., 2015; Wechalekar et al., 2016). ATTR is marked by its low prevalence, multisystem involvement, and the challenges in clinical and differential diagnosis (Maurer et al., 2019; Adams et al., 2021). The clinical phenotypes primarily include transthyretin amyloid polyneuropathy (ATTR-PN) and transthyretin amyloid cardiomyopathy (ATTR-CM) (Adams et al., 2019; Maurer et al., 2019; Ruberg et al., 2019). Approximately 70% of ATTR patients present with peripheral neuropathy (Siddiqi and Ruberg, 2018). Neuropathies in ATTR patients may include carpal tunnel syndrome, lumbar spinal stenosis, small fiber neuropathy, and autonomic dysfunction. As the disease progresses, patients may also experience loss of reflexes, reduced motor skills, and muscle weakness (Cortese et al., 2017; Barge-Caballero et al., 2019; Carr et al., 2019). Accurate global prevalence estimates for ATTR remain elusive, however, recent research has broadened our understanding. A retrospective study estimated the global prevalence of ATTR-PN at 10,186 (range 5,526–38,468) (Schmidt et al., 2018). Another study highlighted geographical variations in the prevalence of certain ATTR genotypes. Specifically, the Val30Met genotype is most prevalent in endemic countries, while genotypes in non-endemic countries are primarily categorized as "other" (Waddington-Cruz et al., 2019). The average survival period after the onset of ATTR ranges from 6 to 12 years (Adams et al., 2021). Previously, treatment options for ATTR were limited. Apart from symptomatic treatment for neuropathy, heart failure, and arrhythmias, liver transplantation was the only effective treatment (Sekijima, 2015; Maurer et al., 2018). However, liver transplantation has limited efficacy in halting disease progression and is associated with high costs, surgical complications, and transplant-related rejection reactions in clinical practice (Carvalho et al., 2015). In recent years, the introduction of TTR inhibitors has provided new treatment options for ATTR patients. They primarily function by inhibiting the translation process of TTR mRNA. As of the third quarter of 2023, only patisiran (approval time: 2018), vutrisiran (approval time: 2022), and inotersen (approval time: 2018), three TTR inhibitors, have been approved by the FDA for the treatment of adult hereditary ATTR-PN (Benson et al., 2018; Maurer et al., 2018; Park et al., 2019; Darrow et al., 2020; Nie et al., 2023).

All TTR inhibitors received Orphan Drug Designation (ODD) or Fast Track designation during their FDA approval process. In previous limited clinical studies, AEs to patisiran included upper respiratory tract infections, infusion-related reactions, indigestion, dyspnea, arthralgia, muscle spasms, etc. (Adams et al., 2018; Maurer et al., 2023), while inotersen's AEs included glomerulonephritis, thrombocytopenia, injection site reactions, nausea, headaches, etc. (Benson et al., 2018). AEs to amvuttra included injection AEs, dyspnea, arthralgia, and vitamin A deficiency (Habtemariam et al., 2021). It is important to note that the FDA has warned about inotersen causing thrombocytopenia and glomerulonephritis through a black box warning. It is noteworthy that due to the rarity of the disease, challenges in diagnosis, and limited follow-up time in clinical trials, large-scale clinical studies investigating the drug safety of TTR inhibitors remain insufficient, making rare drug-related AEs difficult to observe. Therefore, post-marketing surveillance of drug-related AEs for TTR inhibitors is crucial.

The FAERS database is a project operated by the FDA to identify potential correlations between drugs and AEs within the scope of post-marketing drug safety surveillance (FAERS, 2023). This public platform encourages medical professionals, patients, pharmaceutical companies, and the public to report AEs through the MedWatch program. Earlier studies have utilized the FAERS database for assessing the real-world safety of drugs. For instance, Lindsy Pang and others evaluated post-marketing AEs of non-stimulant attention deficit hyperactivity disorder medications using the FAERS database. Natalia Gonzalez Caldito and others analyzed the differences in reported AEs between rituximab and ocrelizumab using the FAERS database (Caldito et al., 2021; Pang and Sareen, 2021).

The FAERS database is updated quarterly and currently holds a vast dataset of over ten million reports. The purpose of our study is to extract reports of AEs related to TTR inhibitors in the real world from the extensive data of the FAERS database and further conduct retrospective pharmacovigilance research based on these critical data. The results of the study will be beneficial for the clinical practice of TTR inhibitors, providing valuable references for medical professionals.

Materials and methods

Data source

We conducted a real-world pharmacovigilance study on three TTR inhibitors using the latest data from the FAERS database. Since the FDA first approved the TTR inhibitor patisiran in 2018, we extracted report data from the FAERS database from the first quarter of 2018 to the third quarter of 2023. The analysis utilized four sub-databases: DEMO, DRUG, REAC, and THER, they respectively provide demographic clinical characteristics (such as gender, age, reporting time), medication usage information (drug names, routes of administration, dosages), adverse event details (names of AEs), and medication date information (start and end dates of drug treatment).

Data preprocess

To enhance the reliability of our research, we preprocessed the initially obtained data, with the detailed process illustrated in Figure 1. Firstly, we identified patisiran, vutrisiran, and inotersen as target drugs. Considering that the FAERS database allows the use of multiple names for drugs when reporting AEs, both the drug and brand names of these three drugs were used for retrieval in the FAERS database to avoid missing related data. We obtained reports of AEs caused by TTR inhibitors as the primary suspect (PS) drug from the first quarter of 2018 to the third quarter of 2023 by searching for patisiran (ALN-TTR02, onpattro, patisiran sodium), vutrisiran (amvuttra, vutrisiran sodium), and inotersen (inotersen sodium, tegsedi) in the FAERS database. Secondly, we removed duplicates based on CASEID, FDA_DT, and PRIMARYID in the FAERS database, as demonstrated in Table 1 (Yu et al., 2023).

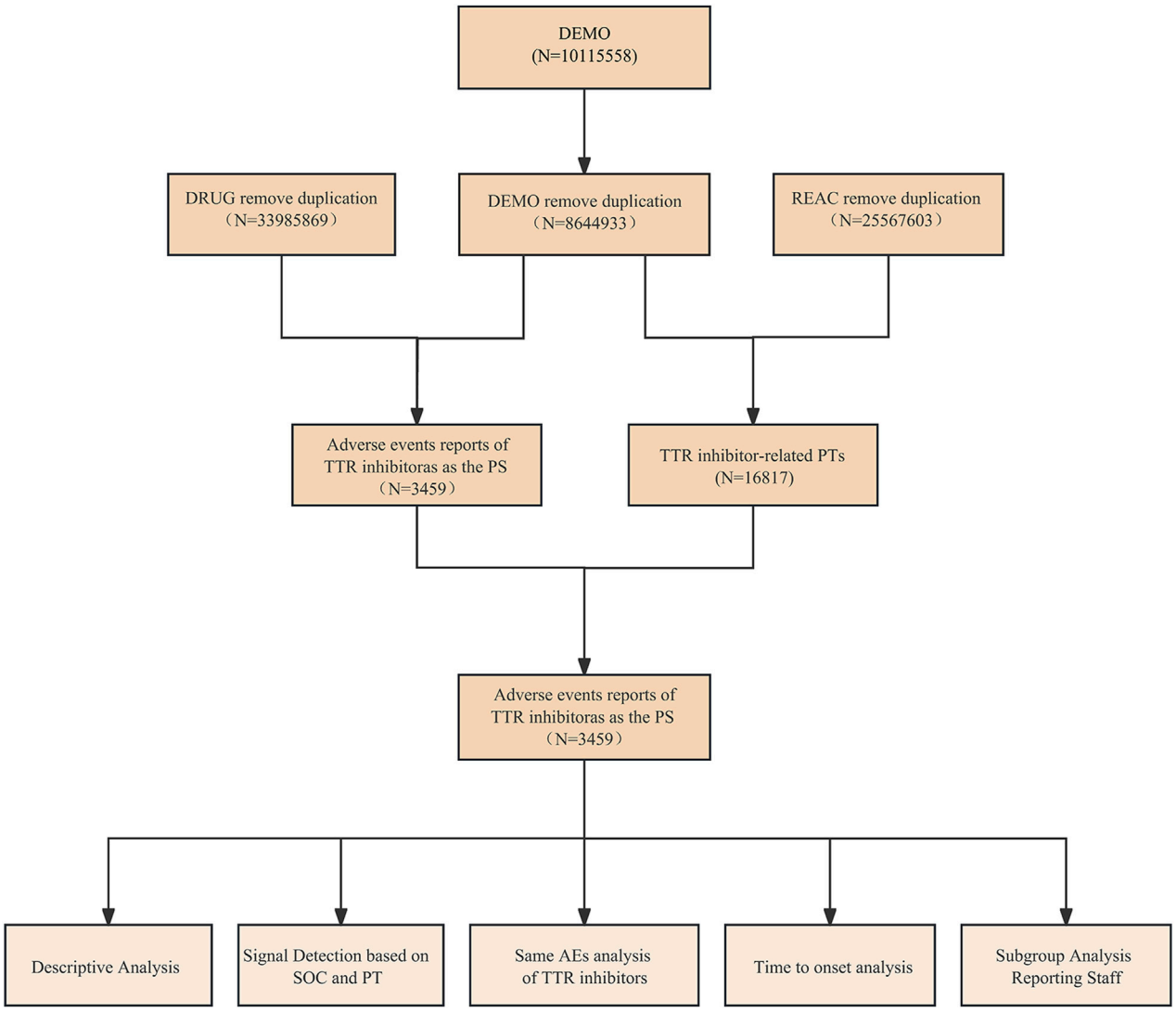

FIGURE 1
Flow diagram of this study.

TABLE 1 Example of FAERS database duplicate report removal rule.

CASEID	FDA_DT	PRIMARYID	Delete or save
2,751,007	40,064,207	51,321,061	DELETE
2,751,007	40,064,345	51,364,244	SAVE
2,720,901	40,064,112	26,542,012	DELETE
2,720,901	40,064,112	27,532,429	SAVE

Finally, we analyzed the data based on the hierarchical structure of the International Medical Dictionary (MedDRA) version 26.1, from the SOC and the PT levels (Brown, 2002; Brown, 2003). SOC is the top-level classification in MedDRA, typically involving a particular system or organ of the body. PT refers to the preferred term for specific symptoms or diagnoses. Furthermore, we manually reviewed and revised the names of SOCs and PTs in the FAERS database according to MedDRA.

Descriptive analysis

Following the aforementioned process, we examined the final dataset related to TTR inhibitors and summarized the clinical characteristics of the population, including gender, age group, reporter, and year of report.

Disproportionality analysis

We first examined the adverse event data of the three TTR inhibitors at the SOC level, calculating the number of reports for various AEs, the reporting odds ratio (ROR), and its 95% Confidence Interval (CI) for each drug. Subsequently, at the PT level, we ranked the AEs based on the number of reports, generating a list of the top 50 AEs for each of the three TTR inhibitors, and then calculated their ROR and 95% CI. ROR is used to assess the correlation between TTR inhibitors and specific AEs and has been successfully applied in previous studies based on the FAERS

database, with the formula and standards presented in Supplementary Table S1 (Ooba and Kubota, 2010; Musialowicz et al., 2023). During our analysis at the PT level, we excluded data related to outcomes, injections or infusions, and clinical characteristics of ATTR-CM and ATTR-PN, except for data on arrhythmias. When analyzing at the PT level, we excluded data related to outcomes, injections or infusions, and symptoms caused by the disease itself. Additionally, we summarized the same AEs already listed in the drug labels of the three TTR inhibitors and the same unexpected significant signals obtained from this study. In this study, an unexpected significant signal is defined as: a specific adverse event at the PT level that meets the ROR algorithm standards and is not mentioned in the most recent version of the drug labels to date.

Time to onset analysis

Time-to-onset was determined based on the interval between EVENT_DT (date of adverse event occurrence) and START_DT (date of initiating drug treatment) in the THER sub-database. We excluded reports with inaccurate dates, missing dates, and those where the start date of drug treatment was after the date of the adverse event occurrence. The assessment utilized median, quartiles, and the WSP test. The WSP test identifies the rate of change in the incidence of AEs, with the scale parameter α and shape parameter β obtained from the test being critical in determining the scale and shape of the distribution function. Based on the shape parameter β, the risk in a reference population can be assessed, categorized as follows: when $\beta < 1$ and its 95% CI < 1, it is considered that the risk of drug-related AEs decreases over time (early failure-type profile); when β is equal to or close to 1 and its 95% CI includes 1, it is considered that the risk of drug-related AEs occurs continuously over time (random failure-type profile); when $\beta > 1$ and its 95% CI > 1, it is considered that the risk of drug-related AEs increases over time (wear-out failure-type profile) (Cornelius et al., 2012). Additionally, the Kaplan-Meier method was used to plot the cumulative incidence of AEs related to the three drugs in figures for comparison purposes.

Subgroup analyses

We conducted subgroup analyses based on whether the reporter was a medical professional, with the following method: extracting reports of AEs related to the three TTR inhibitors reported by both healthcare and non-medical professionals; at the PT level, selecting the top 50 AEs by number of reports; and calculating the ROR value and its 95% CI for signal mining.

In this study, ROR was calculated by comparison with the FAERS database. Data processing and statistical analysis were conducted using Microsoft Excel 2019 and R software version 4.3.1. Tables were created using Microsoft Word 2019, and figures were produced using R software version 4.3.1.

Results

Descriptive analysis

Between the first quarter of 2018 and the third quarter of 2023, the FAERS database received a total of 10,115,558 case reports. After eliminating duplicate reports, there were 8,644,933 patient cases with 25,567,603 reported AEs. Within these data, there were 3,459 reports of AEs caused by TTR inhibitors as the PS drugs. The summarized clinical characteristic information can be seen in Table 2.

TABLE 2 Clinical Characteristics of Reports with transthyretin inhibitors from the FAERS Database.

	Patisiran	Vutrisiran	Inotersen
Total number of reports	2158	258	1,043
Sex			
Female	213 (9.9%)	0	248 (23.8%)
Male	400 (18.5%)	0	409 (39.2%)
Missing	1,545 (71.6%)	258 (100%)	386 (37.0%)
Age (years)			
<18	0	0	0
18–65	94 (4.4%)	0	237 (22.7%)
>65	153 (7.1%)	0	379 (36.4%)
Missing	1911 (88.6%)	258 (100%)	427 (40.9%)
Reporting Staff			
Medical professionals	1,275 (59.1%)	89 (34.5%)	623 (59.7%)
Non-medical professionals	866 (40.1%)	169 (65.5%)	419 (40.2%)
Missing	17 (0.8%)	0	1 (0.1%)
Reporting year			
2018	23 (1.1%)	0	0
2019	337 (15.6%)	0	64 (6.1%)
2020	478 (22.2%)	0	268 (25.7%)
2021	456 (21.1%)	0	156 (15.0%)
2022	511 (23.7%)	18 (7.0%)	216 (20.7%)
2023	353 (16.3%)	240 (93.0%)	339 (32.5%)

In reports related to patisiran, the proportion of males (18.5%) was higher than that of females (9.9%), with 71.6% of reports having an unknown gender; the largest age group was over 65 years (7.1%), followed by 18–65 years (4.4%), with no reports under 18 years and 88.6% having an unknown age; reports uploaded by medical professionals accounted for 59.1% compared to 40.1% by non-medical professionals, with 0.8% unknown reporters; the year with the most reports was 2022 (23.7%), followed by 2020 (22.2%), 2021 (21.1%), 2023 (16.3%), 2019 (15.6%), and 2018 (1.1%).

In reports related to vutrisiran, all reports had unknown gender and age; reports uploaded by non-medical professionals accounted for 65.5%, higher than those by medical professionals (34.5%), with no reports having an unknown reporter; the year with the most reports was 2023 (93.0%), followed by 2022 (7.0%).

In reports related to inotersen, the proportion of males (39.2%) was higher than that of females (23.8%), with 37.0% of reports having an unknown gender; the largest age group was over 65 years (36.4%), followed by 18–65 years (22.7%), with no reports under 18 years and 40.9% having an unknown age; reports uploaded by medical professionals accounted for 59.7% compared to 40.2% by non-medical professionals, with 0.1% unknown reporters; the year with the most reports was 2023 (32.5%), followed by 2020 (25.7%), 2022 (20.7%), 2021 (15.0%), and 2019 (6.1%).

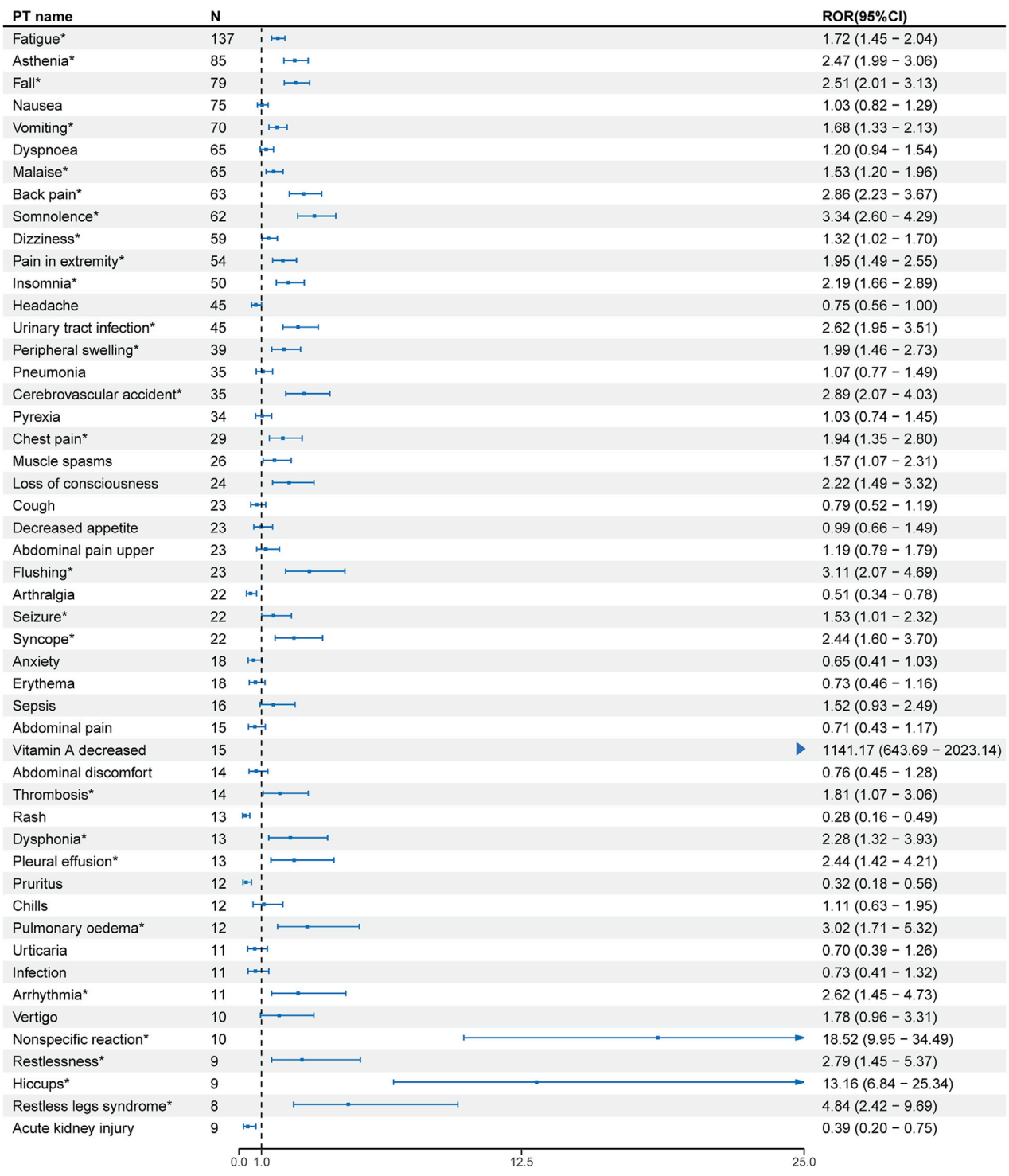

FIGURE 2
Signal strength of the top 50 AEs for patisiran ranked by report frequency at the preferred term (PT) Level in the FDA Adverse Event Reporting System (FAERS) N:number of drug-related AEs *: mentioned in the drug label and $ROR_{025} > 1$ and $N \geq 2$.

Disproportionality analysis

At the SOC level, the number of reports and signal strength of AEs related to the three TTR inhibitors are presented in Supplementary Figure S1–S3. We found that AEs related to patisiran involved 26 organ systems. Significant SOC meeting the criteria included social circumstances, ear and labyrinth disorders, metabolic and nutritional disorders, various types of injuries, poisonings and procedural complications, general disorders and administration site conditions, vascular and lymphatic disorders, various neurological disorders, cardiac disorders, and various surgeries and medical procedures. AEs related to vutrisiran

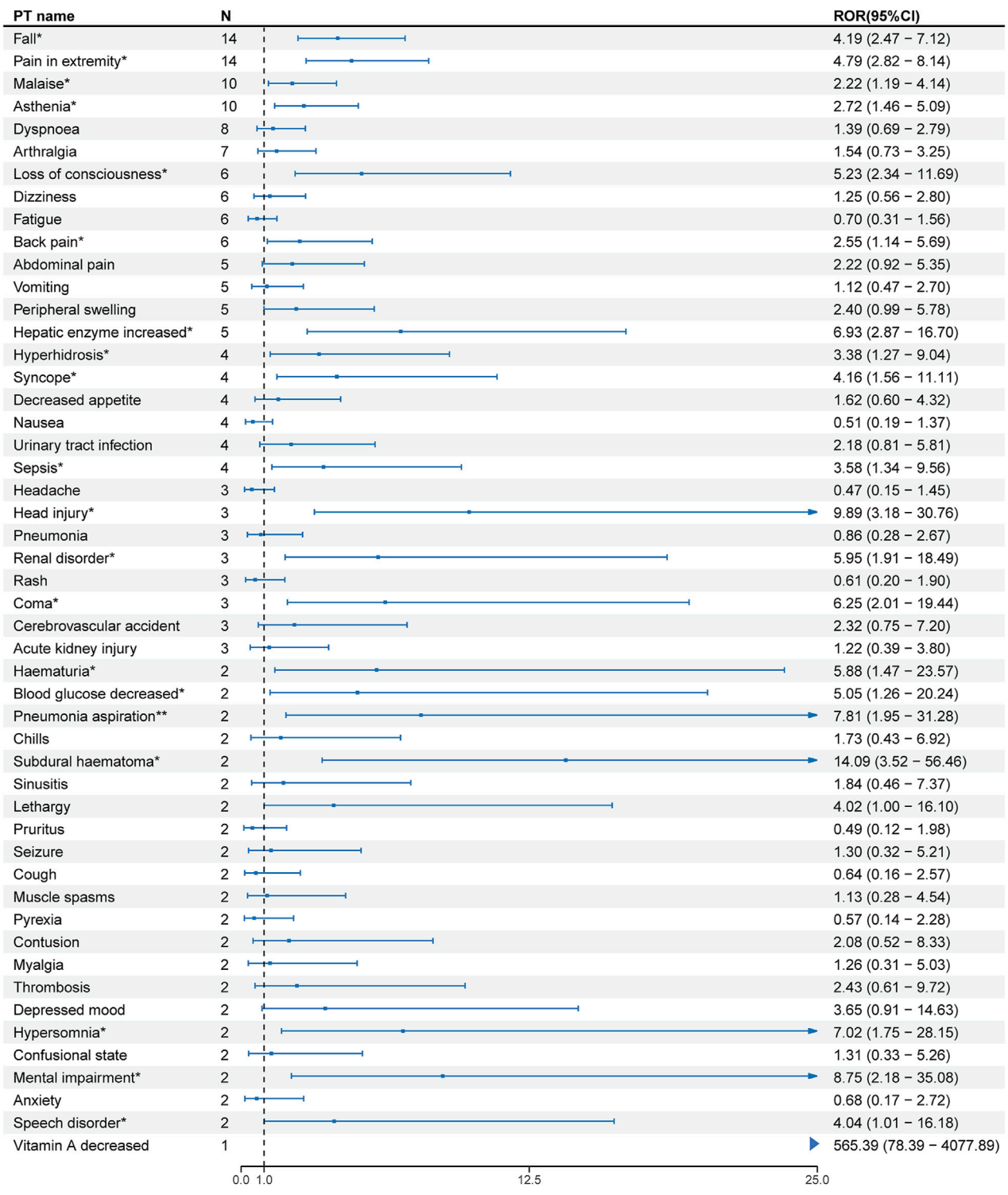

FIGURE 3
Signal strength of the top 50 AEs for vutrisiran ranked by report frequency at the preferred term (PT) Level in the FDA Adverse Event Reporting System (FAERS) N:number of drug-related AEs *: mentioned in the drug label and $ROR_{025} > 1$ and $N \geq 2$.

involved 23 organ systems, with significant SOC including various musculoskeletal and connective tissue disorders, cardiac disorders, various neurological disorders, and various surgeries and medical procedures. AEs related to inotersen involved 26 organ systems, with significant SOC including social circumstances, renal and urinary disorders, and various investigations.

At the PT level, the number of reports and signal strength of the top 50 most common AEs related to the three TTR inhibitors are

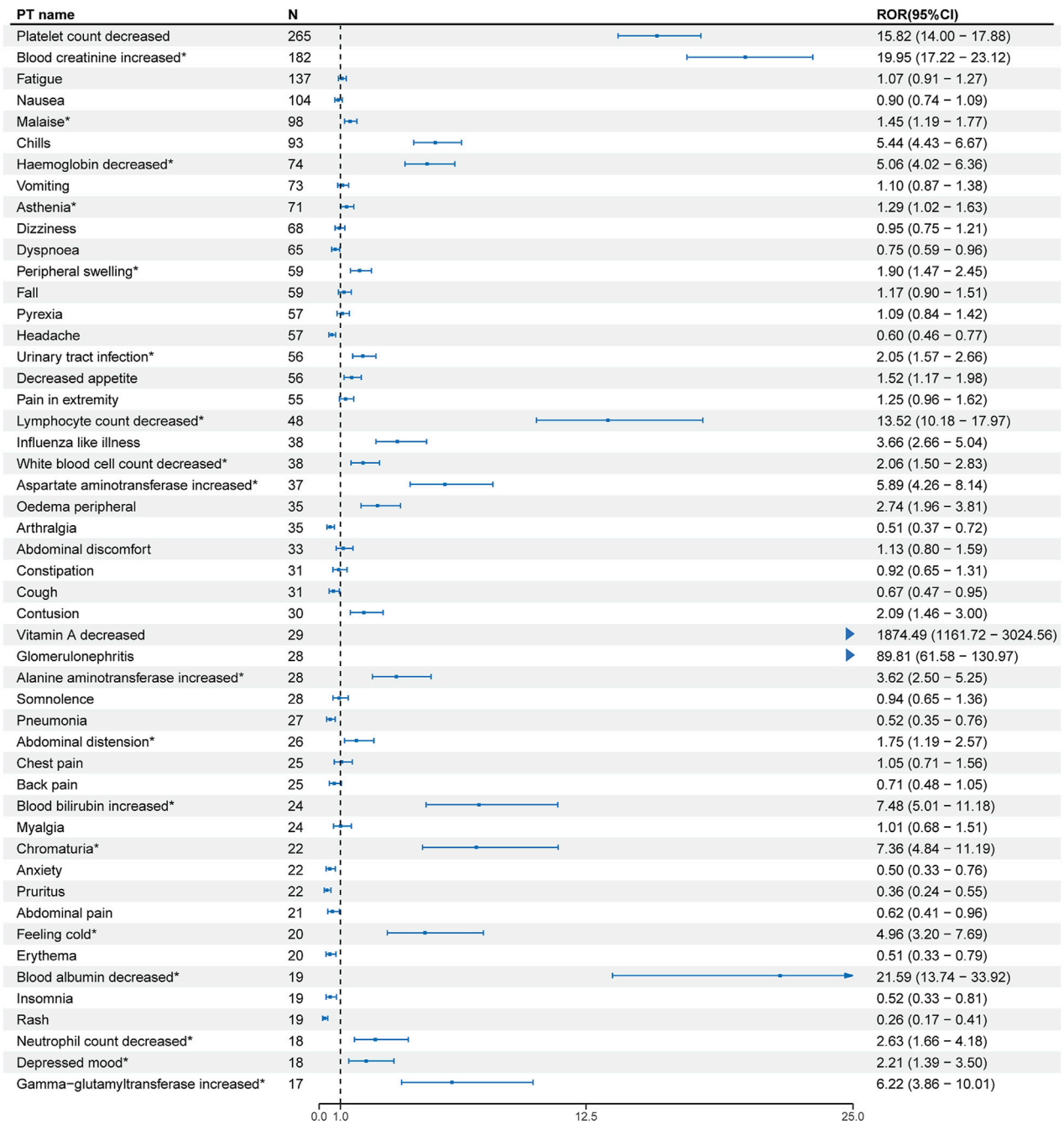

FIGURE 4
Signal strength of the top 50 AEs for inotersen ranked by report frequency at the preferred term (PT) Level in the FDA Adverse Event Reporting System (FAERS) N:number of drug-related AEs *: mentioned in the drug label and $ROR_{025} > 1$ and $N \geq 2$.

shown in Figures 2–4. The top 10 reported AEs related to patisiran were fatigue, asthenia, fall, nausea, vomiting, dyspnoea, malaise, back pain, somnolence, and dizziness. A total of 29 AEs were significant signals, with vitamin A decreased and muscle spasms mentioned in the drug label, and the other 27 as unexpected significant signals. The top 10 reported AEs related to vutrisiran were fall, pain in extremity, malaise, asthenia, dyspnoea, arthralgia, loss of consciousness, dizziness, fatigue, and back pains, with 19 being significant signals not mentioned in the latest drug label. The top 10 reported AEs related to inotersen were platelet count decreased, blood creatinine increased, fatigue, nausea, malaise, chills, haemoglobin decreased, vomiting, asthenia, and dizziness, with 25 being significant signals, including decreased appetite, contusion, oedema peripheral, influenza like illness, chills, platelet count decreased, glomerulonephritis, and vitamin A decreased mentioned in the drug label, and the other 19 as unexpected significant signals.

We compared the AEs mentioned in the latest version of the drug labels of the three TTR inhibitors with the unexpected significant signals obtained from this study, finding that vitamin

Drug	Case reports	Median(d)(25%-75%)	Scaleparameter:α(95% CI)	Shapeparameter:β(95% CI)	Type
Patisiran	447	207.0(63.0-582.5)	338.87(298.26-379.48)	0.81(0.75-0.87)	Early failure
Vutrisiran	73	103.0(61-169)	134.26(112.56-155.96)	1.48(1.21-1.76)	Wear-out failure
Inotersen	311	242(75-500)	311.29(266.53-356.05)	0.81(0.73-0.88)	Early failure

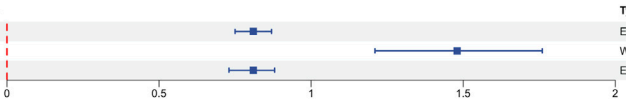

FIGURE 5
Weibull shape parameter test for AEs associated with transthyretin inhibitors CI:confidence interval.

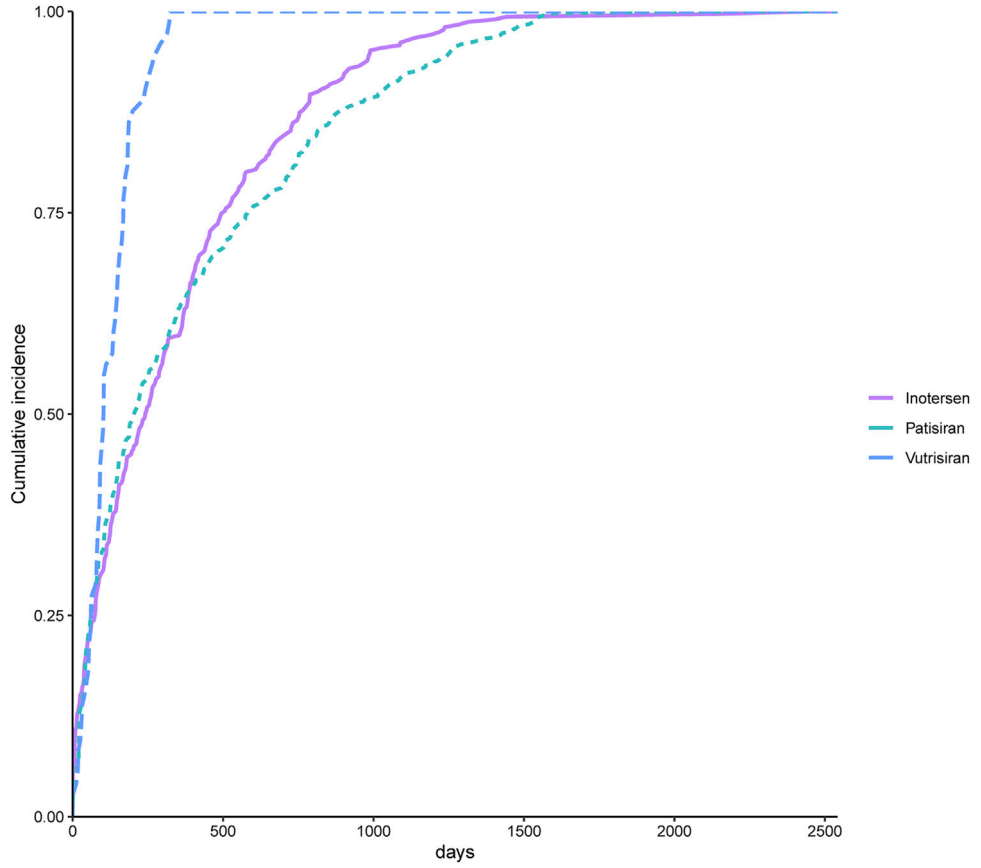

FIGURE 6
Comparison between cumulative incidences of AEs between patients treated with transthyretin inhibitors.

A decreased, arthralgia, and dyspnea were the same AEs mentioned in the drug labels, with malaise and asthenia as the same unexpected significant signals.

Time to onset analysis

We included reports of 447 AEs related to patisiran, 73 AEs related to vutrisiran, and 311 AEs related to inotersen for time-to-onset analysis, with detailed results presented in Figure 5. The median time-to-onset for AEs related to patisiran was 207 days (63–582.5 days), with the WSP test's β and its 95% CI being 0.81 (0.75–0.87), indicating an early failure-type profile. The median time-to-onset for AEs related to vutrisiran was 103 days (61–169 days), with the WSP test's β and its 95% CI being 1.48 (1.21–1.76), indicating a wear-out failure-type profile. The median time-to-onset for AEs related to inotersen was 242 days (75–500 days), with the WSP test's β and its 95% CI being 0.81 (0.73–0.88), indicating an early failure-type profile. Figure 6 shows the cumulative incidence of AEs related to the three TTR inhibitors. The percentage of AEs occurring within 30 days of starting patisiran treatment was 14.3%, and within 180 days was 46.8%. For vutrisiran, the percentage of AEs within 30 days of treatment was 12.3%, and within 180 days was 79.5%. For inotersen, the percentage of AEs within 30 days of treatment was 15.4%, and within 180 days was 44.4%.

Subgroup analyses

Our subgroup analysis results based on whether the reporter was a medical professional are presented in Supplementary Table S2–S4.

In reports of AEs related to patisiran, common significant signals included fatigue, insomnia, pain in extremity, asthenia, fall, back pain, chest pain, somnolence, urinary tract infection, cerebrovascular accident, vitamin A decreased, peripheral swelling, and syncope. Unique significant signals reported by medical professionals included flushing, seizure, pleural effusion, restlessness, dysphonia, pulmonary edema, influenza-like illness, thrombosis, hiccups, and restless legs syndrome. Unique significant signals reported by non-medical professionals included muscle spasms, muscle weakness, loss of consciousness, sepsis, vertigo, limb discomfort, and taste disorder.

In reports of AEs related to vutrisiran, pain in extremity was a common significant signal. Unique significant signals reported by medical professionals included hepatic enzyme increased, sepsis, malaise, abdominal pain, and syncope. Unique significant signals reported by non-medical professionals included fall, asthenia, loss of consciousness, peripheral swelling, hyperhidrosis, urinary tract infection, head injury, renal disorder, limb discomfort, subdural hematoma, coma, hypersomnia, and mental impairment.

In reports of AEs related to inotersen, common significant signals included platelet count decreased, blood creatinine increased, malaise, chills, urinary tract infection, haemoglobin decreased, contusion, vitamin A decreased, feeling cold, and lymphocyte count decreased. Unique significant signals reported by medical professionals included decreased appetite, peripheral swelling, alanine aminotransferase increased, aspartate aminotransferase increased, influenza-like illness, glomerulonephritis, blood bilirubin increased, abdominal distension, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, and depressed mood. Unique significant signals reported by non-medical professionals included pyrexia, asthenia, vomiting, chest pain, red blood cell count decreased, anemia, aspartate aminotransferase abnormal, alanine aminotransferase abnormal, and pulmonary oedema.

Discussion

TTR inhibitors are important therapeutic drugs for patients with ATTR. TTR inhibitors developed based on Small interfering RNA (siRNA) or antisense oligonucleotide (ASO) have been proven to be highly effective in blocking the expression of TTR in human liver in several clinical trials, with drugs based on siRNA including patisiran and vutrisiran, and the drug based on ASO being inotersen (Aimo et al., 2022). In this study, we extracted reports of AEs related to TTR inhibitors from the FAERS database and conducted drug safety signal mining at both SOC and PT levels, identifying several significant signals not mentioned in drug labels. To our knowledge, this is the first study to conduct a real-world pharmacovigilance analysis on multiple TTR inhibitors.

The results indicate that patisiran, inotersen, and vutrisiran have different AEs spectra in the real world. Ranked by report numbers, the top three AEs for patisiran are fatigue, asthenia, and fall; for inotersen, they are platelet count decreased, blood creatinine increased, and fatigue; and for vutrisiran, they are fall, pain in extremity and malaise.

Patisiran is the first TTR inhibitor approved by the FDA, specifically inhibiting the synthesis of TTR in the liver (Adams et al., 2018). After excluding AEs related to death, outcomes, and symptoms caused by the disease itself at the PT level, fatigue is the most reported adverse event for patisiran, with 137 reports and not mentioned in the drug label. siRNA drugs may cause off-target reactions in clinical applications, leading to drug toxicity reactions. We speculate the potential mechanism is that siRNA drugs and their delivery carriers might activate the innate immune system, leading to inflammatory responses, which could cause systemic fatigue and weakness (Jackson and Linsley, 2010). A meta-analysis using siRNA to treat acute intermittent porphyria also found fatigue as a common adverse event (Patel et al., 2023).

Inotersen is a 2′- O-methoxyethyl-modified antisense oligonucleotide. Renal and urinary disorders were significant signals at the SOC level, and increased blood creatinine was the second most reported significant signal at the PT level, with glomerulonephritis ranking 30th. The FDA has warned about inotersen causing glomerulonephritis in a boxed warning on its label, and our study re-emphasizes the need to be vigilant about inotersen's renal toxicity in clinical practice. Notably, thrombocytopenia is the most reported significant signal at the PT level. Thrombocytopenia is an important adverse event, and the FDA has also warned about it in a boxed warning on the drug label, consistent with our study results. A clinical study of 172 adult patients not only found thrombocytopenia as the most common severe adverse event of inotersen but also detected anti-platelet IgG antibodies shortly before or at the time of severe thrombocytopenia occurrence. The reaction between anti-platelet IgG antibodies and EDTA can cause platelet aggregation, leading to inexplicable platelet measurement results, which delays diagnosis and treatment (Benson et al., 2018). We speculate that ASO may be one of the causes of thrombocytopenia induced by inotersen. Clinical trials of two other ASO drugs also found thrombocytopenia as a drug-related adverse event (Shamsudeen and Hegele, 2022; Thornton et al., 2023). According to the results of one drug trial, the possible mechanisms of ASO-induced thrombocytopenia include ASO forming polymers, the nucleic acid part of the polymer interacting with plasma proteins and platelets to form aggregates, and platelets bound to aggregates being activated, leading to platelet aggregation and reduction in circulating platelet count (Harada et al., 2023).

Vutrisiran is a subcutaneously administered transthyretin-directed siRNA. Since vutrisiran was the latest of the three drugs to be approved (2022), there are fewer safety studies and reports related to vutrisiran in this study compared to the other two drugs. Through pharmacovigilance analysis, we found fall and asthenia as common significant signals with patisiran, with the activation of immune responses and inflammatory reactions by siRNA being a possible mechanism for both causing fall and asthenia (Jackson and Linsley, 2010).

The same AEs mentioned in the drug labels of all three TTR inhibitors include vitamin A decreased, arthralgia, and dyspnea. Vitamin A decreased ranked 33rd in patisiran-related reports, 50th in vutrisiran-related reports, and 29th in inotersen-related reports. TTR is a 55 kDa tetramer transport protein consisting of four identical subunits of 127 amino acids (Li and Buxbaum, 2011). Human TTR can carry retinol-binding protein bound to retinol, and

to transport retinol, TTR needs to form a tetramer and bind to retinol-binding protein (Vieira and Saraiva, 2014). The TTR-RBP complex is a very stable form of retinol transport, safely transporting it to target tissues without being filtered and degraded by the kidneys (Goodman, 1984; Noy et al., 1992). TTR inhibitors block the formation of TTR protein, slowing the progression of ATTR disease, and also block the transport pathway of retinol, preventing retinol from forming a stable transport structure and possibly being degraded and excreted in the blood circulation, ultimately leading to vitamin A deficiency in patients. Previous animal experiments found that TTR knockout (KO) mice compared to wild-type (WT) animals showed significantly lower serum retinol levels, indicating TTR's important role in maintaining normal vitamin A levels in the body (Episkopou et al., 1993). Consistent with FDA recommendations, our study results also emphasize the need for patients using TTR inhibitors to supplement and monitor vitamin A to avoid related diseases such as night blindness.

Previous clinical trial results with TTR inhibitors support arthralgia as a common adverse event for all three TTR inhibitors. One clinical trial found a higher frequency of arthralgia in patients treated with patisiran compared to the placebo group. Another clinical trial found patients tolerated vutrisiran well, with the only two more common AEs compared to the placebo group being limb pain and arthralgia. A clinical trial of inotersen also found a 5% higher frequency of arthralgia in the inotersen group compared to the placebo group (Maurer et al., 2023; Nie et al., 2023). However, the mechanism of TTR inhibitors causing arthralgia is currently unclear.

In our study, asthenia and malaise are the same unexpected significant signals for all three TTR inhibitors, both being nonspecific symptoms. Since ATTR is a multisystem disease, the progression of the disease may also lead to asthenia and malaise, so more research is needed to clarify the relationship between TTR inhibitors and asthenia and malaise.

The WSP test showed that AEs related to vutrisiran have a wear-out failure-type profile, indicating that the risk of AEs related to vutrisiran increases over time. The WSP test also showed that AEs related to patisiran and inotersen have an early failure-type profile, indicating that the risk of drug-related AEs decreases over time. The pharmacokinetic characteristics of the three drugs may help explain the differences in the characteristics of adverse event onset. The median time to onset of AEs for vutrisiran is shorter than the other two drugs. It should be noted that vutrisiran has been on the market for a shorter time, and those AEs with longer onset times have not yet occurred and been reported, which may cause bias in the statistical results.

In our subgroup analysis based on whether the reporter was a medical professional, we found differences in AEs for different subgroups of TTR inhibitors. Medical professionals are more precise in classifying AEs, while non-medical professionals are more general. For example, in the subgroup analysis results for inotersen, both subgroups reported drug-induced liver function abnormalities, with medical professionals reporting them more accurately as elevated AST or ALT, while non-medical professionals reported them as abnormal AST or ALT. Moreover, at the PT level, AEs reported by non-medical professionals are mainly related to symptoms, while disease-related AEs requiring medical knowledge are more often reported by medical professionals. For example, in our study, 82.1% of reports of glomerulonephritis caused by inotersen and 75.0% of reports of restless legs syndrome caused by patisiran were reported by medical professionals. This shows that non-medical professionals have limitations in judging drug-related AEs compared to medical professionals.

Our study also has some limitations. Firstly, pharmacovigilance analysis through the FAERS database can only indicate the correlation between a specific drug and specific AEs, and cannot infer causality. Secondly, the FAERS database has incomplete reporting information, such as missing gender and age in vutrisiran-related reports, and a high proportion of missing gender or age in reports related to the other two TTR inhibitors. Therefore, in this study, we only conducted subgroup analysis based on whether the reporter was a medical professional. Finally, the FAERS database has some inherent biases, such as a greater likelihood of not reporting AEs that are too mild or too complex. Due to the voluntary nature of the FAERS database, it may lead to inconsistent reporting, including an increased propensity to report AEs considered related to a given drug. Despite these limitations, the FAERS database provides an opportunity to assess the drug safety of drugs used to treat rare diseases in the real world.

Conclusion

In summary, by utilizing the extensive data from the FAERS database, we compared the similarities and differences in drug safety of three TTR inhibitors in the real world. The results show that not only do these drugs share common AEs, but they also exhibit differences in terms of drug safety. This study contributes to enhancing medical professionals' understanding of the safety of TTR inhibitors and provides valuable insights for clinical practice. Future pharmacological epidemiology studies are needed to further explore the drug safety of TTR inhibitors.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

YL: Writing–original draft. HL: Writing–original draft. CH: Writing–original draft. LT: Writing–original draft. PY: Writing–original draft. ZL: Writing–original draft. SZ: Writing–original draft. LS: 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 grants from the National Natural Science Foundation of China (81974036).

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1368244/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 June 2024
DOI 10.3389/fphar.2024.1339505

OPEN ACCESS

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RECEIVED 16 November 2023
ACCEPTED 28 May 2024
PUBLISHED 24 June 2024

CITATION
Hu H, Fu Z, Liu J, Zhang C, Li S, Zhang Y and You R (2024), Pulmonary haemorrhage and haemoptysis associated with bevacizumab-related treatment regimens: a retrospective, pharmacovigilance study using the FAERS database.
Front. Pharmacol. 15:1339505.
doi: 10.3389/fphar.2024.1339505

Pulmonary haemorrhage and haemoptysis associated with bevacizumab-related treatment regimens: a retrospective, pharmacovigilance study using the FAERS database

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Background: Bevacizumab (BV) is widely used in routine cancer treatment and clinical therapy in combination with many other agents. This study aims to describe and analyse post-market cases of pulmonary haemorrhage and haemoptysis reported with different BV treatment regimens by mining data from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: Data were collected from the FAERS database between 2004 Q1 and 2023 Q1. Disproportionality analysis including the reporting odds ratio (ROR) was employed to quantify the signals of disproportionate reporting of pulmonary haemorrhage and haemoptysis adverse events (AEs) associated with BV-related treatment regimens. The demographic characteristics, time to onset and outcomes were further clarified.

Results: A total of 55,184 BV-associated reports were extracted from the FAERS database, of which 497 reports related to pulmonary haemorrhage and haemoptysis. Overall, the median onset time of pulmonary haemorrhage and haemoptysis AEs was 43 days (interquartile range (IQR) 15-117 days). In the subgroup analysis, BV plus targeted therapy had the longest median onset time of 90.5 days (IQR 34-178.5 days), while BV plus chemotherapy had the shortest of 40.5 days (IQR 14–90.25). BV plus chemotherapy disproportionately reported the highest percentage of death (148 deaths out of 292 cases, 50.68%). Moreover, the BV-related treatments including four subgroups in our study demonstrated the positive signals with the association of disproportionate reporting of pulmonary haemorrhage and haemoptysis. Notably, BV plus chemotherapy showed a significant higher reporting risk in pulmonary haemorrhage and haemoptysis signals of disproportionate reporting in comparison to BV monotherapy (ROR 5.35 [95% CI, 4.78–6.02] vs. ROR 4.19 [95% CI, 3.56–4.91], p = 0.0147).

Conclusion: This study characterized the reporting of pulmonary haemorrhage and haemoptysis, along with the time to onset and demographic characteristics among different BV-related treatment options. It could provide valuable evidence for further studies and clinical practice of BV.

KEYWORDS

bevacizumab, pulmonary haemorrhage, haemoptysis, pharmacovigilance analysis, FAERS

1 Introduction

Bevacizumab (BV), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF), inhibits tumour growth by blocking angiogenesis (Kanbayashi et al., 2022). By specifically binding to VEGF ligand, BV inhibits VEGF ligand-receptor binding and thereby prevents new vessel formation, regresses existing vessels and normalizes tumour vessel permeability (Garcia et al., 2020). BV was first approved for metastatic colorectal cancer (CRC) by the United States Food and Drug Administration (FDA), and then extended to its application for a variety of advanced solid tumors, including non-small cell lung cancer (NSCLC), glioblastoma, metastatic renal cell cancer (RCC), advanced cervical cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer and hepatocellular carcinoma (HCC) (Ferrara et al., 2004; Bai et al., 2021; Giantonio et al., 2023).

Effective pharmacotherapy with BV requires appropriate management of adverse events (AEs) that may occur with BV treatment. Though BV is a well-tolerated anti-tumor drug with a relative safety profile and manageable AEs, it is worth noting that the side effects of BV are different from those of traditional chemotherapy. In contrast to the common bone marrow suppression and gastrointestinal toxicity with chemotherapy, AEs reported with BV include hypertension, hemorrhage, proteinuria, and gastrointestinal perforation (Hatake et al., 2016; Motoo et al., 2019; Kanbayashi et al., 2020). The importance of BV-associated hemorrhage is highlighted by a warning issued by the FDA which recognizes that severe or fatal hemorrhage, including haemoptysis (the spitting of blood derived from the lungs or bronchial tubes as a result of pulmonary hemorrhage), gastrointestinal bleeding, hematemesis, central nervous system (CNS) hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving BV compared to patients receiving chemotherapy alone (Shimoyama et al., 2009). Serious or fatal pulmonary haemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving BV with chemotherapy compared to none of the patients receiving chemotherapy alone (Garcia et al., 2020). Hemorrhage events such as pulmonary haemorrhage and haemoptysis, represent some of the most severe AEs associated with BV therapy in clinical trials, with certain cases resulting in fatalities (Reck et al., 2009; Dansin et al., 2012; Allegra et al., 2013; Bennouna et al., 2013; Cunningham et al., 2013; Johnson et al., 2023).

Despite the severity of BV-induced pulmonary haemorrhage and haemoptysis, there have been few descriptive studies to characterise these AEs, lacking detailed AE information. The risk of pulmonary haemorrhage and haemoptysis events during the different treatments with BV in cancer patients has also not been elucidated clearly. In addition, due to the intricate biological interactions inherent in BV combination therapies, the emergence of new AEs and the exacerbation of existing ones are possible (Gu et al., 2023), current research on the comparison of pulmonary haemorrhage and haemoptysis between different combination treatments related to BV is extremely limited. In addition, the systematic study on pulmonary haemorrhage and haemoptysis event signals of disproportionate reporting related to BV-related treatment regimens based on large international and real-world databases remains still insufficient.

Spontaneous reporting system (SRS) has become an important information source for exploring post-marketing drug safety with the characteristics of a wide monitoring range and earlier detection of suspected AE signals of disproportionate reporting (Gu et al., 2023). The United States Food and Drug Administration Adverse Event Reporting System (FAERS) is a public and accessible database designed to support the FDA's post-marketing safety monitoring of drugs and therapeutic biologic products. Previously unknown potential drug-AE associations and well-established clinical associations can be identified by mining the FAERS database.

Herein, we performed a retrospective pharmacovigilance study to investigate the pulmonary haemorrhage and haemoptysis reported in association with BV-related therapies and examine the difference between pulmonary haemorrhage and haemoptysis events and different BV-related treatment regimens (including BV monotherapy, BV plus chemotherapy, BV plus ICI and BV plus targeted therapy) based on the FAERS (Oshima et al., 2018; Salem et al., 2018; Zhu et al., 2021). We identified the pulmonary haemorrhage and haemoptysis AEs signals of disproportionate reporting using the reporting odds ratio (ROR), and further clarified the demographic characteristics, time to onset and outcomes.

2 Materials and methods

2.1 Data sources

This retrospective pharmacovigilance study utilized data from the FDA adverse event reporting system (FAERS) database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). FAERS database is a publicly available post-marketing database for the safety surveillance of a drug, which collects adverse events (AEs) reported by consumers, health professionals and others. It contains seven datasets, including demographic and administrative information (DEMO), drug information (DRUG), indications of drugs (INDI), outcome information (OUTC), adverse drug reaction information (REAC), report sources (RPSR), therapy start and end dates of the reported drugs (THER).

TABLE 1 Summary of chemotherapy, ICIs, and targeted therapy drug names.

Categories	Drug names
Chemotherapy	Platinum drugs: Cisplatin; Carboplatin; Paraplatin; Nedaplatin; Oxaliplatin
	Pemetrexed: Pemetrexed; Alimta
	Gemcitabine: Gemcitabine; Gemzar
	Taxoid drugs: Paclitaxel; Taxol; Albumin-bound paclitaxel; Nab-paclitaxel; Abraxane; Docetaxel; Taxotere; Anzatax
	Vindesine: Vindesine; Vinorelbine; Navelbine
	Etoposide: Etoposide; VP-16
	Other drugs: Irinotecan; Topotecan; Mitomycin; Amrubicin; Ifosfamide; Cyclophosphamide; Bortezomib; Everolimus; Temozolomide; Thalomid; Capecitabine; Fluorouracil; 5-FU
ICIs	Anti-PD-1 inhibitors: Nivolumab; Pembrolizumab; Cemiplimab; Opdivo; Keytruda; Libtayo
	Anti-PD-L1 inhibitors: Atezolizumab; Durvalumab; Avelumab; Imfinzi; Bavencio; Tecentriq
	Anti-CTLA4 inhibitors: Ipilimumab; Tremelimumab; Yervoy
Targeted therapy	EGFR-TKI: Iressa; Gefitinib; Tarceva; Erlotinib; Gilotrif; Afatinib; Tagrisso; Osimertinib; Dacomitinib; Vizimpro; Lapatinib; Tykerb; Icotinib; Conmana
	EGFR antibody: Cetuximab; Erbitux
	ALK-TKI: Crizotinib; Xalkori; Alectinib; Alecensa; Ceritinib; Zykadia; Entrectinib; Rozlytrek; Brigatinib; Alunbrig; Lorlatinib; Lorviqua
	Other drugs: Cediranib; Temsirolimus (CCI-779); Endostatin; Sorafenib; Herceptin; Trastuzumab; Rituxan; Rituximab; Trebananib (AMG 386); Endostatin; Faslodex; Lucentis

2.2 Data extraction and cleaning

The FAERS database inevitably includes duplicate data because of the spontaneity of the reports. Therefore, the deduplication process is necessary to minimize both false-negatives and false-positives. According to FDA recommendations, with the same CASEID, the latest FDA_DT is selected, or when the CASEID and FDA_DT were the same, the higher PRIMARYID was selected to remove duplicate records (Poluzzi et al., 2012). In this study, We extracted AE data from the FAERS quarterly data files from the first quarter of 2004 (Q1 2004) to the first quarter of 2023 (Q1 2023) using the search terms "Bevacizumab" and "Avastin" (not including biosimilar forms of bevacizumab). AEs in the FAERS database are coded according to the preferred terms (PTs) derived from the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. Cases with the preferred term Pulmonary haemorrhage and Haemoptysis were included. Then, according to the medication regimen, these data were divided into the following four categories: BV monotherapy, BV plus chemotherapy, BV plus immune checkpoint inhibitor (ICI), and BV plus targeted therapy. Details for these drug names encompassed within chemotherapy, ICI, and targeted therapy are listed in Table 1.

2.3 Time-to-onset analysis

The onset time of pulmonary haemorrhage and haemoptysis was calculated by subtracting the event start date (EVENT_DT) in the "DEMO" file from the treatment start date (START_DT) in the "THER" file. To ensure the accuracy of calculation, we excluded cases with partial date or without date, and then further excluded cases with input errors (EVENT_DT earlier than START_DT). Cumulative distribution curves were used for the demonstration of time-to-onset across comparison groups.

2.4 Descriptive analysis

A comprehensive descriptive analysis was performed to summarize the clinical characteristics of FAERS reports documenting BV-related haemoptysis/pulmonary haemorrhage events. We retrieved and described detailed information, including gender, indication, outcome, reported country and the type of reporter (health professional or others) whenever this data was available. It should be noted that the descriptive analysis of age information was not conducted, because age information was only reported for three cases and missed for the others.

2.5 Statistical analysis

Disproportionality analysis, which is a widely used approach in pharmacovigilance study, was used to detect potential AE signals of disproportionate reporting for BV in this studies. The reporting odds ratio (ROR) was used to compare the number of haemoptysis/pulmonary haemorrhage events related to different BV combined treatment strategies to the full database. Calculations of ROR and 95% confidence interval (CI) were based on 2 × 2 contingency table (Zhai et al., 2019; Gu et al., 2023), the 2 × 2 contingency table was shown in Table 2. Specific formulas were shown below:

TABLE 2 A 2 × 2 contingency table for disproportionality analysis.

	Pulmonary haemorrhage and haemoptysis AEs	Non-pulmonary haemorrhage and haemoptysis AEs	Total
Drugs of interest (BV-related subgroup)	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

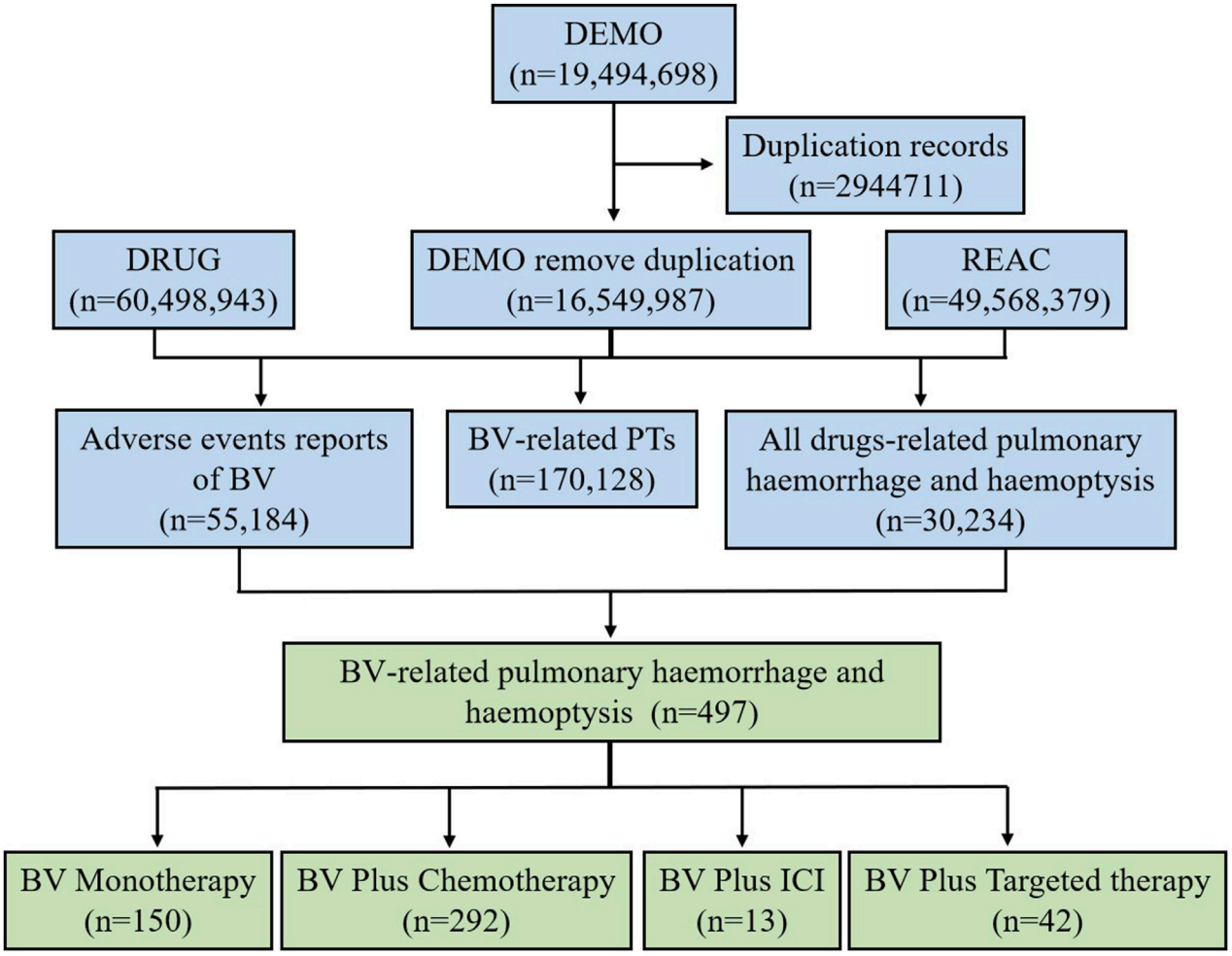

FIGURE 1
The flow diagram of selecting pulmonary haemorrhage and haemoptysis cases reported in association with BV-related regimens from the FAERS database.

$$ROR = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{a^{*}d}{b^{*}c}$$

$$95\%CI = e^{\ln(ROR)\pm 1.96^{*}\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The positive signal of disproportionate reporting was defined when the lower limit of the 95% CI of ROR exceeded one, with at least three cases (Guo et al., 2023). In this study, all data processing and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States), Microsoft EXCEL 2016 and GraphPad Prism 6.0 (GraphPad Software, CA, United States). A chi-square test was used to compare the differences between subgroups. The result of $p < 0.05$ was considered statistically significant.

3 Results

3.1 Data preparation

During the period of this study (Q1 2004-Q1 2023), a total of 19,494,698 reports were extracted from the FAERS database. After

TABLE 3 Clinical characteristics of pulmonary haemorrhage and haemoptysis cases reported for BV-related regimens from the FAERS database.

Characteristics	Overall (n = 497)	BV monotherapy (n = 150)	BV plus chemotherapy (n = 292)	BV plus ICI (n = 13)	BV plus targeted therapy (n = 42)
Gender					
Female	172 (34.6%)	42 (28.0%)	111 (38.0%)	3 (23.1%)	16 (38.1%)
Male	213 (42.9%)	66 (44.0%)	121 (41.4%)	9 (69.2%)	17 (40.5%)
Unknown	112 (22.5%)	42 (28.0%)	60 (20.5%)	1 (7.7%)	9 (21.4%)
Reporting year					
2019–2023	91 (18.3%)	27 (18.0%)	47 (16.1%)	13 (100.0%)	4 (9.5%)
2014–2018	178 (35.8%)	67 (44.7%)	91 (31.2%)	0 (0.0%)	20 (47.6%)
2009–2013	143 (28.8%)	31 (20.7%)	105 (36.0%)	0 (0.0%)	7 (16.7%)
2008 and before	85 (17.1%)	25 (16.7%)	49 (16.8%)	0 (0.0%)	11 (26.2%)
Indications					
Lung cancer	264 (53.1%)	60 (40.0%)	176 (60.3%)	10 (76.9%)	18 (42.9%)
Colorectal cancer	61 (12.3%)	21 (14.0%)	39 (13.4%)	0 (0.0%)	1 (2.4%)
Breast cancer	35 (7.0%)	7 (4.7%)	24 (8.2%)	0 (0.0%)	4 (9.5%)
Renal cancer	19 (3.8%)	14 (9.3%)	3 (1.0%)	0 (0.0%)	2 (4.8%)
Gastric cancer	9 (1.8%)	0 (0.0%)	4 (1.4%)	0 (0.0%)	5 (11.9%)
Head and neck cancer	8 (1.6%)	2 (1.3%)	5 (1.7%)	0 (0.0%)	1 (2.4%)
Ovarian cancer	7 (1.4%)	2 (1.3%)	4 (1.4%)	0 (0.0%)	1 (2.4%)
Uterus cancer	7 (1.4%)	1 (0.7%)	6 (2.1%)	0 (0.0%)	0 (0.0%)
Liver cancer	6 (1.2%)	2 (1.3%)	1 (0.3%)	3 (23.1%)	0 (0.0%)
Others	27 (5.4%)	12 (8.0%)	9 (3.1%)	0 (0.0%)	6 (14.3%)
Unspecified	54 (10.9%)	29 (19.3%)	21 (7.2%)	0 (0.0%)	4 (9.5%)
Serious outcomes					
Death (DE)	226 (45.5%)	57 (38.0%)	148 (50.7%)	6 (46.2%)	15 (35.7%)
Life-threatening (LT)	8 (1.6%)	1 (0.7%)	6 (2.1%)	1 (7.7%)	0 (0.0%)
Hospitalization–initial or prolonged (HO)	96 (19.3%)	25 (16.7%)	53 (18.2%)	3 (23.1%)	15 (35.7%)
Disability (DS)	3 (0.6%)	0 (0.0%)	3 (1.0%)	0 (0.0%)	0 (0.0%)
Other serious (important medical event) (OT)	121 (24.3%)	48 (32.0%)	59 (20.2%)	2 (15.4%)	12 (28.6%)
Unspecified	43 (8.7%)	19 (12.7%)	23 (7.9%)	1 (7.7%)	0 (0.0%)
Reported countries					
United states	241 (48.5%)	96 (64.0%)	114 (39.0%)	3 (23.1%)	28 (66.7%)
Japan	71 (14.3%)	8 (5.3%)	56 (19.2%)	5 (38.5%)	2 (4.8%)
China	32 (6.4%)	12 (8.0%)	17 (5.8%)	0 (0.0%)	3 (7.1%)
United Kingdom	27 (5.4%)	5 (3.3%)	18 (6.2%)	1 (7.7%)	3 (7.1%)
Germany	30 (6.0%)	8 (5.3%)	19 (6.5%)	0 (0.0%)	3 (7.1%)
Others	79 (15.9%)	17 (11.3%)	55 (18.8%)	4 (30.8%)	3 (7.1%)
Unspecified	17 (3.4%)	4 (2.7%)	13 (4.5%)	0 (0.0%)	0 (0.0%)

(Continued on following page)

TABLE 3 (*Continued*) Clinical characteristics of pulmonary haemorrhage and haemoptysis cases reported for BV-related regimens from the FAERS database.

Characteristics	Overall (n = 497)	BV monotherapy (n = 150)	BV plus chemotherapy (n = 292)	BV plus ICI (n = 13)	BV plus targeted therapy (n = 42)
Reporters					
Physicians (MD)	291 (58.6%)	77 (51.3%)	178 (61.0%)	10 (76.9%)	26 (61.9%)
Pharmacist (PH)	27 (5.4%)	15 (10.0%)	10 (3.4%)	0 (0.0%)	2 (4.8%)
Consumer (CN)	46 (9.3%)	25 (16.7%)	19 (6.5%)	1 (7.7%)	1 (2.4%)
health professional (HP)	25 (5.0%)	3 (2.0%)	18 (6.2%)	2 (15.4%)	2 (4.8%)
Other health professional (OT)	98 (18.7%)	25 (16.7%)	58 (19.9%)	0 (0.0%)	10 (23.8%)
Unspecified	15 (3.0%)	5 (3.3%)	9 (3.1%)	0 (0.0%)	1 (2.4%)

the deduplication, culminating in the extraction of 16,549,987 unique AE reports. Among these, there were 55,184 AE reports associated with the use of BV. A cumulative total of 30,234 pulmonary haemorrhage and haemoptysis cases that remained in the dataset (for all drugs, drug-event pairs). And there were 170,128 BV-related PTs (drug-event pairs). After processing, we obtained 497 reports of the BV reporting pulmonary haemorrhage and haemoptysis. Then the 497 reports were divided into the following four BV-related subgroups according to the medication regimen: BV monotherapy (n = 150), BV plus chemotherapy (n = 292), BV plus ICI (n = 13), and BV plus targeted therapy (n = 42). The flow diagram of our study is shown in Figure 1.

3.2 Demographics description

The demographical characteristics are described in Table 3. The proportion of men was greater than that of women (42.9% vs. 34.6%), this trend was also observed in each subgroup. Most cases were reported in 2014-2018 (35.8%), whereas the BV plus ICI group all reported in 2019-2023, indicating the increased application of ICIs in recent years. According to the data, lung cancer was the most reported indication (53.1%). Death was the most frequently reported serious outcome, accounting for 45.5%. Among them, 148 (50.7%) death cases were reported by the BV plus chemotherapy group, higher than other groups. The United States (48.5%) reported the most pulmonary haemorrhage and haemoptysis AE, followed by Japan (14.3%), China (6.4%), Germany (6.0%), and the United Kingdom (5.4%). In addition, more than half of the reports (58.6%) were submitted by physicians (MD), while other health professionals (OT) were the second largest source of reports, accounting for 18.7%.

3.3 Time to event onset

After data cleaning, a total of 217 records were used for time-to-onset analysis, with 43 records in the BV monotherapy, 150 records in the BV plus chemotherapy, 4 records in the BV plus ICI and 20 records in the BV plus targeted therapy. The onset time of pulmonary haemorrhage and haemoptysis for each BV-related regimen is shown in Figure 2A and Supplementary Table S1. Overall, the median onset time of pulmonary haemorrhage and haemoptysis AEs was 43 days (interquartile range (IQR) 15-117 days) after all BV-related categories initiation. As shown in Figure 2B and Supplementary Table S2, the longest median onset time was 90.5 (IQR 34–178.5) days for BV plus targeted therapy, while the shortest of 40.5 (IQR 14–90.25) days for BV plus chemotherapy, and 41 (IQR 25.25–54.5) days for plus ICI, 55 (IQR 18–153) days for BV monotherapy, respectively.

3.4 Outcome

To explore the prognosis of reports with pulmonary haemorrhage and haemoptysis AEs after the use of various BV-related treatments, our study evaluated the outcome of reports by death and alive proportions. Overall, death accounted for 45.5% of all BV-related pulmonary haemorrhage and haemoptysis AEs records with available outcome information (Table 2). Further subgroup analysis showed the records and proportions of death and alive in patients with pulmonary haemorrhage and haemoptysis when receiving BV-related regimens (Figure 3). As a result, BV plus chemotherapy had the highest percentage of death among the studied cases (148 deaths out of 292 cases, 50.7%), followed by BV plus ICI (6 deaths out of 13 cases, 46.2%), BV monotherapy (57 deaths out of 150 cases, 38.0%), and BV plus targeted therapy had the lowest (15 deaths out of 42 cases, 35.7%). Subsequently, we conducted a comprehensive statistical analysis to describe the clinical characteristics of the death cases, as summarized in Supplementary Table S3. Of the 226 death cases, the proportion of males was higher than females (42.9% vs. 34.6%). Notably, a significant proportion of death cases originated in the United States, accounting for 51.7% (n = 117). Furthermore, among the death cases, the indications for treatment predominantly encompassed lung cancer (59.7%, n = 135), followed by colorectal cancer (11.1%, n = 25), and breast cancer (8.4%, n = 19).

3.5 Disproportionality analysis

The ROR of pulmonary haemorrhage and haemoptysis AEs was calculated for each of the four treatment strategies. The results are shown in Figure 4. A signal of disproportionate reporting was shown

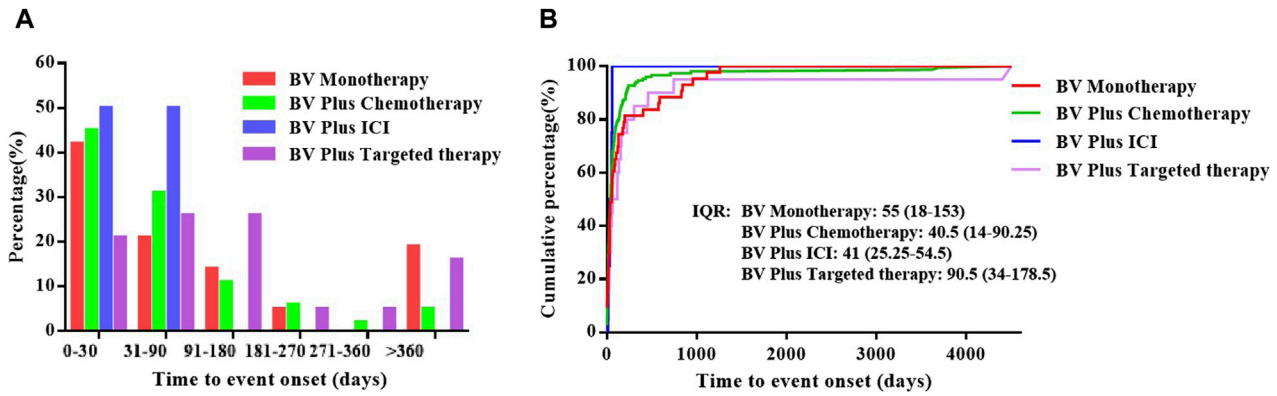

FIGURE 2
The time to onset of pulmonary haemorrhage and haemoptysis cases reported for BV-related regimens in different subgroups. **(A)** The percentage of the onset time of pulmonary haemorrhage and haemoptysis cases reported in association with BV-related regimens, **(B)** The cumulative distribution curve of time to event onset.

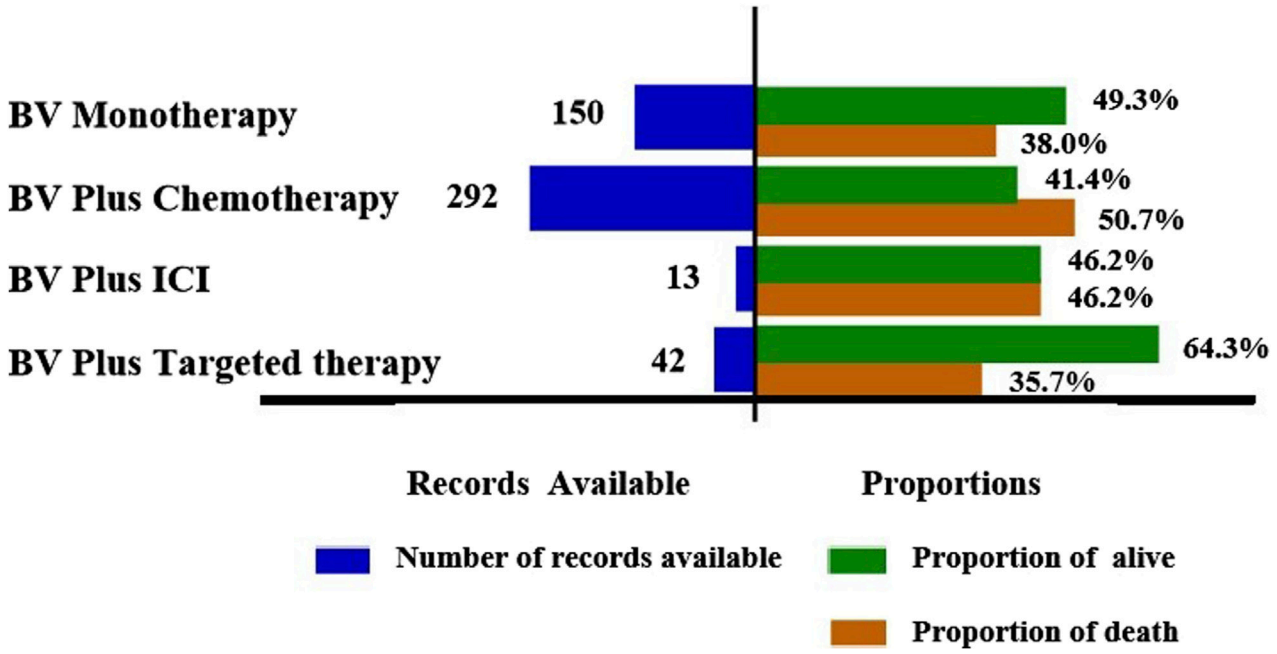

FIGURE 3
Records and proportions of death and alive in patients with pulmonary haemorrhage and haemoptysis when receiving BV-related regimens.

when the lower limit of the 95% Cl of ROR exceeded 1, with at least three cases. Among all the treatments, we identified that each of the four BV-related subgroups observed a positive signal of disproportionate reporting (BV monotherapy: ROR 4.19, 95% CI 3.56–4.91; BV plus chemotherapy: ROR 5.36, 95% CI 4.78–6.02; BV plus ICI: ROR 4.13, 95% CI 2.40–7.12; BV plus targeted therapy: ROR 4.41, 95% CI 3.26–5.97). It is noteworthy that there was a significant difference in pulmonary haemorrhage and haemoptysis signals of disproportionate reporting in BV plus chemotherapy as compared with BV monotherapy (ROR 5.35 [95% CI, 4.78–6.02] vs. ROR 4.19 [95% CI, 3.56–4.91], $p = 0.0147$).

4 Discussion

As BV is widely used in routine cancer treatment and monotherapy or combination with other agents, it will be especially important to recognize the risks of AEs and intervene promptly to reduce its morbidity and mortality. Of all the common AEs, hemorrhagic events are frequently reported in clinical trials associated with BV (Dotan et al., 2012; Allegra et al., 2013; Bennouna et al., 2013; Cunningham et al., 2013). Among them, BV-induced pulmonary haemorrhage and haemoptysis are rare but the most severe and fatal AEs.

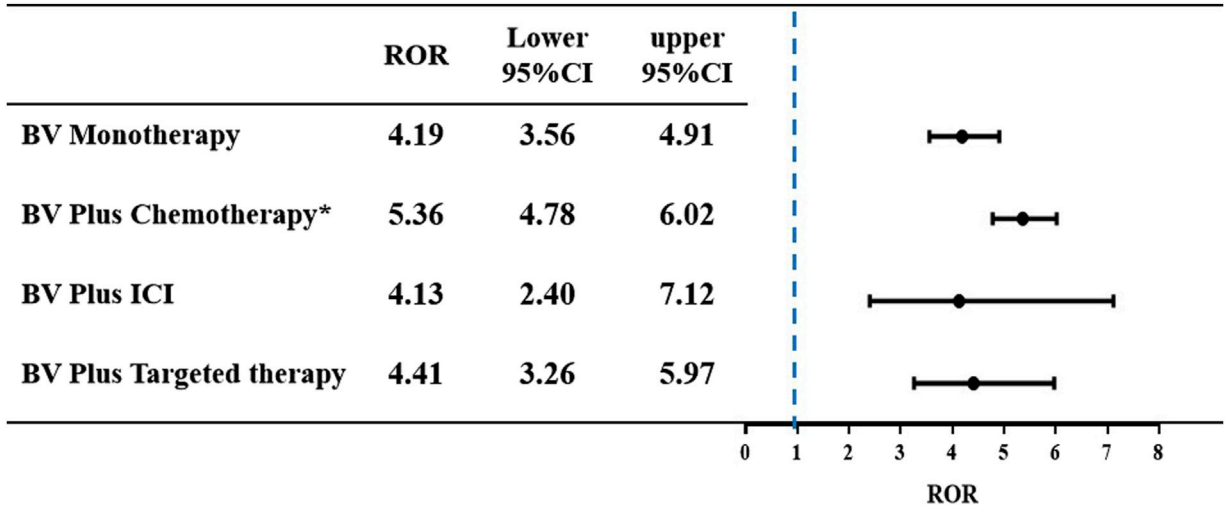

FIGURE 4
The ROR and 95% CI of pulmonary haemorrhage and haemoptysis cases reported in association with BV-related regimens. *$p < 0.05$ compared to BV monotherapy group.

Although the mechanisms of hemorrhage regarding BV have not been clarified, the interaction of BV and VEGF could be one of the possible interpretations. As suggested by Hapani et al., BV might damage vascular integrity by inhibiting endothelial survival and proliferation, particularly in tissues with a high VEGF dependence, such as injured mucosal membrane of the airway or peptic ulcers (Hapani et al., 2010). It is also consistent with our results, lung cancer and colorectal cancer are the two largest proportions of reported indications, accounting for 53.1% and 12.3%, respectively. Haemoptysis and pulmonary haemorrhage were disproportionately reported in patients with lung cancer and colorectal cancer, suggesting the necessity of monitoring haemorrhage in these patients. Moreover, Verheul et al. showed that BV might inhibit the coagulation cascade regulated by tissue factor, whose expression on endothelial cells was induced by VEGF (Verheul and Pinedo, 2007). Consistently, the BV-related treatments including four subgroups in our study demonstrated the positive signals of disproportionate reporting of haemoptysis and pulmonary haemorrhage. Overall, these findings are consistent with those of prior studies.

In this study, cases of pulmonary haemorrhage and haemoptysis identifying BV as a suspect product were reported as having occurred shortly after initiating therapy and often documented death as an outcome, the median onset time was 43 days (IQR 15-117 days) after all BV-related categories initiation, these findings are consistent with previous results in some clinical trials (Hapani et al., 2010; Reck et al., 2012; Amit et al., 2013). Further subgroup analyses showed that the longest median onset time was 90.5 (IQR 34–178.5) days for BV plus targeted therapy, while the shortest of 40.5 (IQR 14–90.25) days for BV plus chemotherapy, and 41 (IQR 25.25–54.5) days for BV plus ICI, 55 (IQR 18–153) days for BV monotherapy, respectively. Clinicians should be alert to the onset of symptoms of pulmonary haemorrhage and haemoptysis immediately from the initial stages of BV-related treatment, especially BV plus chemotherapy and BV plus ICI. On the other hand, although it is not available whether the risk of pulmonary haemorrhage and haemoptysis increased in a dose-dependent manner in our research, continuous monitoring is recommended throughout and beyond the entire treatment period, as some cases of pulmonary haemorrhage and haemoptysis were reported during the long term after the start of administration. Pulmonary haemorrhage and haemoptysis were still observed after more than 360 days in over 15% of cases in both BV plus targeted therapy and monotherapy. In our analyses, death was reported as an outcome in 45.5% of pulmonary hemorrhage and hemoptysis cases, suggesting that clinicians need to pay more attention to preventing pulmonary hemorrhage and hemoptysis, especially the patients with lung cancer or when they are treated with BV plus chemotherapy.

Pulmonary haemorrhage and haemoptysis caused by BV have attracted considerable attention due to its high discontinuation and mortality rates. The increasing application of BV in clinical treatment will undoubtedly result in an increased absolute burden and mortality of pulmonary haemorrhage and haemoptysis. A meta-analysis revealed that BV significantly increased the risk of high-grade pulmonary haemorrhage (RR 3.15; 95% CI 1.15–8.61), among 29 patients with fatal bleeding, pulmonary haemorrhage is most common (67%), followed by central nervous system (CNS) hemorrhage (14%) and GI hemorrhage (12%) (Hapani et al., 2010). Another Japan prospective nested case-control study showed that out of a total of 6,774 patients registered, 23 patients (0.3%) experienced grade ≥3 haemoptysis, of whom 8 (34.8%) recovered, 1 (4.3%) had sequela of impaired consciousness and 14 (60.9%) patients died from haemoptysis (Goto et al., 2016). Although the mortality from BV-related pulmonary haemorrhage and haemoptysis was noted in these previous studies, no further analysis of treatment options was performed. However, when contemplating combination therapy for treatment, it is imperative to thoroughly assess both the clinical benefits and the potential overlapping toxicities of the agents involved. In our study, death was most commonly reported as an outcome among the BV plus chemotherapy subgroup (50.68%), and least commonly reported as an outcome among the BV plus targeted therapy subgroup (35.71%). Disproportionality analysis revealed BV

plus chemotherapy (ROR 5.36, 95% CI 4.78–6.02), BV plus targeted therapy (ROR 4.41, 95% CI 3.26–5.97), BV monotherapy (ROR 4.19, 95% CI 3.56–4.91) and BV plus ICI (ROR 4.13, 95% CI 2.40–7.12) are associated with disproportionate reporting of pulmonary haemorrhage and haemoptysis. This might due to the disruption of vascular integrity and the suppression of coagulation cascade by BV. In addition, BV plus chemotherapy group showed a significant higher reporting risk in pulmonary haemorrhage and haemoptysis signals of disproportionate reporting as compared with BV monotherapy (p = 0.0147). This result may be attributed to the mechanisms involved. BV might indirectly induce significant damage to the vascular walls infiltrated by cancer cells by enhancing the cytotoxic effect of chemotherapy on tumors (Eskens and Verweij, 2006; Kamba and McDonald, 2007). BV might enhance the thrombocytopenia associated with concurrent chemotherapy, thus promoting hemorrhage (Weltermann et al., 1999). Most chemotherapy agents have hematologic toxicities, such as carboplatin, paclitaxel, 5-fluorouracil and so on. William M. Sikov et al. found that grade ≥3 thrombocytopenia was more common with carboplatin and paclitaxel, which might increase the risk of hemorrhage (Sikov et al., 2015). It should be emphasized that these results still need further studies to confirm, especially BV plus ICI group and BV plus targeted therapy group, their small numbers of records, only 13 and 42 cases, respectively, potentially leading to reporting bias.

Our study has the following limitations: first, Due to the vast amount of information in the FAERS database, some information may be lost (e.g., missing patient demographic information) or duplicated (Bate and Evans, 2009). To reduce the effect, reports were cleaned before analysis. According to the deduplication protocol, the deduplication only eliminated exact duplicate records that were associated with follow-up reports. This means that several probable duplicate records remained in the dataset. So duplicate records and missing information remain a limitation of our study. Database reporting is spontaneous and voluntary, potentially leading to reporting bias and underreporting (Nomura et al., 2015). In the FAERS database, any of the reported events reported by non-healthcare professionals might be associated with limited verification as they might lack standardized clinical confirmation. Second, In terms of signal mining methods, the ROR method itself will bring some inevitable false positive signals. Moreover, the lack of information about the total number of drug-exposed patients is another limitation because it makes impossible to calculate event rates in the absence of denominators. Third, the reporting of the association between BV-related treatments and pulmonary haemorrhage and haemoptysis AEs risk may be influenced by the clinical status of the patient, comorbid conditions and other concomitant drugs (e.g., chemotherapy, ICIs or targeted therapy), those potential confounding factors could lead to pulmonary haemorrhage and haemoptysis AEs. Notably, clinical data are not available (or do not allow to fully assess the role of comorbidities). Fourth, the disproportionality analyses do not inform on actual risk and may be subject to reporting biases. It was unable to infer an exact causal relationship, the disproportionality analysis neither quantified risk nor existed causality, but only provided an estimation of the signal of disproportionate reporting strength, which was only statistically significant (Huang et al., 2020). Therefore, prospective clinical studies are still needed to confirm the causal relationship between them. Despite these limitations, this retrospective pharmacovigilance study investigated the pulmonary haemorrhage and haemoptysis reported in association with BV-related therapies and identified the pulmonary haemorrhage and haemoptysis AEs signals of disproportionate reporting using the ROR based on the FAERS, which could provide valuable evidence for further studies and clinical practice in this field.

5 Conclusion

In conclusion, the present study utilizing real-world data from the FAERS database describes and analyses post-market cases of pulmonary haemorrhage and haemoptysis reported with different BV-related treatments. The disproportionality analysis revealed that the four BV-related treatments (BV plus chemotherapy, BV monotherapy, BV plus ICI and BV plus targeted therapy) are associated with disproportionate reporting of pulmonary haemorrhage and haemoptysis, BV plus chemotherapy showed a significant higher reporting risk in comparison to BV monotherapy. Death was most commonly reported as an outcome of pulmonary hemorrhage and hemoptysis cases. Thus, it is advisable to pay more attention to the pulmonary haemorrhage and haemoptysis AEs in clinical practice of BV-related treatments. Further research and clinical validation are essential to deepen our understanding of this complex relationship and inform refined clinical guidelines for the management of patients receiving BV-related treatments.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

HH: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Writing–original draft. ZF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Software, Writing–original draft. JL: Data curation, Investigation, Validation, Visualization, Writing–review and editing. CZ: Data curation, Validation, Visualization, Writing–review and editing. SL: Formal Analysis, Software, Writing–review and editing. YZ: Investigation, Methodology, Validation, Writing–review and editing. RY: Conceptualization, Data curation, 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 work was supported by the National Natural Science Foundation of China (No. 82204758).

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1339505/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 02 July 2024
DOI 10.3389/fphar.2024.1365706

OPEN ACCESS

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RECEIVED 04 January 2024
ACCEPTED 10 June 2024
PUBLISHED 02 July 2024

CITATION
Liu F, Zheng J-x and Wu X-d (2024), Clinical adverse events to dexmedetomidine: a real-world drug safety study based on the FAERS database.
Front. Pharmacol. 15:1365706.
doi: 10.3389/fphar.2024.1365706

Clinical adverse events to dexmedetomidine: a real-world drug safety study based on the FAERS database

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Objective: Adverse events associated with dexmedetomidine were analyzed using data from the FDA's FAERS database, spanning from 2004 to the third quarter of 2023. This analysis serves as a foundation for monitoring dexmedetomidine's safety in clinical applications.

Methods: Data on adverse events associated with dexmedetomidine were standardized and analyzed to identify clinical adverse events closely linked to its use. This analysis employed various signal quantification analysis algorithms, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS).

Results: In the FAERS database, dexmedetomidine was identified as the primary suspect in 1,910 adverse events. Our analysis encompassed 26 organ system levels, from which we selected 346 relevant Preferred Terms (PTs) for further examination. Notably, adverse drug reactions such as diabetes insipidus, abnormal transcranial electrical motor evoked potential monitoring, acute motor axonal neuropathy, and trigeminal cardiac reflex were identified. These reactions are not explicitly mentioned in the drug's specification, indicating the emergence of new signals for adverse drug reactions.

Conclusion: Data mining in the FAERS database has elucidated the characteristics of dexmedetomidine-related adverse drug reactions. This analysis enhances our understanding of dexmedetomidine's drug safety, aids in the clinical management of pharmacovigilance studies, and offers valuable insights for refining drug-use protocols.

KEYWORDS

dexmedetomidine, FDA adverse event reporting system, real-world data analysis, adverse events, adverse drug reaction

1 Introduction

Dexmedetomidine, a potent α2 adrenergic receptor agonist with high selectivity, facilitates perioperative sedation, anxiolytic and analgesic effects by targeting postsynaptic α2 receptors (Carollo et al., 2008). Although it was initially approved only for short-term (less than 24 h) sedation in adult intensive care units (Venn et al., 1999), its use in clinical practice has ranged from sedation of non-intubated patients to adjunctive use in surgical anesthesia over the past few years (Paris and Tonner, 2005; Liu et al., 2021; Kong et al., 2023). Dexmedetomidine induces a

unique mode of sedation that mimics natural sleep and therefore facilitates perioperative sedation by minimal respiratory depression (Akeju et al., 2018). Recent clinical trials have highlighted its efficacy in managing acute agitation in patients with schizophrenia and bipolar disorder (Citrome et al., 2022; Preskorn et al., 2022). Meanwhile, dexmedetomidine's molecular mechanisms of organ protection through its anti-inflammatory and activation of specific anti-apoptotic signaling pathways are likewise the focus of current clinical researchers (Bao and Tang, 2020). However, while the clinical use of dexmedetomidine is growing, its associated adverse effects, including bradycardia, delayed recovery, respiratory and circulatory depression require significant attention (De Cassai et al., 2021; Baumgartner et al., 2023). Furthermore, despite existing clinical trials and basic research providing insights into dexmedetomidine's safety profile, a more comprehensive analysis of its adverse effects in real-world clinical settings remains necessary.

Data mining techniques, including signal detection algorithms, are increasingly utilized to scrutinize medical databases, analyzing extensive data to uncover potential drug-adverse event associations that might not be evident in clinical trials (Wilson et al., 2004; Chakraborty, 2015). The FDA's Adverse Event Reporting System (FAERS) is among the largest databases for post-market safety monitoring of approved drugs and biologics (Xu and Wang, 2014). This public database platform encourages multiple parties, including healthcare professionals, consumers, and pharmaceutical companies, to assess the real-world safety of drugs post-market through spontaneous reporting of adverse drug events.

This study aims to analyze dexmedetomidine associated adverse drug reaction signals using various disproportionate analysis methods, including the Reporting Odds Ratio (ROR) (Rothman et al., 2004), Proportional Reporting Ratio (PRR) (Evans et al., 2001), Bayesian Confidence Propagation Neural Network (BCPNN) (Bate et al., 1998), and Multi-Item Gamma Poisson Shrinker (MGPS) algorithms (Almenoff et al., 2006). Employing multiple disproportionality analysis methods in retrospective pharmacovigilance studies enhances the confidence in results and rigorously screens for significant positive signals. The objective is to provide valuable data on the safety of dexmedetomidine administration to support more prudent use in the future, offering a reliable evidence-based foundation for expanding its clinical applications.

2 Materials and methods

2.1 Study design and data source

This observational, retrospective study conducted a disproportionality analysis, which using data from the publicly available FAERS database, spanning from the first quarter of 2004 to the third quarter of 2023. The data, comprising adverse drug reaction events, were extracted from 79 quarterly ASCII data packages and analyzed using R software (version 4.2.2) after thorough data cleaning.

2.2 Data extraction and descriptive analysis

The FAERS database comprises seven data files: patient demographics (DEMO), drug information (DRUG), adverse event information (REAC), patient outcome information (OUTC), report source information (RPSR), medication therapy date information (THER), and medication indications (INDI). Adverse drug reactions in FAERS are categorized and standardized according to the Medical Dictionary for Regulatory Activities (MedDRA) (Brown, 2004). In FAERS, each report employs MedDRA's preferred terms (PTs), which are linked to various levels such as High-Level Terminology (HLT), High-Level Group Terminology (HLGT), and System Organ Class (SOC). This study adheres to MedDRA's definitions.

In this study, records related to dexmedetomidine were identified using "dexmedetomidine" and its trade name "Precedex" as keywords, with "role_cod" set to PS (Primary Suspect). To eliminate duplicate reports, as recommended by the FDA, we sorted the DEMO table's PRIMARYID, CASEID, and FDA_DT fields by CASEID and FDA_DT. We retained the report with the latest FDA_DT for each CASEID, and in cases of identical CASEID and FDA_DT, the report with the largest PRIMARYID was kept.

Adverse drug reaction reports were statistically analyzed to describe clinical characteristics such as gender, age, reporter type, reporting region, report timing, and outcomes. Notably, serious outcomes encompassed death, life-threatening conditions, hospitalization, disability, and other significant health impacts. However, the count of serious outcomes may surpass the total report count, as some reports indicated multiple serious outcomes. The methodology, including data extraction, processing, and analysis, is illustrated in Figure 1.

2.3 Statistical analysis

Given that the Faers database consists of spontaneous reports and lacks complete real-world adverse drug reaction denominator data, directly calculating the incidence of adverse drug reaction events is not feasible. However, disproportionality analysis effectively identifies signals of adverse drug reaction events in retrospective pharmacovigilance studies (Almenoff et al., 2007). To overcome the limitations of single algorithms and enhance the reliability and accuracy of data mining results, we employed multiple algorithms for data analysis. Thus, we used disproportionality methods, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS), to detect adverse drug event signals in the present study.

ROR and PRR methods are designed to identify the excessive frequency of adverse event reports, indicating potential risks associated with dexmedetomidine (Evans et al., 2001; Rothman et al., 2004). BCPNN is a valuable adjunct for accurately detecting potential associations between drugs and adverse events (Bate et al., 1998). MGPS offers a comprehensive analysis by quantifying adverse event signals, considering report counts and background risk (Almenoff et al., 2006). For high-frequency adverse event reporting, ROR is more applicable due to its ability to minimize bias and assess relative risk through the rational selection of control samples (Rothman et al., 2004). Additionally, MGPS is better suited for detecting rare adverse drug reactions

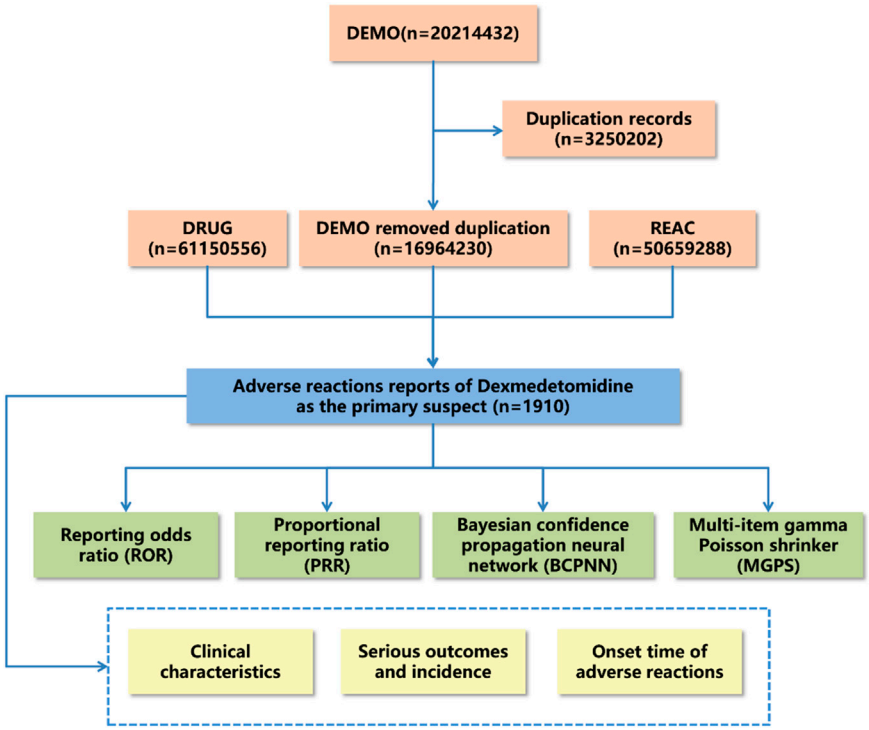

FIGURE 1
Flow diagram for the selection of adverse events associated with dexmedetomidine from FAERS database.

because it is less confounded by demographic factors, and provides high specificity and more stable results with fewer reports (Almenoff et al., 2006). The methodologies, including detailed formulas and procedures, are outlined in Supplementary Tables S1, S2. For initial screening, preferred terms (PTs) with report counts ≥3 were selected, utilizing MedDRA (Medical Dictionary for Regulatory Activities) PT and System Organ Class (SOC) for coding, classifying, and localizing the signals to analyze the specific SOC involved in the adverse event signals.

In summary, disproportionately positive signals were defined according to the following criteria: the number of reported cases was three or more, the lower limit of the 95% confidence interval between ROR and PRR was greater than one, the chi-square value (χ^2) was at least four, IC025 was greater than zero, and EBGM was greater than two (Kinoshita et al., 2020).

In order to enhance the reliability of the findings, separate disproportionate analyses were conducted, stratified by patient age (<18 years, 18–65 years, >65 years), gender (male, female), and weight (<50 kg, 50–100 kg, >100 kg).

3 Results

3.1 Basic information of dexmedetomidine related adverse events reports

As of the third quarter of 2023, 1,910 adverse events reports related to dexmedetomidine were analyzed by applying specific selection criteria. The data processing flow is depicted in Figure 1. The analysis revealed an increasing trend in dexmedetomidine-associated adverse events cases annually from 2004 to 2023 Q3, with 223 cases reported in 2023 alone, the highest yearly count, representing 11.68% of the total. Notably, adverse events reports from the last 5 years comprised 53.72% of the total. Female patients were more frequently reported than male patients (48.8% vs. 28.7%) in dexmedetomidine-related adverse events. The majority of cases were in the 18–64 age group, accounting for 31.2%. Medical practitioners, predominantly physicians, submitted most reports, totaling 589 (30.8%). The United States was the primary reporting country, contributing 43% of reports. Regarding serious outcomes, events leading to or prolonging hospitalization were most common (495 cases, 19.9%), followed by life-threatening events (342 cases, 13.8%). Most dexmedetomidine adverse drug reactions occurred within 7 days of dosing. These findings (detailed in Table 1) offer insights into the demographic and clinical characteristics of dexmedetomidine-related adverse events reports, aiding in the evaluation and optimization of clinical dosing regimens.

3.2 Signal mining for dexmedetomidine-related clinical adverse drug reactions

Adverse event signals associated with dexmedetomidine as the primary suspect were identified using ROR, PRR, BCPNN, and MGPS analyses. At the SOC level, dexmedetomidine was implicated in 26 categories, of which the top three most prevalent are cardiac organ disorders (n = 984; ROR 8.52; PRR 7.09; IC 2.82; EBGM 7.08),

TABLE 1 Basic information on adverse reactions related to dexmedetomidine from the FAERS database (2004 to 2023Q3).

Characteristics	Number of events (%)
Gender	
Female	549 (28.7%)
Male	933 (48.8%)
Unknown	428 (22.4%)
Age	
≤17	300 (15.7%)
18~64	596 (31.2%)
65~85	367 (19.2%)
≥86	19 (1.0%)
Missing	628 (32.9%)
Reporter	
Consumer	43 (2.3%)
Health professional	484 (25.3%)
Physician	589 (30.8%)
Other health-professional	463 (24.2%)
Pharmacist	275 (14.4%)
Registered nurse	1 (0.1%)
Missing	55 (2.9%)
Reported countries	
United States	821 (43.0%)
Australia	30 (1.57%)
Japan	436 (22.83%)
Other	623 (32.62%)
Reported year	
2004	12 (0.63%)
2005	11 (0.58%)
2006	33 (1.73%)
2007	20 (1.05%)
2008	30 (1.57%)
2009	38 (1.99%)
2010	23 (1.2%)
2011	13 (0.68%)
2012	23 (1.2%)
2013	59 (3.09%)
2014	62 (3.25%)
2015	67 (3.51%)
2016	178 (9.32%)
2017	171 (8.95%)
2018	144 (7.54%)
2019	209 (10.94%)
2020	180 (9.42%)
2021	206 (10.79%)
2022	208 (10.89%)
2023 Q1-Q3	223 (11.68%)
Serious outcomes	
Death	147 (5.9%)
Disability	24 (1.0%)
Hospitalization - initial or prolonged	495 (19.9%)
Life-threatening	342 (13.8%)
Adverse event occurrence time - medication date (days)	
0–7	137 (7.17%)
8–28	31 (1.62%)
29–60	5 (0.26%)
≥60	3 (0.16%)
Unknown	1734 (90.79%)

(Continued in next column)

TABLE 1 (*Continued*) Basic information on adverse reactions related to dexmedetomidine from the FAERS database (2004 to 2023Q3).

injury, poisoning and procedural complications (n = 766; ROR 1.59; PRR 1.50; IC 0.58; EBGM 1.50), and general disorders and administration site conditions (n = 641; ROR 0.67; PRR 0.71; IC −0.49; EBGM 0.71). Additionally, this study identified emerging adverse drug reactions not listed in the drug insert, including infections and infestations (n = 101; ROR 0.36; PRR 0.38; IC −1.41; EBGM 0.38), endocrine disorders (n = 79; ROR 6.20; PRR 6.12; IC 2.61; EBGM 6.12), and musculoskeletal and connective tissue disorders (n = 56; ROR 0.20; PRR 0.21; IC −2.28; EBGM 0.21). These findings (detailed in Table 2) underscore the importance of cautious dexmedetomidine administration in clinical practice, considering patient safety and pre-existing medical conditions.

Our examination of Preferred Terms (PT) signals identified 346 significant PTs meeting the criteria of all four algorithms. These were ranked using the Empirical Bayesian Geometric Mean (EBGM) algorithm, with the top 30 PTs, each reported in three or more cases, presented in Table 3. Consistent with the drug specifications, the most common clinical adverse reactions were bradycardia, cardiac arrest and hypotension. The results indicated notable signal strength in conditions not listed in the drug instructions, such as transcranial electrical motor evoked potential abnormalities (n = 5; ROR 2723.16; PRR 2720.53; IC 11.06; EBGM 2129.33), acute motor axonal neuropathy (n = 10; ROR 1509.67; PRR 1506.76; IC 10.35; EBGM 1305.99) and trigeminal cardiac reflex (n = 7; ROR 1204.39; PRR 1202.76; IC 10.07; EBGM 1071.32). Additionally, the top five clinical adverse reactions with the highest case numbers following EBGM sequencing were diabetes insipidus (n = 75; ROR 389.00; PRR 383.37; IC 8.53; EBGM 368.97), arteriospasm coronary (n = 65; ROR 211.78; PRR 209.13; IC 7.68; EBGM 204.78), upper airway obstruction (n = 37; ROR 498.61; PRR 495.05; IC 8.88; EBGM 471.28), sinus arrest (n = 30; ROR 233.43; PRR 232.08; IC 7.82; EBGM 226.73), and sedation complications (n = 30; ROR 162.20; PRR 161.26; IC 7.31; EBGM 158.66).

Due to the potential confounding effect of variations in baseline data on the reliability of disproportionate analysis results (de Vries et al., 2020), sensitivity analyses were undertaken. These analyses encompassed age stratifications (<18 years, 18–65 years, >65 years), gender categorization (male, female), and body weight consideration (subgroups with <50 kg, 50–100 kg, and subgroups >100 kg were omitted due to underreporting) aimed at enhancing result precision.

Withdrawal hypertension (n = 4; ROR 808.29; PRR 804.9; IC 9.12; EBGM 557.54) exhibited a significant signal in the <18 years group (Supplementary Figure S1) but was absent from the top 30 adverse event signals in both the 18–65 years group (Supplementary Figure S2) and >65 years group (Supplementary Figure S3). Conversely, in the >65 years group, the most pronounced signal pertained to central sleep apnea syndrome (n = 6; ROR 5829.52; PRR 5798.77; IC 11.82; EBGM 3624.6). Moreover,

TABLE 2 The adverse reactions of dexmedetomidine at the SOC level in FAERS database (2004 to 2023Q3).

System organ class	n	Percentage (%)	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Cardiac disorders	984	19.03	8.52 (7.95–9.13)	7.09 (6.70–7.50)	5,284.53	2.82 (1.16)	7.08 (6.68)
Injury, poisoning and procedural complications	776	15.00	1.59 (1.47–1.71)	1.50 (1.40–1.60)	143.21	0.58 (−1.08)	1.50 (1.41)
General disorders and administration site conditions	641	12.39	0.67 (0.62–0.73)	0.71 (0.66–0.76)	91.18	−0.49 (−2.16)	0.71 (0.66)
Nervous system disorders	464	8.97	1.05 (0.95–1.15)	1.05 (0.96–1.14)	0.98	0.06 (−1.60)	1.05 (0.96)
Investigations	462	8.93	1.48 (1.35–1.63)	1.44 (1.32–1.57)	66.21	0.53 (−1.14)	1.44 (1.33)
Respiratory, thoracic and mediastinal disorders	458	8.86	1.97 (1.79–2.16)	1.88 (1.72–2.05)	198.32	0.91 (−0.75)	1.88 (1.74)
Vascular disorders	288	5.57	2.67 (2.37–3.01)	2.58 (2.30–2.88)	283.92	1.37 (−0.30)	2.58 (2.33)
Psychiatric disorders	201	3.89	0.67 (0.58–0.77)	0.68 (0.60–0.78)	31.73	−0.55 (−2.22)	0.68 (0.61)
Gastrointestinal disorders	152	2.94	0.32 (0.28–0.38)	0.34 (0.29–0.40)	207.31	−1.54 (−3.20)	0.34 (0.30)
Infections and infestations	101	1.95	0.36 (0.30–0.44)	0.38 (0.31–0.46)	110.20	−1.41 (−3.08)	0.38 (0.32)
Renal and urinary disorders	97	1.88	0.97 (0.79–1.18)	0.97 (0.79–1.18)	0.12	−0.05 (−1.72)	0.97 (0.82)
Metabolism and nutrition disorders	92	1.78	0.81 (0.66–1.00)	0.82 (0.67–1.00)	3.92	−0.29 (−1.96)	0.82 (0.69)
Skin and subcutaneous tissue disorders	88	1.70	0.30 (0.25–0.38)	0.32 (0.26–0.39)	137.29	−1.66 (−3.33)	0.32 (0.27)
Endocrine disorders	79	1.53	6.20 (4.96–7.74)	6.12 (4.92–7.62)	338.90	2.61 (0.95)	6.12 (5.08)
Musculoskeletal and connective tissue disorders	56	1.08	0.20 (0.15–0.26)	0.21 (0.16–0.27)	180.18	−2.28 (−3.94)	0.21 (0.17)
Immune system disorders	52	1.01	0.92 (0.70–1.20)	0.92 (0.70–1.20)	0.40	−0.13 (−1.79)	0.92 (0.73)
Product issues	38	0.73	0.47 (0.34–0.65)	0.47 (0.34–0.65)	22.61	−1.08 (−2.75)	0.47 (0.36)
Pregnancy, puerperium and perinatal conditions	27	0.52	1.19 (0.81–1.74)	1.19 (0.82–1.73)	0.81	0.25 (−1.42)	1.19 (0.87)
Hepatobiliary disorders	26	0.50	0.55 (0.37–0.81)	0.55 (0.37–0.81)	9.67	−0.86 (−2.53)	0.55 (0.40)
Surgical and medical procedures	22	0.43	0.32 (0.21–0.49)	0.33 (0.21–0.49)	31.03	−1.62 (−3.28)	0.33 (0.23)
Eye disorders	21	0.41	0.20 (0.13–0.31)	0.21 (0.13–0.32)	65.71	−2.28 (−3.95)	0.21 (0.14)
Congenital, familial and genetic disorders	20	0.39	1.22 (0.79–1.89)	1.22 (0.79–1.89)	0.80	0.29 (−1.38)	1.22 (0.85)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13	0.25	0.09 (0.05–0.16)	0.09 (0.05–0.16)	118.50	−3.43 (−5.10)	0.09 (0.06)
Blood and lymphatic system disorders	10	0.19	0.11 (0.06–0.21)	0.11 (0.06–0.21)	69.44	−3.12 (−4.79)	0.11 (0.07)
Ear and labyrinth disorders	2	0.04	0.09 (0.02–0.35)	0.09 (0.02–0.35)	18.80	−3.49 (−5.16)	0.09 (0.03)
Social circumstances	2	0.04	0.08 (0.02–0.33)	0.08 (0.02–0.33)	20.21	−3.58 (−5.25)	0.08 (0.03)

across all age subgroups, bradycardia was the most frequently reported adverse drug reaction among the top 30 signals.

Gender disparities might affect the sensitivity to dexmedetomidine-associated sedation (Vincent et al., 2023). Hence, we conducted subgroup analyses to examine the potential influence of gender on dexmedetomidine-associated adverse effects among men and women. The outcomes are delineated in Supplementary Figures S4, S5. Noteworthy adverse events particular to the male subgroup included transcranial electrical motor evoked potential abnormalities, acute motor axonal neuropathy, central sleep apnea syndrome, cardiac arrest neonatal, postresuscitation encephalopathy, intestinal pseudo-obstruction, hypocapnia, withdrawal hypertension, atrioventricular dissociation, and epidermolysis bullosa.

High-risk adverse drug events specific to the female subgroup comprise pheochromocytoma crises, recurrence of neuromuscular blockade, airway complication of anaesthesia, tachyphylaxis, laryngospasm, cerebral artery occlusions, thyrotoxic crises, drug withdrawal convulsions, bradyarrhythmias, and atrioventricular block second degree.

Finally, we performed similar sensitivity analyses to assess the effect of body weight on adverse drug reactions signal in different subgroups (Supplementary Figures S6, S7). Our results suggested that glossoptosis is the symptom that signals the strongest adverse effect in the 50–100 kg group, with diabetes insipidus following only behind. In contrast, arteriospasm coronary showed significant signal strength in the <50 kg subgroup.

The subgroup analyses described above provide important insights for refining strategies for the clinical use of dexmedetomidine, enabling healthcare professionals to develop appropriate early warning treatment plans for adverse drug

TABLE 3 The top 30 clinical adverse reactions of dexmedetomidine ranked by EBGM at the PTs level in FAERS database ($n \geq 3$, 2004 to 2023Q3).

Preferred terms	n	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Transcranial electrical motor evoked potential monitoring abnormal	5	2,723.16 (1,010.65–7,337.50)	2,720.53 (1,010.43–7,324.91)	10,637.74	11.06 (9.29)	2,129.33 (929.07)
Acute motor axonal neuropathy	10	1,509.67 (775.35–2,939.47)	1,506.76 (774.71–2,930.52)	1,3041.24	10.35 (8.65)	1,305.99 (747.82)
Trigemino-cardiac reflex	7	1,204.39 (549.10–2,641.72)	1,202.76 (548.87–2,635.65)	7,486.01	10.07 (8.36)	1,071.32 (555.26)
Glossoptosis	19	1,079.59 (671.73–1,735.12)	1,075.63 (670.31–1,726.04)	18,380.44	9.92 (8.24)	969.29 (651.67)
Central sleep apnoea syndrome	7	707.73 (328.49–1,524.81)	706.78 (328.36–1,521.28)	4,601.4	9.36 (7.67)	659.27 (346.85)
Floppy iris syndrome	21	623.90 (401.04–970.58)	621.37 (400.09–965.02)	12,230.84	9.19 (7.52)	584.36 (403.73)
Phaeochromocytoma crisis	7	524.05 (244.87–1,121.49)	523.34 (244.78–1,118.88)	3,464.28	8.96 (7.27)	496.84 (262.87)
Postresuscitation encephalopathy	3	498.28 (156.15–1,590.03)	498.00 (156.16–1,588.09)	1,415.99	8.89 (7.18)	473.95 (179.50)
Upper airway obstruction	37	498.61 (357.96–694.52)	495.05 (356.21–688.00)	17,365.35	8.88 (7.21)	471.28 (357.15)
Diabetes insipidus	75	389.00 (308.35–490.74)	383.37 (304.88–482.08)	27,526.81	8.53 (6.86)	368.97 (303.78)
Recurrence of neuromuscular blockade	5	379.98 (155.45–928.79)	379.61 (155.43–927.13)	1,817.61	8.51 (6.83)	365.48 (173.01)
Cardiac arrest neonatal	4	350.05 (129.07–949.37)	349.78 (129.07–947.93)	1,343.17	8.40 (6.71)	337.76 (146.57)
Intestinal pseudo-obstruction	29	347.47 (239.69–503.72)	345.53 (238.83–499.89)	9,623.04	8.38 (6.71)	333.79 (244.64)
Withdrawal hypertension	6	338.11 (149.77–763.32)	337.72 (149.73–761.74)	1,947.21	8.35 (6.67)	326.50 (165.18)
Airway complication of anaesthesia	7	336.52 (158.34–715.20)	336.07 (158.28–713.53)	2,260.91	8.34 (6.67)	324.95 (172.92)
Mechanical ventilation complication	3	299.99 (95.07–946.58)	299.81 (95.08–945.42)	866.91	8.18 (6.49)	290.94 (111.23)
Central venous pressure increased	3	277.35 (88.01–874.02)	277.19 (88.01–872.95)	802.85	8.07 (6.39)	269.58 (103.18)
Mean arterial pressure decreased	5	245.08 (100.86–595.53)	244.85 (100.85–594.46)	1,184.65	7.90 (6.22)	238.90 (113.65)
Neonatal hypotension	8	242.95 (120.40–490.23)	242.57 (120.34–488.95)	1,878.12	7.89 (6.21)	236.74 (131.57)
Sinus arrest	30	233.43 (162.36–335.62)	232.08 (161.75–333.00)	6,743.02	7.82 (6.16)	226.73 (167.33)
Arteriospasm coronary	65	211.78 (165.40–271.18)	209.13 (163.83–266.97)	13,183.35	7.68 (6.01)	204.78 (166.52)
Hypocapnia	6	170.53 (76.05–382.39)	170.33 (76.03–381.60)	992.75	7.39 (5.71)	167.43 (85.19)
Product closure removal difficult	11	164.83 (90.77–299.29)	164.48 (90.69–298.29)	1,757.83	7.34 (5.67)	161.78 (98.21)
Sedation complication	30	162.20 (112.96–232.90)	161.26 (112.54–231.08)	4,700.79	7.31 (5.64)	158.66 (117.22)
Delayed recovery from anaesthesia	12	157.91 (89.21–279.50)	157.54 (89.12–278.49)	1,837.07	7.28 (5.61)	155.06 (96.17)
Hyperthermia malignant	19	156.03 (99.09–245.69)	155.46 (98.89–244.39)	2,870.35	7.26 (5.59)	153.05 (104.67)
Rhythm idioventricular	4	149.64 (55.72–401.84)	149.53 (55.72–401.23)	581.26	7.20 (5.53)	147.29 (64.45)
Drug withdrawal convulsions	22	141.06 (92.52–215.06)	140.46 (92.29–213.77)	3,003.3	7.11 (5.45)	138.49 (97.31)
Epidermolysis bullosa	3	134.24 (42.95–419.59)	134.16 (42.95–419.08)	391.16	7.05 (5.37)	132.36 (51.01)
Atrioventricular dissociation	3	123.01 (39.38–384.23)	122.94 (39.38–383.76)	358.34	6.92 (5.25)	121.42 (46.82)

events based on the specific characteristics of the corresponding subgroups.

4 Discussion

Dexmedetomidine, a highly selective α2-adrenergic agonist, induces sedation and dose-dependent hypnotic-anesthetic action by acting on α2 receptors in the central nucleus of the locus coeruleus, leveraging its unique pharmacological properties to activate endogenous sleep-promoting neural circuits (Doze et al., 1989; Weerink et al., 2017; Belur Nagaraj et al., 2020). This sedation, distinct from other sedatives, preserves a natural non-rapid eye movement sleep state with minimal respiratory impact (Purdon et al., 2015). Additionally, dexmedetomidine possesses anxiolytic and analgesic properties, making it well-suited for intensive care,

surgical sedation, and pain management (Anger, 2013). Its mechanism of action, involving the hyperpolarization of noradrenergic neurons leading to reduced norepinephrine release, distinctively modulates pain and stress responses (Yu et al., 2018). In recent years, dexmedetomidine has gradually gained attention for its organ-protective role related to anti-inflammatory responses. Numerous animal experiments have demonstrated that dexmedetomidine reduces the expression of serum and tissue inflammatory mediators (Li et al., 2021; Zhang et al., 2021; Han et al., 2022). Dexmedetomidine can reduce neuroinflammation in neurological disorders by mediating anti-inflammatory effects in microglia (Yamazaki et al., 2022). The mechanisms of action include the upregulation of microglial anti-inflammatory polarization and the reduction of microglial expression of M1-related inflammatory marker genes (Sun et al., 2018; Qiu et al., 2020).

Sedation management, crucial in treating agitation and anxiety in critically ill patients, aims to achieve a state where patients are sedated yet cooperative, easily aroused, and able to communicate their needs, particularly regarding analgesia (Stollings et al., 2022). Dexmedetomidine is effectively used for sedating mechanically ventilated patients in intensive care units (Hughes et al., 2021), providing surgical sedation, and serving as an anesthetic adjunct to enhance analgesia and reduce anesthetic requirements (Mahmoud and Mason, 2015). Additionally, sublingual dexmedetomidine has been approved for treating schizophrenia and acute agitation in bipolar disorder (Citrome et al., 2022; Preskorn et al., 2022). With the increasing clinical use of dexmedetomidine (Liu et al., 2021; Kong et al., 2023), its safety profile remains a focus, and ongoing real-world studies monitoring its adverse effects are essential for ensuring medication safety.

Prior safety studies on dexmedetomidine have often been constrained to single clinical trial data, lacking a comprehensive representation of real-world scenarios due to strict trial designs. In this study, we conducted a systematic evaluation of dexmedetomidine-related adverse reactions using extensive real-world data, analyzing the FAERS database from 2004 to the third quarter of 2023. By employing an ADR signal calculation method, the study not only clarified existing descriptive information about dexmedetomidine but also identified new potential safety risks, thereby providing detailed and reliable data for its future clinical application.

With the expansion of approved indications and the increased use of dexmedetomidine, there has been a notable rise in its adverse reaction reports from 2019 to Q3 2023, comprising 53.72% of total reports, underscoring the need for serious consideration of dexmedetomidine-related adverse reactions. Concurrently, the utilization of dexmedetomidine in sedation during custodial care has been increasingly recognized amidst the backdrop of the COVID-19 pandemic from 2019 to 2023. Previous studies have demonstrated that dexmedetomidine significantly reduces mortality and effectively treats COVID-19-related acute respiratory distress syndrome (ARDS) in patients afflicted with COVID-19 (Hamilton et al., 2021; Zhao et al., 2021; Simioli et al., 2023). Nonetheless, managing COVID-19-related ARDS frequently necessitates prolonged periods of invasive ventilation and heightened sedation levels, potentially resulting in aberrant hemodynamic variability and delirium onset (Bernard-Valnet et al., 2022). Investigating multimodal sedation regimens, such as the combination of ketamine and dexmedetomidine, offers a potential avenue to attain accelerated sedation onset and establish a more consistent hemodynamic state (Riccardi et al., 2023). Our analysis reveals that the majority of these reports (94.9%) were submitted by healthcare professionals, likely due to the prevalence of cardiac disorders as major adverse reactions, necessitating vigilant medical supervision. Additionally, the predominance of reports from the United States (43%) suggests regional variations in adverse reaction profiles, influenced by local expert consensus and other factors. A significant limitation in our study was the absence of specific timing data for a large proportion of adverse reactions (90.79%), restricting our investigation into the time to onset. The following section discusses specific clinical adverse reactions associated with dexmedetomidine:

Our analysis identified a range of adverse reactions associated with dexmedetomidine, affecting a total of 26 organ systems. Consistent with the drug's insert, the primary focus of dexmedetomidine-associated adverse reactions was the cardiovascular system (Piao and Wu, 2014). And notably, our study found that endocrine system disorders also have high-intensity signals, such as diabetes insipidus. In line with existing literature (Kraus et al., 2023), dexmedetomidine is frequently implicated in sedation-related diabetes insipidus in critically ill ICU patients. Potential mechanisms include dexmedetomidine's reduction of central arginine vasopressin (AVP) release and diminished renal response to AVP in canine and rat models (Rouch and Kudo, 1996; Kudo et al., 1999; Villela et al., 2005). When ICU patients exhibit diabetes insipidus symptoms, ongoing dexmedetomidine use should be considered in the differential diagnosis. However, given the limited case reports and studies, further large-scale prospective cohort studies are warranted to elucidate its mechanistic effects on diabetes insipidus.

From the data mining process, 892 dexmedetomidine-associated risk signals (Preferred Terms, PTs) were identified. To minimize false positives and enhance detection accuracy, only PTs with three or more reported cases were selected, resulting in 346 PTs included in our analysis. The most frequently reported adverse reactions to dexmedetomidine were bradycardia, cardiac arrest and hypotension (Piao and Wu, 2014; Lewis et al., 2022), consistent with our findings and attributable to its central sympatholytic effects. These adverse effects underscore the importance of vigilant monitoring of patients' hemodynamic parameters and prompt management of complications during dexmedetomidine administration, particularly in patients with cardiac insufficiency. Beyond the anticipated adverse events, our study also uncovered some unexpected adverse events, such as abnormal transcranial electrical stimulation motor evoked potential monitoring, acute motor axonal neuropathy, and trigeminal cardiac reflex, which merit further investigation and evaluation.

Real-time intraoperative monitoring of motor evoked potentials (MEPs) via transcranial electrical stimulation is crucial for assessing the integrity of motor nervous system pathways and reducing the risk of neurological injury (Legatt et al., 2016). The impact of dexmedetomidine on intraoperative neuromonitoring remains a subject of debate. While some studies suggest avoiding dexmedetomidine in children undergoing posterior spinal fusion surgery (PSFS) to prevent interference with neurophysiological monitoring (Mahmoud et al., 2010; Holt et al., 2020; Abdelaal

Ahmed Mahmoud Metwally Alkhatip et al., 2023), other research indicates that dexmedetomidine as an anesthetic adjuvant does not significantly affect somatosensory or motor evoked potential responses in complex spinal surgeries (Bala et al., 2008). This study's findings indicate that abnormal transcranial electrical stimulation motor evoked potential monitoring may be a potential adverse event associated with perioperative dexmedetomidine use, shedding light on its clinical risks.

Acute motor axonal neuropathy (AMAN), a subtype of Guillain-Barre syndrome (GBS), often presents with autonomic dysfunction, including unstable blood pressure and heart rate (Hamel and Logigian, 2023), which can influence anesthesia choices. Additionally, case reports indicate that conditions mimicking AMAN, such as certain neuropathies, may lead to misdiagnosis, complicating anesthetic management (Fodale et al., 2005; Xu et al., 2021). Therefore, it is crucial for clinicians to be aware of the patient's medical history and to conduct thorough preoperative neurological function assessments.

The trigeminal cardiac reflex (TCR), a prevalent brainstem reflex in maxillofacial neurosurgery, involves the trigeminal nerve, vagus nerve, and central brainstem nuclei, leading to symptoms like hemodynamic changes, apnea, and hypergastricity (Chowdhury et al., 2015; Schaller and Chowdhury, 2021). Dexmedetomidine's central sympatholytic effect, which suppresses the sympathetic nervous system and reduces sympathetic activity in the heart, can result in TCR, often manifesting as peripheral vasodilation, decreased heart rate, and reduced blood pressure (Bond et al., 2016; Arnold et al., 2018). Minimizing dexmedetomidine use and enhancing intraoperative hemodynamic monitoring are potential strategies for managing TCR during procedures that may trigger it.

The <18 years subgroup analyses indicated that the signal intensity of hemodynamic-related adverse events was more pronounced. Previous studies have shown that during dexmedetomidine infusion, hypotension occurs in 27%–53% of pediatric patients, bradycardia in 21%–25%, and hypertension in 27%–53% (Carney et al., 2013; Banasch et al., 2018). These results suggest that the use of dexmedetomidine in pediatric patients requires careful monitoring of adverse hemodynamic events. Additionally, in the >65 years subgroup, central sleep apnea syndrome warrants clinical attention. A case report suggests that the combined use of perioperative opioids and dexmedetomidine may trigger central sleep apnea syndrome (Ho et al., 2005). Moreover, descriptive baseline population data suggest proportional differences in the gender distribution of adverse effects. Basic studies have demonstrated that gender differences influence the anxiolytic and sedative effects of dexmedetomidine (Jang et al., 2019; Vincent et al., 2023). Identifying biological or social factors associated with gender may provide guidance for monitoring dexmedetomidine adverse reactions.

It is crucial to note that the discussion of dexmedetomidine's adverse events and their potential mechanisms is based on preliminary analyses of existing literature and data mining. The occurrence and reporting of adverse events are influenced by various factors, including drug properties, individual patient differences, and underlying health conditions. Consequently, establishing exact causality necessitates further large-scale, multicenter clinical studies. Furthermore, drug-induced adverse reactions frequently correlate with dosage, formulation, and administration methods. Research indicates a decreased incidence of adverse cardiovascular events with perioperative dexmedetomidine administration at a push dose below 0.5 $\mu g\,kg^{-1}$ or continuous infusion without a push (Demiri et al., 2019). Conversely, higher rates of bradycardia and hypotension were observed in recipients of dexmedetomidine at push doses of 0.75 or 1.0 $\mu g\,kg^{-1}$ compared to those receiving 0.5 $\mu g\,kg^{-1}$ (Kim et al., 2013). Employing perioperative continuous low-dose infusion and minimizing push administration may mitigate adverse effects. Moreover, findings from a pharmacologic clinical trial revealed a 30% likelihood of specific adverse events with sublingual film administration of dexmedetomidine at doses of 120 μg or 180 μg, despite its efficacy in reducing agitation scores. Given that the FAERS database primarily comprises self-reported adverse events, data gaps exist, such as standardized documentation of dosage and route of administration. Consequently, additional clinically oriented studies are imperative to elucidate the pathogenesis of these adverse reactions. Meanwhile, healthcare professionals are advised to continue vigilant monitoring of adverse events during the clinical use of dexmedetomidine and to implement timely interventions.

While this study offers scientific analyses of real-world data for evaluating the safety of dexmedetomidine from multiple perspectives, there are inherent limitations. First, the reliance on voluntary reporting to the FAERS database may result in incomplete data, lacking of detailed clinical information on patients, such as comorbidities, underlying diseases, and relevant medication history. Second, reporter bias could affect data quality, potentially leading to overrepresentation of certain rare nonclinical adverse events. Third, the analysis of disproportionate data is limited to assessing the strength of the adverse reaction signal and does not allow for quantification of risk or identification of drug-related causation. Finally, to support more prudent use of dexmedetomidine in the future, large-scale prospective studies combining clinical trials with epidemiologic studies are recommended. This study would provide a more reliable evidence-based rationale for the safe use of dexmedetomidine and inform further clinical practice.

5 Conclusion

Our analysis of dexmedetomidine's adverse event reports, sourced from the FAERS database, and our results suggest that dexmedetomidine-associated cardiovascular adverse reactions are common and require focused attention, accounting for 24.59% in addition to the total number of overall adverse reactions. In addition, our study highlighted clinical adverse events with rare but significant signal intensity, including diabetes insipidus and trigeminal cardiac reflexes. This research enriches our understanding of dexmedetomidine's safety profile, aiding healthcare professionals in making informed treatment decisions. While the FAERS database offers extensive data on drug-related adverse events, its reliance on voluntary reporting and susceptibility to reporting bias necessitates careful interpretation of these findings. Nevertheless, our preliminary results improve the understanding of the drug safety of dexmedetomidine, support effective clinical management in pharmacovigilance studies, and provide important insights for optimizing drug use regimens.

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 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

FL: Writing–original draft, Visualization, Software, Methodology, Investigation, Data curation. J-xZ: Methodology, Supervision, Writing–review and editing. X-dW: Supervision, Methodology, 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 research was supported by the National Natural Science Foundation of China (No. 82271238), the Fujian Provincial Health Research Talent Cultivation Program (No. 2020CXA009), and the Fujian Provincial Science and Technology Innovation Joint Funding Program (No. 2020Y9029).

Acknowledgments

This study was performed using the FAERS source that was provided by the FDA. The information, results, or interpretation of the current study do not represent any opinion of the FDA.

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.2024.1365706/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 12 July 2024
DOI 10.3389/fphar.2024.1377232

OPEN ACCESS

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RECEIVED 18 April 2024
ACCEPTED 17 June 2024
PUBLISHED 12 July 2024

CITATION
Tinchon A, Brait J, Klee S, Graichen U, Baumgartner C, Friedrich O, Freydl E, Oberndorfer S, Struhal W, Hain B, Waiß C and Stoiber D (2024), How enoxaparin underdosing and sex contribute to achieving therapeutic anti-Xa levels.
Front. Pharmacol. 15:1377232.
doi: 10.3389/fphar.2024.1377232

How enoxaparin underdosing and sex contribute to achieving therapeutic anti-Xa levels

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Introduction: Anti-Xa serves as a clinical surrogate for assessing the efficacy and bleeding risk in patients treated with enoxaparin for thromboembolic events. Evidence from the literature and empirical observations suggest that patients are underdosed in clinical practice to avoid bleeding complications. This study aimed to investigate such underdosing of enoxaparin and its potential impact on achieving therapeutic anti-Xa levels.

Methods: This multicentric, retrospective, observational study included patients with acute ischemic stroke due to atrial fibrillation. All patients received enoxaparin in the therapeutic setting with subsequent anti-Xa measurements. The one-sample, one-tailed Wilcoxon signed-rank test was used to identify a significant difference between the doses administered and the recommended daily dose. Logistic regression model analysis was performed to identify additional predictors affecting achievement of the therapeutic anti-Xa target range. Stepwise forward-backward selection with Akaike's information criterion as metric was applied to refine the logistic regression model.

Results: A total of 145 patients from the university hospitals of St. Pölten and Tulln in Lower Austria were included. The median daily enoxaparin dose administered was 1.23 mg/kg, resulting in an overall target range achievement rate of 66%. As compared to recommended therapeutic doses, significant underdosing of enoxaparin was evident in both participating centers ($p < 0.001$). The calculated threshold dose to achieve the therapeutic target range with a 90% probability was 1.5 mg/kg

Abbreviations: LMWH, Low molecular weight heparins; TIA, Transient ischemic attack; CrCl, Creatinine clearance; BMI, Body mass index; VIF, Variance Inflation Factor; AIC, Akaike Information Criterion.

enoxaparin daily. Female sex was found to be a strong independent predictor of achieving a therapeutic target range (OR 9.44; 95% CI 3.40–30.05, $p < 0.001$).

Conclusion: Despite the underdosing observed in both centers, therapeutic anti-Xa levels were achieved with lower than recommended doses of enoxaparin, and women required even lower doses than men. These findings warrant further confirmation by prospective studies.

KEYWORDS

anti-Xa, enoxaparin, underdosing, sex, gender, therapeutic, target range, anti-Xa levels

Highlights

- What is the current knowledge on the topic?
  In certain patient cohorts, elevated anti-Xa levels have been observed with enoxaparin therapy, resulting in the need for dose adjustments to minimize the risk of bleeding. However, underdosing is noted beyond high-risk groups and there is limited documentation on the prevalence and consequences of this occurrence in routine clinical practice.
- What question did this study address?
  The study aimed to identify real-world therapeutic underdosing of enoxaparin, its impact on achieving therapeutic anti-Xa levels, and relevant clinical variables influencing this target range achievement.
- What does this study add to our knowledge?
  In clinical practice, enoxaparin is commonly underdosed for therapeutic purposes. Despite this underdosing, sufficient anti-Xa levels are often achieved, especially in women.
- How might this change clinical pharmacology or translational science?
  Enoxaparin doses for sufficient therapeutic anticoagulation may be lower than recommended.

Introduction

Low molecular weight heparins (LMWH) play a crucial role in human anticoagulation. They are characterized by their reduced molecular size compared to unfractionated heparin, with a molecular size of approximately 5,000 Da in contrast to 12,000–15,000 Da (Aguilar and Kleiman, 2000; Garcia et al., 2012). LMWH offer several advantages over unfractionated heparin, including an extended half-life, reduced susceptibility to heparin-induced thrombocytopenia, increased bioavailability, improved predictability to the anticoagulant dose-response, and the omission of routine laboratory monitoring (Aguilar and Kleiman, 2000; Garcia et al., 2012).

Predominantly, LMWH are used for the chemoprophylaxis of deep vein thrombosis and pulmonary embolism in immobilized patients (Zee et al., 2017). Enoxaparin is one of the most commonly prescribed agents for this purpose (Sherman et al., 2007; Rentsch et al., 2021; Taylor et al., 2021). Simultaneously, enoxaparin is utilized in therapeutic applications, primarily in the management of established venous thromboembolism or the treatment of low-to intermediate-risk pulmonary embolism (Leentjens et al., 2017; Robertson and Jones, 2017). Other examples include non-ST-segment-elevation myocardial infarction and cerebral venous thrombosis (Hulot et al., 2005; Yusuf et al., 2006; Ferro et al., 2017; Liu et al., 2021).

The assessment of the expected therapeutic effect of LMWH often relies on surrogate markers such as anti-Xa. This approach has the potential to identify patients at risk of suboptimal or excessive dosing, providing an opportunity for dose adjustments to mitigate the risk of recurrent thrombotic events or bleeding complications. The merits of this strategy remain a topic of debate within the medical literature, marked by conflicting findings (Dhillon et al., 2018; Karcutskie et al., 2018; van den Broek et al., 2022). However, there is sufficient evidence that anti-Xa levels outside the target range are associated with increased event or bleeding rates (Wu et al., 2020; May et al., 2022; John et al., 2023; Tischler et al., 2023).

Avoiding bleeding complications is the main reason for administering lower therapeutic doses in certain populations such as severely obese or renally insufficient patients (Hulot et al., 2005; Deal et al., 2011; Sacha et al., 2016; Jaspers et al., 2022). Dose reductions were also reported in a larger sample of patients with acute coronary syndrome and suspected increased bleeding risk (Montalescot et al., 2004). In ischemic stroke arising from atrial fibrillation, therapeutic doses of LMWH have often been used to prevent recurrent stroke while minimizing the risk of bleeding compared to conventional oral anticoagulants (IST, 1997; Berge et al., 2000). Potential fear of a possible overdose and subsequent bleeding may also led to underdosing in this population, which in turn could result in reduced anti-Xa levels. Thus, the primary objective was to assess the achievement of therapeutic anti-Xa levels based on the administered enoxaparin doses. Secondary objectives involved identifying clinical predictors and exploring optimal dose thresholds for achieving therapeutic anti-Xa levels.

Materials and methods

Patient selection

This study included patients from two large urban teaching hospitals in the federal state of Lower Austria who were admitted to a neurology department between 1 January 2013, and 28 February 2019. Inclusion criteria were age >18 years, diagnosis of acute ischemic stroke or transient ischemic attack (TIA) due to atrial fibrillation, and subsequent administration of enoxaparin in a therapeutic setting. Exclusion criteria included active bleeding, latelet counts below 100,000 per µl, congenital or acquired coagulopathies with a prothrombin time below 60 s, creatinine clearance (CrCl) below 30 mL/min, concomitant use of oral anticoagulants, improperly

performed anti-Xa measurements, incomplete clinical records and pregnant women. Ethical approval was obtained from the local ethics committee (Ethics Committee of the Karl Landsteiner University of Health Sciences, No: 1016/2020) prior to study initiation.

Data collection and analysis

Clinical data were extracted from electronic and handwritten medical records. A retrospective analysis was performed including the following variables: newly diagnosed ischemic stroke or TIA, sex, age, body weight, height, body mass index (BMI), enoxaparin doses administered, serum anti-Xa levels, prothrombin time, platelet count, CrCl, and clinical event rates, including recurrent stroke and bleeding. BMI categories were defined as < 18.5 for underweight, 18.5–25.0 for normal weight, 25.0–30.0 for overweight and >30.0 kg/m^2 for obesity.

Material

All patients received subcutaneous enoxaparin (*Lovenox*®, Sanofi-Aventis GmbH, Vienna, Austria) daily every 12 h as prescribed by a physician (Lovenox prescribing information, 2022). Plasma anti-Xa levels were determined by a chromogenic assay (BIOPHEN Heparin LRT, Hyphen BioMed) after at least three previous consecutive administrations at peak levels 4 h after subcutaneous injection. Briefly, peripheral blood was collected by standard venipuncture into a 2-mL plastic tube containing 3.2% sodium citrate and centrifuged for 10 min with 1,865 g at room temperature. The plasma sample obtained was diluted with 0.9% NaCl (dilution factor 1:2). The chromogenic anti-Xa assay is based on the inhibition of a predetermined amount of factor Xa (added to each sample) by heparins or other factor Xa inhibitors in the presence of endogenous antithrombin (AT), followed by the cleavage of a factor Xa-specific chromogenic substrate (SXa-11) by the remaining factor Xa. During this reaction, the dye para-nitroaniline (pNA) is released from the chromogenic substrate, and correlates with the residual activity of factor Xa. The color development, measured at a wavelength of 405 nm, is thus inversely proportional to the anti-factor Xa activity of heparins or other factor Xa inhibitors in the sample. The therapeutic anti-Xa target range was set at 0.4–1.0 IU/mL.

Study endpoints and statistical analysis

The primary objective was the achievement of a therapeutic target range at the actual doses of enoxaparin administered. Secondary objectives were the identification of clinical predictors and determination of enoxaparin threshold doses for achieving the therapeutic target range. In addition, the incidence of recurrent strokes and bleeding events was recorded. Recurrent stroke was defined as new cerebral ischemia detected by CT or MRI during the same hospitalization, categorized by size as < 1/3 (mild) and > 1/3 (moderate to severe) of the affected arterial supply area. Hemorrhages were classified by severity as mild to moderate and severe, and by location as intracerebral and extracerebral. Severe intracranial hemorrhage was defined by a clinically relevant mass effect, whereas severe extracranial hemorrhage was characterized by a clinically significant drop in hemoglobin requiring transfusion.

The threshold dose of enoxaparin required to achieve the therapeutic target range at 90% and 95%, respectively, was determined using a logistic regression model. Descriptive statistics were used to present patient demographics and clinical characteristics. The Shapiro-Wilk test was used to check the normal distribution of samples with continuous values. A one-sided, one-sample, Wilcoxon signed-rank test was used to check whether the median of a sample with continuous values was smaller than a given standard value. The Wilcoxon effect size was determined. A p-value <0.05 was considered significant. The Benjamini-Hochberg procedure was applied to correct for alpha inflation in multiple testing.

Multiple logistic regression techniques were used for exploratory analysis of the impact of various predictors. Thus, for this type of analysis, the sample size was estimated using the approach presented by Hsieh et al. (Hsieh et al., 1998). In this approach, the necessary sample number is estimated for a simple model and subsequently adjusted for the multiple logistic regression model, taking into account the variance inflation factor (VIF). In the simple model, we used the weight-based dose as the only predictor. We expected a strong influence on the outcome (achieving the anti-Xa target range); therefore we expected a log (odds) of at least 4. Furthermore, we assumed that the weight-based dose is nearly normally distributed. Within the process of data analysis, the VIF was used to test predictors for multicollinearity and predictors with a VIF >2.5 were removed from the model. Thus, for sample size estimation, a VIF = 2.5 or equivalently $R^2 = 0.6$ was assumed. For the sample size estimation, we assumed a type 1 error rate of alpha = 0.05 and a statistical power of (1–beta) = 0.8. Taking all these conditions and assumptions into account, a minimum sample number of 92 was necessary.

A logistic regression model was used to identify predictors that influence the achievement of the therapeutic anti-Xa target range. The following predictors were included in the initial logistic regression model: sex, age in years, weight in kg, BMI, weight-based daily dose, prothrombin time in %, baseline platelets in 10^3 cells/μL, CrCl 60 ≥ mL/min, diagnosis (stroke, TIA), atrial fibrillation, and latency from start of LMWH to anti-Xa measurement in days. First, the multicollinearity of the predictors of the initial model was tested. The VIF was used as a metric. A VIF greater than 2.5 was found for the two predictors weight and BMI. As the predictor weight was considered more important in the context of the research question, BMI was removed from the list of predictors in the model. For further refinement of the logistic regression models, the approach of stepwise model selection with forward-backward search was used. The Akaike Information Criterion (AIC) was utilized as a metric to quantify the model quality (balancing model fitness and model complexity). After model refinement, sex, baseline platelets in 10^3 cells/μL, diagnosis (stroke, TIA) and daily weight-based dose in mg/kg remained in the predictor list. To evaluate the effect size, coefficient of determination (Tjur's R^2) was calculated for the logistic regression model (Tjur, 2009). Statistical analysis was conducted using Gnu R software version 4.3.1.

Results

Patient screening and inclusion

Out of 4,726 initially screened patients diagnosed with newly diagnosed ischemic stroke, 1,064 had atrial fibrillation. In 683 of

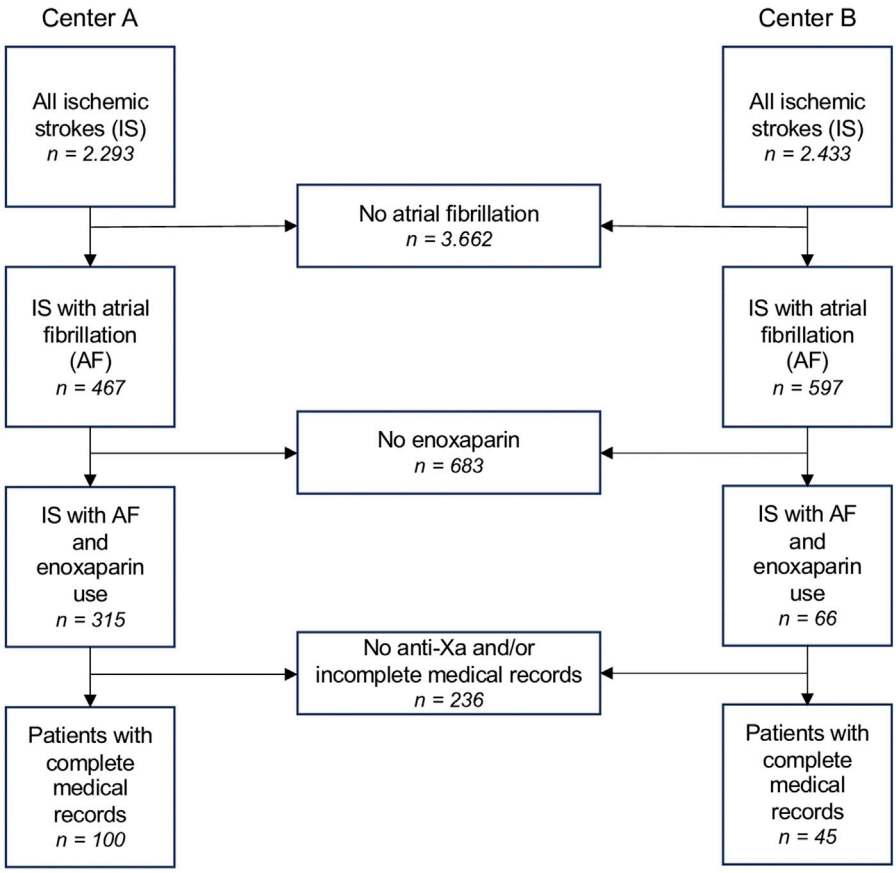

FIGURE 1
Patient selection flow chart for both centers (University Hospital St. Pölten = Center A, University Hospital Tulln = Center B). Abbreviations: IS, ischemic stroke; AF, atrial fibrillation.

these cases, no enoxaparin or other LMWH was administered. Of the remaining 381 patients, 236 either had no anti-Xa measurement, no anti-Xa peak level or incomplete medical records, leaving 145 patients for the final analysis (Figure 1).

Demographics

The patient cohort was predominantly male (59%), with a median age of 77 (68, 84) years, a median weight of 77 (68, 90) kg and a median BMI of 27.0 (24.2, 30.1) kg/m^2. Stroke was diagnosed in 89% of patients, while 11% experienced TIA. Laboratory values, including prothrombin time and platelet count, were within normal reference ranges, with median values of 89 (81, 96)% and 219 (182, 256) 10^3/μL, respectively. CrCl was greater than 60 mL/min in 74% and between 30 and 60 mL/min in 26% of patients. No statistically significant differences were observed in these parameters between the two centers (Table 1).

The median enoxaparin dose administered was 1.23 (1.04, 1.60) mg/kg (daily dose administered in two single doses every 12 h), with a significant difference between the two centers (1.17 (1.01, 1.45) versus 1.50 (1.21, 1.83) mg/kg). Thus, anti-Xa levels also differed significantly, with values of 0.44 (0.34, 0.59) versus 0.70 (0.53, 0.87) IU/mL (Table 1).

Overall, 66% of patients achieved the therapeutic target range with the enoxaparin doses specified above. Due to the different dosing in the two centers, the achievement of the therapeutic target range also differed significantly at 57% versus 87% (Table 1).

Despite significant differences in dosing, enoxaparin was administered well below the recommended daily dose of 2 mg/kg in both centers (Wilcoxon signed rank test: Center A: $p < 0.001$, $r = 0.87$; Center B: $p < 0.001$, $r = 0.80$; Figure 2).

Predictors for achieving the therapeutic anti-Xa target range

Following refinement of the logistic regression models, sex, diagnosis, weight-based dose and baseline platelet count remained significant predictors. The coefficient of determination R^2_{Tjur}, indicative of effect size, was calculated for the logistic regression model $R^2_{\text{Tjur}} = 0.458$. The odds of reaching the therapeutic target range were higher for women than for men (OR *9.44*, 95% CI: 3.40–30.05, $p < 0.001$, Table 2). Patients with TIA were more likely to achieve the therapeutic target range than patients with ischemic stroke (OR *5.36*, 95% CI: 1.12–33.07, $p = 0.047$, Table 2). Lower platelet counts were associated with a higher probability to reach the target range (OR *0.99*; 95% CI: 0.99–1.00, $p = 0.047$, Table 2).

TABLE 1 Patient demographics.

Characteristics[a]	Overall, n = 145[b]; Race: white (n = 145, 100%).	Center		*p*-value[c]
		A, n = 100[b]	B, n = 45[b]	
Sex				0.4
Male	85 (59%)	56 (56%)	29 (64%)	
Female	60 (41%)	44 (44%)	16 (36%)	
Age in years	77 (68, 84)	76 (68, 84)	77 (69, 83)	0.8
Weight in kg	77 (68, 90)	75 (68, 86)	82 (68, 98)	0.4
BMI in kg/m^2	27.0 (24.2, 30.1)	26.7 (24.2, 28.9)	28.1 (24.7, 32.3)	0.2
BMI categories				0.4
Underweight	0 (0%)	0 (0%)	0 (0%)	
Normal weight	42 (33%)	34 (34%)	8 (28%)	
Overweight	53 (41%)	43 (43%)	10 (34%)	
Obesity	34 (26%)	23 (23%)	11 (38%)	
Prothrombin time in %	89 (81, 96)	88 (80, 94)	91 (83, 103)	0.078
Baseline platelets in 10^3 cells/μL	219 (182, 256)	217 (183, 250)	228 (182, 294)	0.4
CrCl < 60 mL/min	38 (26%)	27 (27%)	11 (24%)	0.8
Diagnosis				0.7
Stroke	129 (89%)	90 (90%)	39 (87%)	
TIA	16 (11%)	10 (10%)	6 (13%)	
Daily weight-based dose in mg/kg	1.23 (1.04, 1.60)	1.17 (1.01, 1.45)	1.50 (1.21, 1.83)	<0.001
Patients with doses <2 mg/kg daily[d]	138 (95%)	98 (98%)	40 (89%)	0.068
Anti-Xa IU/mL	0.52 (0.35, 0.67)	0.44 (0.34, 0.59)	0.70 (0.53, 0.87)	<0.001
Anti-Xa ≥ 0.4 IU/mL	96 (66%)	57 (57%)	39 (87%)	0.002

Description of patient cohort.
[a]BMI: body mass index; CrCl: creatinine clearance; TIA: transient ischemic attack.
[b]n (%): Median (IQR).
[c]Benjamini-Hochberg correction for multiple testing.
[d]Recommended therapeutic enoxaparin dose = 1 mg/kg body weight every 12 h.

Calculated doses for achieving the therapeutic anti-Xa target range

The calculated enoxaparin threshold doses required to reach the therapeutic range were found to be lower than the recommended dose of 2 mg/kg daily dose and exhibited differentiation according to sex. To achieve the target range with a 95% probability, the required daily dose was 1.66 mg/kg for the entire cohort, with it being 1.32 mg/kg for females and 1.82 mg/kg for males. In order to attain the target range with a 90% probability, the doses were 1.51 mg/kg for the entire cohort, 1.22 mg/kg for females, and 1.67 mg/kg for males (Figure 3).

Clinical event and bleeding rates

During the initial hospitalization, three patients (2.1%) experienced recurrent strokes, and nine patients (6.2%) had bleeding events. Two of the strokes were mild, with one having a therapeutic anti-Xa level (0.85 IU/mL) and one having a subtherapeutic level (0.36 IU/mL). One moderate stroke was also linked to a subtherapeutic anti-Xa level (0.15 IU/mL). Of the nine bleeding events, eight were classified as mild to moderate, including three extracranial and six intracranial cases. One severe, non-fatal extracranial bleeding occurred with a supratherapeutic anti-Xa level (1.15 IU/mL). Of the mild to moderate hemorrhages, four had subtherapeutic anti-Xa levels (median 0.28 IU/mL; range 0.15–0.34 IU/mL), while the other four occurred within the therapeutic target range (median 0.61 IU/mL; range 0.47–0.96 IU/mL).

Discussion

This study confirms empirical observations of enoxaparin underdosing in clinical practice.

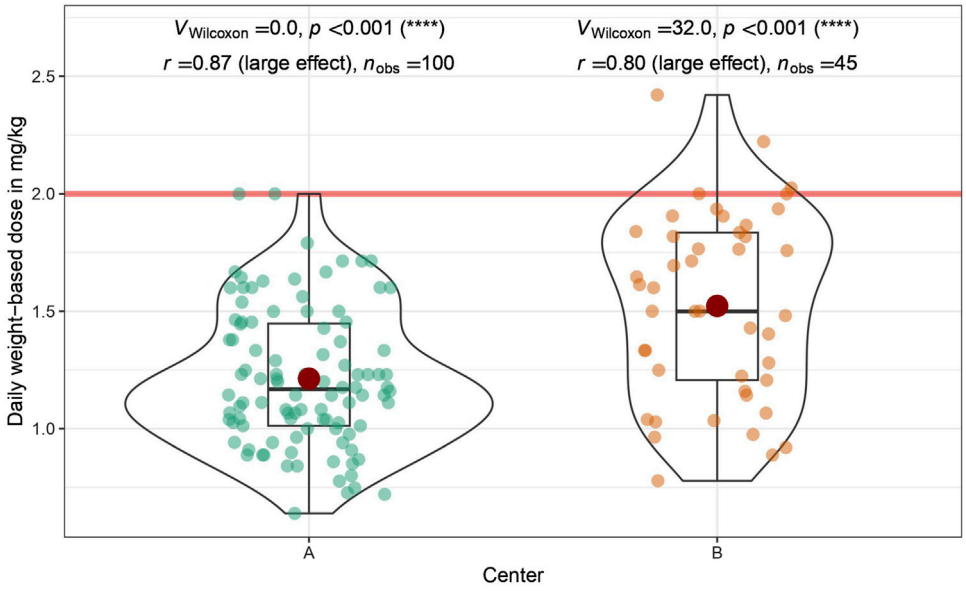

FIGURE 2
Daily weight-based dose of enoxaparin administered: Shown is a comparison between the two participating centers (University Hospital St. Pölten = Center A, University Hospital Tulln = Center B). The daily weight-based dose recommended by the drug manufacturer is marked by a red horizontal line. The doses administered were analyzed by a one-sided one-sample Wilcoxon signed rank test. In both centers, the dose administered is significantly lower than the recommended dose; Center **(A)** $p < 0.001$, $r = 0.87$; Center **(B)** $p < 0.001$, $r = 0.80$.

TABLE 2 Clinical predictors for achieving a therapeutic target range.

Characteristics[a]	anti-Xa ≥ 0.4 IU/mL R^2_{Tjur} = 0.458		
	OR[b]	95% CI[b]	*p*-value[c]
Sex			
Male	—	—	
Female	9.439	3.396, 30.05	<0.001
Baseline platelets in 10^3 cells/μL	0.992	0.985, 1.000	0.047
Diagnosis			
Stroke	—	—	
TIA	5.362	1.120, 33.07	0.047
Daily weight-based dose in mg/kg	371.5	53.29, 4,056	<0.001

Predictors of the logistic regression model for achieving the therapeutic anti-Xa target range. For the nominally scaled variables sex and diagnosis, the values *male* and *stroke* serve as *reference* for the odds ratio; in the table, they are marked by short horizontal dashes. The coefficient of determination R^2_{Tjur}, which can be considered as an effect size, is given for each of the logistic regression models.

[a]TIA: transient ischemic attack; R^2_{Tjur}: Coefficient of determination.

[b]OR: odds ratio; CI: Confidence Interval.

[c]Benjamini-Hochberg correction for multiple testing.

It shows that achieving the desired therapeutic range often requires lower doses than recommended, especially in female patients.

In clinical practice, the conventional therapeutic enoxaparin regimen of 1 mg/kg every 12 h is often modified. Such adjustments can be attributed to a number of factors. For example, patients with severe obesity or impaired renal function have been shown to achieve therapeutic levels of enoxaparin at doses below conventional guidelines (Jaspers et al., 2022). Thus, unadjusted dosing carries the inherent risk of exposing patients to supratherapeutic levels of enoxaparin, thereby increasing their susceptibility to bleeding events (Barras et al., 2008).

A study conducted by Lee et al. on a cohort of overweight patients showed that 50% of them had supratherapeutic anti-Xa levels when given the standard dose of 1 mg/kg every 12 h (Lee et al., 2015). Additionally, Sacha et al. reported that 75% of severely obese

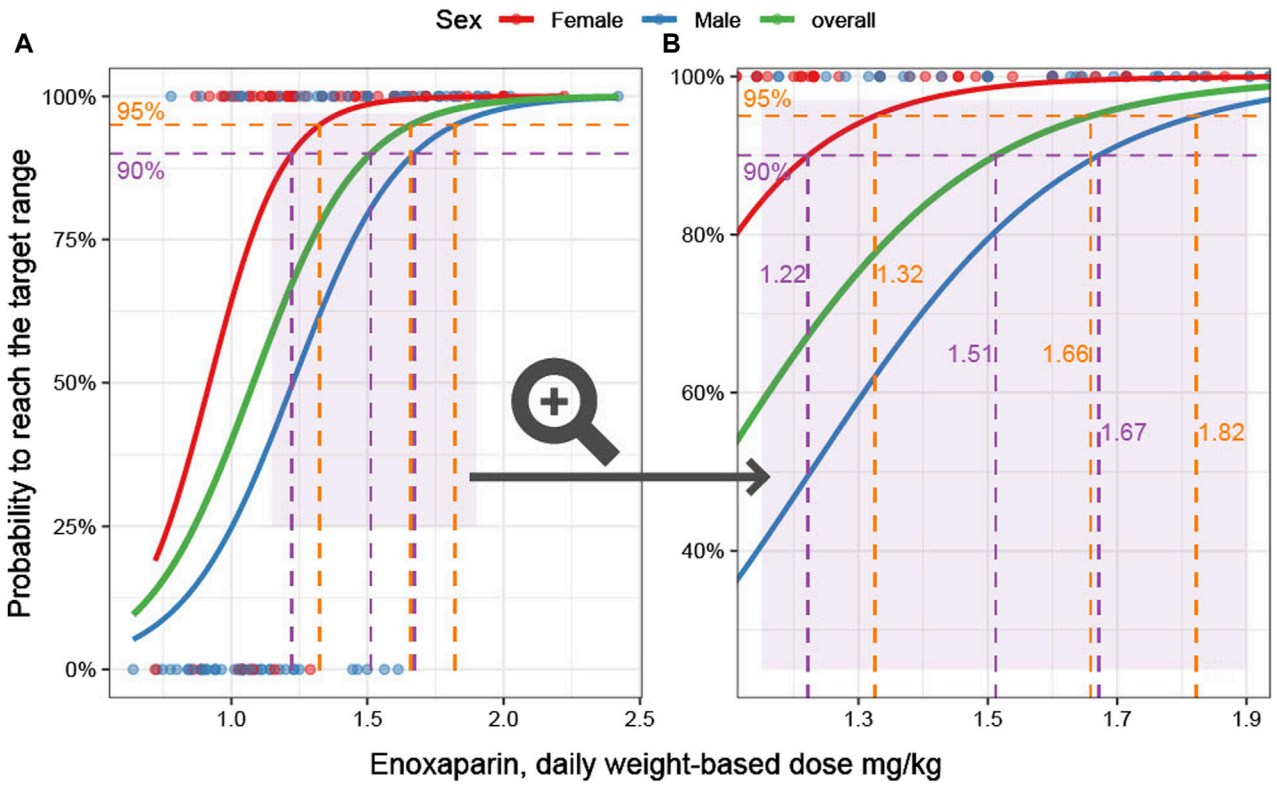

FIGURE 3
Weight-based dose and probability to achieve therapeutic anti-Xa levels. **(A)**: Overview. The probability to reach the anti-Xa target as a function of the predictor weight-based dose is the outcome parameter in this logistic regression model. The characteristics of female (red) and male (blue) patients are modeled separately. In addition, an overall model is given (green). The data underlying the models are visualized as dots. **(B)**: Zoomed-in view of the area marked in light purple in **(A)** is shown. The 90% and 95% probabilities are marked by dashed horizontal purple and orange lines, respectively. The corresponding weight-based doses are displayed on the vertical lines.

patients were underdosed, receiving a median enoxaparin dosage of 0.89 mg/kg per dose (Sacha et al., 2016). An earlier case series by Deal et al. also described a reduced median therapeutic dose of 0.80 mg/kg per dose (Deal et al., 2011). However, these studies were hampered by a limited number of corresponding anti-Xa measurements, making it difficult to establish a definitive correlation with the dose administered.

Body weight may also have affected underdosing in our study population, considering that two-thirds were overweight. Notably, body weight did not appear to have a significant impact on reaching the therapeutic target range. This could be explained by the lower BMI of our patients compared with those in the previous studies. In addition, less obese people have been reported to have anti-Xa activity comparable to that of a non-overweight population (Sanderink et al., 2002). Renal function played a minor role in our sample, as the majority of patients exhibited normal CrCl, and individuals with severe renal insufficiency were excluded from the study.

Patient age may also contribute to underdosing. For example, in the ExTRACT-TIMI 25 trial, the therapeutic dose of enoxaparin was reduced to 0.75 mg/kg every 12 h in patients older than 75 years (Antman et al., 2006). Leri et al. specifically studied patients older than 65 years to describe the benefit of adjusted body-weight dosing versus standard dosing. Again, doses lower than the commonly recommended were used (Leri et al., 2009). Given the average age of 77 years in our sample, age may indeed have played a role in the dosing strategy adopted.

Overall, most of these deviations from the standard dosing regimens appear to be driven by a prevailing concern about the potential risk of iatrogenic bleeding due to an assumed overdose. As a result, even in prospective studies, clinical judgement often guides the decision to administer reduced doses of enoxaparin to patients perceived to be at increased risk of bleeding events (Montalescot et al., 2004). In our study population, concerns about intracranial hemorrhages may also have contributed to the cautious dosing approach (Hallevi et al., 2008).

Enoxaparin underdosing was observed in both participating centers, albeit to varying extents. As expected, this variability was also reflected in the resulting anti-Xa levels. Patients at the more pronounced underdosing Center A only marginally reached the therapeutic anti-Xa levels, whereas patients treated at the less underdosing Center B comfortably achieved anti-Xa levels well within the therapeutic target range. This leads us to question the required dose to consistently attain the therapeutic target range. It was explored that a daily dose of 1.5 mg/kg provided a 90% probability of achieving the therapeutic target range, a dose considerably lower than the standard recommended dose of 2 mg/kg daily. There was also a sex difference, with women needing a significantly lower dose of enoxaparin than men to achieve the therapeutic level with the same likelihood.

Evidence indicates that women attain comparatively higher anti-Xa levels in both prophylactic and therapeutic settings. A recent large retrospective study by Modi et al. reported that male trauma patients were more likely to have subprophylactic anti-Xa levels, while females were more prone to supraprophylactic levels (Modi et al., 2023). Similar findings were observed in burn patients by Cronin et al. and high-risk trauma patients by Farrar et al. (Cronin et al., 2019; Farrar et al., 2021).

These results are consistent with studies conducted in therapeutic settings. For instance, Leri et al. demonstrated that women were more likely to achieve the predefined therapeutic target range with weight-adjusted dosing, while Toss et al. reported higher anti-Xa activity in female patients during the acute treatment of unstable coronary artery disease (Toss et al., 1999; Leri et al., 2009). Oldgren et al. supported these findings in a larger sample, albeit with dalteparin and not enoxaparin, with both drugs differing in several clinical aspects such as antithrombotic potency, bleeding rates and bioavailability (Fareed et al., 1998; Oldgren et al., 2008).

In our study, women required lower doses of enoxaparin to attain the therapeutic range. Collinearity analysis ruled out interactions with other predictors, suggesting a genuine biological effect. The lower water content and reduced plasma volume in women could potentially concentrate hydrophilic substances, such as enoxaparin, in blood (Hakeam et al., 2020; Modi et al., 2023). Additionally, other sex-specific factors, including differences in muscle and adipose tissue distribution, pulmonary and renal function, and hormonal influences, could contribute to varying drug absorption, distribution, excretion, and interaction profiles (Franconi and Campesi, 2017).

An unexpected observation in our analysis concerned the higher probability of achieving a therapeutic anti-Xa range in patients experiencing TIA compared to those with ischemic strokes. TIA, as defined by the American Heart Association/American Stroke Association guidelines, represents a transient episode of neurological dysfunction attributed to focal cerebral, spinal cord, or retinal ischemia in the absence of acute infarction (Easton et al., 2009). Consequently, the primary distinction between TIA and ischemic strokes lies in the transient nature of symptoms. Nevertheless, both diseases share common features in pathophysiology. They are characterized by focal neurologic deficits attributable to impaired cerebral blood flow. Reports of differences in coagulation profiles between TIA and stroke are rare. For instance, Pelz et al. found increased fibrinogen levels in stroke patients, but these findings lost statistical significance after correction for multiple testing. Nonetheless, implementing clinical features and serum biomarkers have shown the potential to discriminate between TIA and stroke (Pelz et al., 2021).

Similarly, in the area of viscoelastometry, a technique to assess changes in blood viscosity by *in vitro* mechanical measurements, Bliden et al. observed a shorter time to initial clot formation in stroke patients than in TIA patients (Bliden et al., 2019). Ryu et al. reported shortened clot formation in stroke patients with worse functional outcomes at 3 months (Ryu et al., 2023). Both results suggest that measurable hypercoagulable coagulation profiles exist at least within the stroke population. Whether these observations support the results of our study must remain open at this time. However, given the small number of cases in this subgroup, incidental findings may also be considered.

Event rates in our sample generally align with those reported in other studies and were in the low percent range for recurrent stroke and bleeding events, rendering them clinically insignificant (Saliba et al., 2011; Lalama et al., 2015; Aleidan et al., 2020). Of note, both critical events corresponded to subtherapeutic or supratherapeutic anti-Xa levels. Although the bleeding rate was comparable with other studies, eight out of nine hemorrhages occurred in the therapeutic or even subtherapeutic target range. However, a larger number of cases will be required to test the plausibility of this observation.

Our study is subject to certain limitations. The retrospective design and number of cases may have biased the data. However, the results are based on a sample size estimation, which makes our number of cases seem sufficient. It should also be noted that these data from a large Austrian commuting area are not necessarily globally representative, particularly in terms of race and other demographic factors.

Due to underdosing, we barely found supratherapeutic anti-Xa levels. Therefore, we are unable to provide insight into the upper limits of the target ranges. It is plausible that the use of higher doses may have resulted in more cases with supratherapeutic anti-Xa levels. Nevertheless, supratherapeutic anti-Xa levels are more likely to be a concern in certain high-risk groups such as patients with severe renal insufficiency or massive obesity. Thus, a rather low number of supratherapeutic anti-Xa levels would have been expected in our sample, even at higher enoxaparin doses.

Our calculation of the enoxaparin dosage required to achieve the therapeutic target range with a 90% or 95% probability is limited by the absence of a recommended dose control for comparison. However, the fact that a considerable number of patients reached the therapeutic target range with notably lower doses provides a potential reference point that merits validation through prospective investigations.

It is important to note that our sample included mainly patients with atrial fibrillation and stroke in whom therapeutic use of LMWH is no longer indicated. Consequently, the generalizability of our results to other medical conditions is limited. However, we had a rigorously selected sample without severe renal dysfunction or morbid obesity. Therefore, similarity to other patient groups without high-risk constellations can be assumed with all due caution. These include, for example, patients with venous thromboembolism, cerebral sinus vein thrombosis or non-ST-segment-elevation myocardial infarction.

To evaluate enoxaparin therapy, we obtained anti-Xa peak levels. Emerging evidence suggests that trough levels provide greater accuracy, and this consideration should be taken into account in future study protocols. In addition, the observed sex differences are susceptible to the limitations associated with retrospective data analysis. Unaddressed confounders may have influenced our observations. Nevertheless, we included common clinical variables in our model and did not identify any confounding predictor.

In conclusion, despite significant underdosing, it was evident that enoxaparin doses below the recommended levels were sufficient to achieve the therapeutic target range. This observation raises the possibility of reassessing the current dose recommendations to potentially lower them, depending on the specific medical indication, as a measure to reduce the risk of bleeding. This is particularly important in high-risk groups such as patients with severe renal insufficiency or concomitant use of other anticoagulants.

In addition, it is prudent to consider sex-specific considerations in future prospective studies, particularly for women, as they may have a different sensitivity to therapeutic enoxaparin treatment compared to men.

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 Ethics Committee of the Karl Landsteiner University of Health Sciences, No: 1016/2020. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent for participation was not required from the participants or the participant's legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. JB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing–original draft, Writing–review and editing. SK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. UG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. CB: Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing–original draft, Writing–review and editing. OF: Formal Analysis, Methodology, Project administration, Supervision, Writing–review and editing. EF: Data curation, Formal Analysis, Investigation, Project administration, Writing–review and editing. SO: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing–review and editing. WS: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing–review and editing. BH: Data curation, Investigation, Project administration, Resources, Software, Writing–review and editing. CW: Investigation, Project administration, Writing–review and editing. DS: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, 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. The article processing charge was covered by the Open Access Publishing Fund of the Karl Landsteiner University of Health Sciences, Krems, Austria.

Acknowledgments

The authors want to appreciate the contribution of NÖ Landesgesundheitsagentur, legal entity of University Hospitals in Lower Austria, for providing the organizational framework to conduct this research. The authors also would like to acknowledge support by Open Access Publishing Fund of Karl Landsteiner University of Health Sciences, Krems, Austria. We also thank Prof. Christine Marosi for her valuable clinical suggestions and Warren Fulton for proofreading.

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.

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 09 September 2024
DOI 10.3389/fphar.2024.1413154

OPEN ACCESS

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RECEIVED 06 April 2024
ACCEPTED 26 August 2024
PUBLISHED 09 September 2024

CITATION
Xia S, Xu J-W, Yan K-X, Noguchi Y, Sarangdhar M and Yan M (2024) Tumor lysis syndrome signal with the combination of encorafenib and binimetinib for malignant melanoma: a pharmacovigilance study using data from the FAERS database.
Front. Pharmacol. 15:1413154.
doi: 10.3389/fphar.2024.1413154

Tumor lysis syndrome signal with the combination of encorafenib and binimetinib for malignant melanoma: a pharmacovigilance study using data from the FAERS database

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Objective: To investigate the potential association between tumor lysis syndrome (TLS) and drugs for the treatment of malignant melanoma (MM).

Methods: Reports of TLS recorded in the FDA Adverse Event Reporting System (FAERS) (January 2004–2023q3) were identified. Demographic and clinical characteristics were described, and disproportionality signals were assessed through the Reporting Odds Ratio (ROR) and Information Component (IC). The latency of TLS with anticancer drugs was described based on parametric models. Subgroup analysis was conducted to explore the differences of TLS signals in different age and sex.

Results: We found 5 (1.49%), 59 (17.61%), 79 (23.58%), 19 (5.67%), 13 (3.88%), 13 (3.88%), 33 (9.85%), 49 (14.63%), 16 (4.78%) TLS reports with pembrolizumab, nivolumab, ipilimumab, dabrafenib, vemurafenib, dacarbazine, "encorafenib and binimetinib", "nivolumab and ipilimumab", "dabrafenib and trametinib", respectively. The combination of encorafenib and binimetinib showed the strongest signal of TLS (IC_{025} = 3.98). The median days of latency of TLS with combination of encorafenib and binimetinib is 2 days, which was much shorter than nivolumab (22.0 days) and ipilimumab (21.5 days). TLS cases associated with drugs for MM were predominantly recorded in females and aged 25–65 years. After excluding confounding factors such as pre-existing diseases and co-treated drugs, the disproportionate signal of TLS with "encorafenib and binimetinib" remained strong.

Conclusions: Stronger disproportionate signal of TLS was detected in MM patients using the combination of encorafenib and binimetinib than other

drugs. Further research is needed to investigate the underlying mechanisms and identify patient-related predisposing factors to support safe prescribing of the combination of encorafenib and binimetinib.

KEYWORDS

encorafenib, binimetinib, tumor lysis syndrome, malignant melanoma, pharmacovigilance, FAERS, disproportionality analysis

1 Introduction

Malignant melanoma (MM) is a highly malignant tumor that originates from melanocytes in the skin (Guy et al., 2015). Its incidence is on the rise worldwide, making it one of the main types of skin cancer. Representing 1.7% of all cancer diagnoses, melanoma is ranked as one of the most common cancers worldwide, probably reaching 57,000 deaths in the same period (Lopes et al., 2022). The cause of malignant melanoma is not fully understood, but long-term ultraviolet exposure, genetic factors, and immune system abnormalities are known risk factors. At present, the treatment options for malignant melanoma include traditional therapies (dacarbazine, high-dose interleukin-2), immune checkpoint inhibitors (single-agent nivolumab, ipilimumab, and combination of nivolumab plus ipilimumab), targeted therapies (single-agent vemurafenib and dabrafenib, and combination of combination of encorafenib plus binimetinib; dabrafenib plus trametinib; cobimetinib plus vemurafenib) as well as one intralesional modified oncolytic herpes virus talimogene laherparepvec (Swetter et al., 2021). Immune checkpoint blockade strategies targeting the PD-1 and CTLA-4 co-inhibitory receptors, and MAP kinase (MAPK) molecular targeted therapy directed at oncogenic BRAF and MEK signaling pathways. Both approaches have proven effective in the treatment of advanced melanoma (Jenkins and Fisher, 2021).

Tumor lysis syndrome (TLS) is a rare and potentially fatal disease that is often associated with anti-cancer therapy (McBride and Westervelt, 2012). The pathogenesis of TLS includes two aspects: on the one hand, tumor cells produce a large number of metabolites such as uric acid and potassium ions during the rapid breakdown process, and on the other hand, the patient's excretory organs such as kidneys and liver are not functional enough to quickly remove these metabolites, resulting in their accumulation in the body (Durani and Hogan, 2020). Typical features of TLS include hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, etc. These metabolic disorders can lead to serious complications (Howard et al., 2016) such as renal insufficiency, arrhythmias, and even life-threatening acute kidney injury. Previous review showed that MM patients had a low incidence of TLS (Kelkar and Wang, 2021).

Studies have found that the combination of encorafenib and binimetinib, a treatment option that can effectively treat malignant melanoma, may cause TLS. Although two studies (Tachibana et al., 2021; Byron et al., 2020) have reported that co-administration of encorafenib and binimetinib may cause TLS, the sample size was small, and these observations need to be confirmed in larger studies. Large pharmacovigilance databases, such as the FAERS and WHO Vigibase, could provide a broader perspective to identify signals of potential associations between drugs and adverse events (AEs) by collecting unpublished reports that occur in unselected subjects in the real-world clinical settings.

In this study, the association between co-treatment of encorafenib plus binimetinib and tumor lysis syndrome was investigated using data from the FAERS database.

2 Methods

2.1 Study design and data sources

This is a retrospective pharmacovigilance study using curated FAERS data from the AERS*Mine* (Sarangdhar et al., 2016) website. AERS*Mine* is a multi-cohort analyzing application designed to mine curated data across millions of patient reports (currently 20, 346, 289) from the FAERS. Several high-impact pharmacovigilance research (Xia et al., 2023; Sarangdhar et al., 2021) utilized data from the AERS*Mine*. The data used for this study was from the first quarter of 2004 to the third quarter of 2023.

In this study, drugs of interest come from FDA-approved drugs for MM, including nivolumab, ipilimumab, trametinib, dabrafenib, vemurafenib, encorafenib, binimetinib, dacarbazine, vemurafenib, pembrolizumab and combinational therapies. The adverse event of interest was tumor lysis syndrome. Ethical approval was not required because this study was conducted by using deidentified data.

2.2 Disproportionality analysis

Case/non-case approach was used to calculate the disproportionate signals of TLS with anti-cancer drugs (Faillie, 2019) There are two methods to calculate the disproportionality signal, which is, namely, frequentist and Bayesian statistical approaches. In this study, the disproportionate signals of TLS with regimens for MM are assessed by calculating Reporting Odd Ratios (ROR) and Information Components (IC) (Bate et al., 1998).

The detection criterion is that there is a statistically significant disproportionate signal when the lower limit of the 95% confidence interval (CI) of the ROR (ROR_{025}) (Moore et al., 2005; van Puijenbroek et al., 2002) > 1 and the lower limit of the 95% confidence interval of the IC_{025} (IC_{025}) were >0.

2.3 Descriptive analysis

The clinical features and demographics (report year, reporter, role code, age, gender and outcome) of TLS with anticancer drugs for MM were collected and analyzed.

2.4 Sensitivity analysis

In order to exclude the influence of confounding factors on the results of the study and to test the robustness of the disproportionate signals, we performed series of sensitivity analyses. Firstly, when the adverse effects studied are also reported with one or more drugs other than the target drug (the drug of interest), bias due to drug-to-drug competition may occur. By reviewing the literature (Barbar and Jaffer Sathick, 2021; Williams and Killeen, 2019; Wang et al., 2021), we removed TLS cases reported with other drugs (but not anticancer drugs for MM in this study), which help us to reduce competition biases. Secondly, to avoid exposure bias, we limited the reports of drugs as suspicious, i.e., primary suspect and secondary suspect. At the same time, the scope of reporting was limited to reports by health professionals. Thirdly, we excluded some pre-existing diseases, such as renal dysfunction, hyperuricemia, etc., to reduce indication bias. Finally, we calculated the disproportionality signals of TLS using the available Standardized MedDRA Query, broad search, (including 39 Preferred Terms) to better reflect co-reported adverse events.

2.5 Subgroup analysis

In the detection of adverse drug reaction signals, subgroup analysis can help to identify potential risk groups, further highlighting those drug-adverse reaction pairs that are overreported in specific subgroups, and thus identifying potential risk groups (Sandberg et al., 2020). A recent review paper (Noguchi and Yoshimura, 2024) summarized detection algorithms for simple two-group comparisons using spontaneous reporting systems, including frequentist statistical approach (relative ROR), Bayesian statistical approach (ICΔ) and Odds Ratio-based method.

In order to explore the treatment effect or prognosis of patients with different characteristics or subgroup criteria, we divided the cases into age and gender, and divided the cases into older than 65 years and less than or equal to 65 years, male and female, and independently explored the effects of age and gender on the TLS signals. In the study, we used the ICΔ as well as its 95% confidence interval (IC_{025} and $IC_{975)}$ to measure the disproportionate signals between subgroups. A significant signal was detected in subgroups if the 95% confidence interval do not include zero. More details about the formula and algorithms could be found in Supplementary File S1. For raw data on subgroup analyses, please refer to Supplementary File S2.

2.6 Time-to-onset (TTO) analysis

TTO modeling (Zhang et al., 2017) is the use of parameter distributions to model the time to onset (Nakamura et al., 2015) of adverse reactions of interest (ADRs) with drugs of interest.

We refer to the dataset that has been cleaned from the AERS*Mine* website. The data included reports from 2004 to 2021 q3. The appropriate model (such as Weibull, log-normal, gamma, exponential, etc.) was selected for data analysis, and the most suitable model was determined by the goodness-of-fit test (Maignen et al., 2010). At the same time, duplicates and reports with missing information were removed to obtain more accurate results. More details about the formula and algorithms could be found in Supplementary File S3. For raw data on Time-to-onset analyses, please refer to Supplementary File S4.

2.7 Global assessment of the evidence

Causality was assessed using the adjusted Bradford Hill criteria used in epidemiology to assess the causality of the entire evidence (Andreae et al., 2016), including multiple dimensions such as biological plausibility, strength, consistency, specificity, coherence, and analogy (Muganurmath et al., 2018).

With these approaches, we hope to assess evidence for the potential association between drugs for MM and tumor lysis syndrome.

3 Result

3.1 Disproportionate signals of TLS with drugs for MM

Using the AERSMine platform, 9303 TLS cases were detected from the FAERS database from 2004q1 to 2023q3. There are 5, 59, 79, 19, 13, 13, 33, 49, 16 TLS reports with pembrolizumab, nivolumab, ipilimumab, dabrafenib, vemurafenib, dacarbazine, “encorafenib and binimetinib”, “nivolumab and ipilimumab”, “dabrafenib and trametinib”, respectively. The ROR and IC of the above drugs were shown in Figure 1.

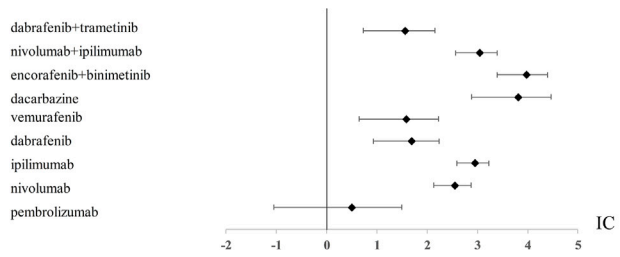
Using other drugs in the FAERS database as the comparator, we found the combination of encorafenib and binimetinib showed the most significant disproportionate signal of TLS compared to other regimens. The IC value of TLS with nivolumab, ipilimumab, encorafenib, binimetinib in different years was presented in Figure 2.

3.2 Clinical characteristics of TLS cases with regimens for MM

TLS cases of “encorafenib and binimetinib” for melanoma were reported from 2006 to 2023q3 with a total of 33 cases. 87.9% (29/33) of the reported cases were concentrated between 2019 and 2023q3, and 63.6% (21/33) of the cases were reported by health professionals. Deaths were recorded in three cases (9.1%). Life-threatening outcomes were recorded in 15.2% and hospitalizations in 60.6%. 63.6% of TLS with “encorafenib and binimetinib” occurred in 25-65-year-olds and 45.5% in female. The clinical features of TLS with various drugs for MM were shown in Table 1.

3.3 Sensitivity analysis of TLS signals

To test the robustness in the results, we performed sensitivity analyses. The association between TLS and some regimens (“dabrafenib plus trametinib”, “nivolumab plus ipilimumab”, “encorafenib plus binimetinib”, dacarbazine, vemurafenib,



Primary Analysis	IC(95%CI)	ROR (95%CI)	TLS cases/All MM cases	TLS cases/ All other drugs in the FAERS database
dabrafenib+trametinib	1.57(0.73-2.16)	3.18(1.95-5.20)	16/11021	9287/20335268
nivolumab+ipilimumab	3.05(2.57-3.39)	9.02(6.81-11.95)	49/11984	9254/20334305
encorafenib+binimetinib	3.98(3.39-4.39)	20.49(14.54-28.89)	33/3565	9270/20342724
dacarbazine	3.82(2.88-4.46)	28.86(16.69-49.90)	13/999	9290/20345290
vemurafenib	1.59(0.65-2.23)	3.26(1.89-5.61)	13/8748	9290/20337541
dabrafenib	1.70(0.93-2.24)	3.46(2.21-5.43)	19/12031	9284/20334258
ipilimumab	2.96(2.59-3.23)	8.22(6.58-10.26)	79/21245	9224/20325044
nivolumab	2.56(2.13-2.87)	6.20(4.80-8.01)	59/20982	9244/20325307
pembrolizumab	0.51(-1.05-1.50)	1.49(0.62-3.58)	5/7342	9298/20338947

FIGURE 1
The comparison of Tumor lysis syndrome signal between "encofenib and binitinib" and controls (other anticancer drugs) in FAERS database. ROR, reporting odds ratio; IC, information component; 95%CI, 95% confidence interval; N, number; AEs, adverse events.

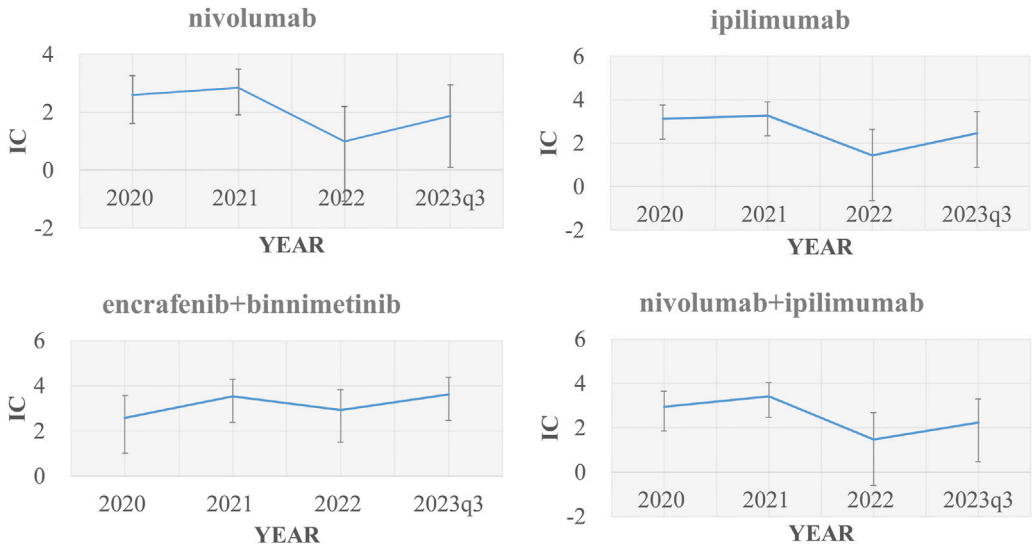


FIGURE 2
Signal values of nivolumab, ipilimumab, "encorafenib and binimetinib" and "nivolumab and ipilimumab" regarding changes in TLS cases over time (2020, 2021, 2022, 2023q1-2023q3) IC, information component.

dabrafenib, ipilimumab, nivolumab, pembrolizumab) remained significant even after taking into account possible confounders (competitive bias due to drug interactions, information bias due to reporting health expertise, and information bias due to indications). The detailed disproportionate signals across multiple sensitivity analysis were displayed in Table 2.

3.4 Subgroup analysis

We found that in the case of a combination of encorafenib and binimetinib, women ($IC\Delta_{975} = -1.95$) were more likely to have TLS adverse events than men, patients aged 25–65 years old ($IC\Delta_{975} = -1.52$) were more likely to have TLS events. Detailed subgroup (age and gender) analysis of TLS reports with drugs for MM was shown in Figure 3.

3.5 Time-to-onset (analyses)

From our results, the median time-to-onset of TLS with nivolumab, ipilimumab, encorafenib, binimetinib, dabrafenib was 22.0, 21.5, 2.0, 2.0, 2.0 days, respectively (Table3). A detailed analysis of the relevant drugs is provided in Figure 4.

3.6 Global assessment of the evidence

By evaluating adopted Bradford Hill criteria, including association strength, consistency, specificity, temporal relationships, experimental evidence, coherence and analogy, we found the associations between "encorafenib plus binimetinib" and tumor lysis syndrome met the causality assessment assessed by the Bradford Hill criteria. More details were shown in Table 4.

TABLE 1 Patient characteristics of TLS reports with "encorafenib and binimetinib" and other drugs in the FAERS database.

Categories	Pembrolizumab	Nivolumab	Ipilimumab	Dabrafenib	Vemurafenib	Dacarbazine	Encorafenib + Binimetinib	Nivolumab + Ipilimumab	Dabrafenib + Trametinib
Reports of TLS	5	59	79	19	13	13	33	49	16
Report Year									
2006–2009	0 (0.0%)	0 (0.0%)	6 (7.6%)	0 (0.0%)	11 (84.6%)	7 (53.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2010–2013	1 (20.0%)	7 (11.9%)	12 (15.2%)	5 (26.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	4 (8.2%)	2 (12.5%)
2014–2018	4 (80.0%)	20 (33.9%)	27 (34.2%)	2 (10.5%)	1 (7.7%)	0 (0.0%)	4 (12.1%)	15 (30.6%)	2 (12.5%)
2019–2023q3	0 (0.0%)	32 (54.2%)	34 (43.0%)	12 (63.2%)	0 (0.0%)	6 (46.2%)	29 (87.9%)	30 (61.2%)	12 (75.0%)
Reporter									
Healthcare professionals	5 (100.0%)	39 (66.1%)	56 (70.9%)	15 (78.9%)	10 (76.9%)	11 (84.6%)	21 (63.6%)	34 (69.4%)	12 (75.0%)
Other	0 (0.0%)	20 (33.9%)	23 (29.1%)	4 (21.1%)	3 (23.1%)	2 (15.4%)	12 (36.4%)	15 (30.6%)	4 (25.0%)
Age Category									
0–14	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
15–24	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
25–65	5 (100.0%)	33 (55.9%)	43 (54.4%)	8 (42.1%)	10 (76.9%)	10 (76.9%)	21 (63.6%)	29 (59.2%)	6 (37.5%)
>65	0 (0.0%)	24 (40.7%)	34 (43.0%)	6 (31.6%)	1 (7.7%)	3 (23.1%)	5 (15.2%)	19 (38.8%)	6 (37.5%)
Data unavailable	0 (0.0%)	2 (3.4%)	2 (2.5%)	5 (26.3%)	1 (7.7%)	0 (0.0%)	7 (21.2%)	1 (2.0%)	4 (25.0%)
Gender									
Male	5 (100.0%)	38 (64.4%)	49 (62.0%)	12 (63.2%)	3 (23.1%)	5 (38.5%)	8 (24.2%)	29 (59.2%)	11 (68.8%)
Female	0 (0.0%)	19 (32.2%)	28 (35.4%)	7 (36.8%)	9 (69.2%)	8 (61.5)	15 (45.5%)	19 (38.8%)	5 (31.3%)
Data Unavailable	0 (0.0%)	2 (3.4%)	2 (2.5%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	7 (21.2%)	1 (2.0%)	0 (0.0%)
Outcome									
Death	2 (40.0%)	16 (27.1%)	31 (39.2%)	10 (52.6%)	2 (15.4%)	3 (23.1%)	3 (9.1%)	8 (16.3%)	9 (56.3%)
Disability	0 (0.0%)	3 (5.1%)	3 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.1%)	0 (0.0%)
Hospitalization - Initial or Prolonged	4 (80.0%)	49 (83.1%)	62 (78.5%)	16 (84.2%)	11 (84.6%)	5 (38.5%)	20 (60.6%)	41 (83.7%)	14 (87.5%)
Life-Threatening	2 (40.0%)	16 (27.1%)	17 (21.5%)	1 (5.3%)	8 (61.5%)	0 (0.0%)	5 (15.2%)	14 (28.6%)	1 (6.3%)
Other Serious (Important Medical Event)	5 (100.0%)	58 (98.3%)	72 (91.1%)	14 (73.7%)	1 (7.7%)	12 (92.3%)	30 (90.9%)	48 (98.0%)	12 (75.0%)

10.3389/fphar.2024.1413154

TABLE 2 Sensitivity analysis of TLS associated with drug of interest ("encorafenib and binimetinib") and with all other drugs in the FAERS database.

	Corrected for drugrelated competition bias, N0/N1, IC (95% CI)	Corrected for suspect drugs and reports from healthcare professionals, N0/N1, IC (95% CI)	Corrected for TLS (SMQ), N0/N1, IC (95% CI)	Corrected for preexisting disease, N0/N1, IC (95% CI)	Signal consistency/robustness
pembrolizumab	4/5,439 0.59 (−1.17–1.67)	1/4,206 −0.69 (−4.48–1.00)	264/4,206 6.77 (6.57–6.92)	1/4,199 −0.69 (−4.47–1.00)	Weak (1/4)
nivolumab	47/15,040 2.69 (2.20–3.03)	39/13,199 2.60 (2.06–2.98)	946/13,199 7.18 (7.07–7.26)	39/13,165 2.60 (2.07–2.98)	Strong (4/4)
ipilimumab	58/15,322 2.96 (2.53–3.28)	55/13,122 3.09 (2.65–3.41)	948/13,122 7.19 (7.08–7.27)	55/13,110 3.10 (2.65–3.42)	Strong (4/4)
dabrafenib	10/9,427 1.13 (0.05–1.85)	15/7,036 2.06 (1.19–2.66)	544/7,036 7.19 (7.05–7.30)	15/7,012 2.06 (1.19–2.67)	Strong (4/4)
vemurafenib	3/5,547 0.21 (−1.86–1.41)	10/6,678 1.56 (0.49–2.29)	667/6,678 7.55 (7.43–7.65)	10/6,642 1.57 (0.49–2.30)	Intermediate (3/4)
dacarbazine	5/495 2.92 (1.36–3.91)	10/592 3.77 (2.69–4.49)	53/592 6.12 (5.66–6.44)	10/592 3.77 (2.69–4.49)	Strong (4/4)
encorafenib + binimetinib	24/2,413 3.93 (3.25–4.41)	12/578 4.03 (3.05–4.70)	117/578 7.26 (6.96–7.49)	12/566 4.04 (30.6–4.71)	Strong (4/4)
nivolumab + ipilimumab	37/8,569 3.09 (2.54–3.48)	9/2077 2.71 (1.57–3.47)	224/2077 7.27 (7.05–7.43)	9/2073 2.73 (1.58–3.48)	Strong (4/4)
dabrafenib + trametinib	7/8,610 0.76 (−0.54–1.61)	9/2,370 2.58 (1.45–3.25)	297/2,370 7.55 (7.36–7.69)	9/2,350 2.59 (1.45–3.25)	Intermediate (3/4)

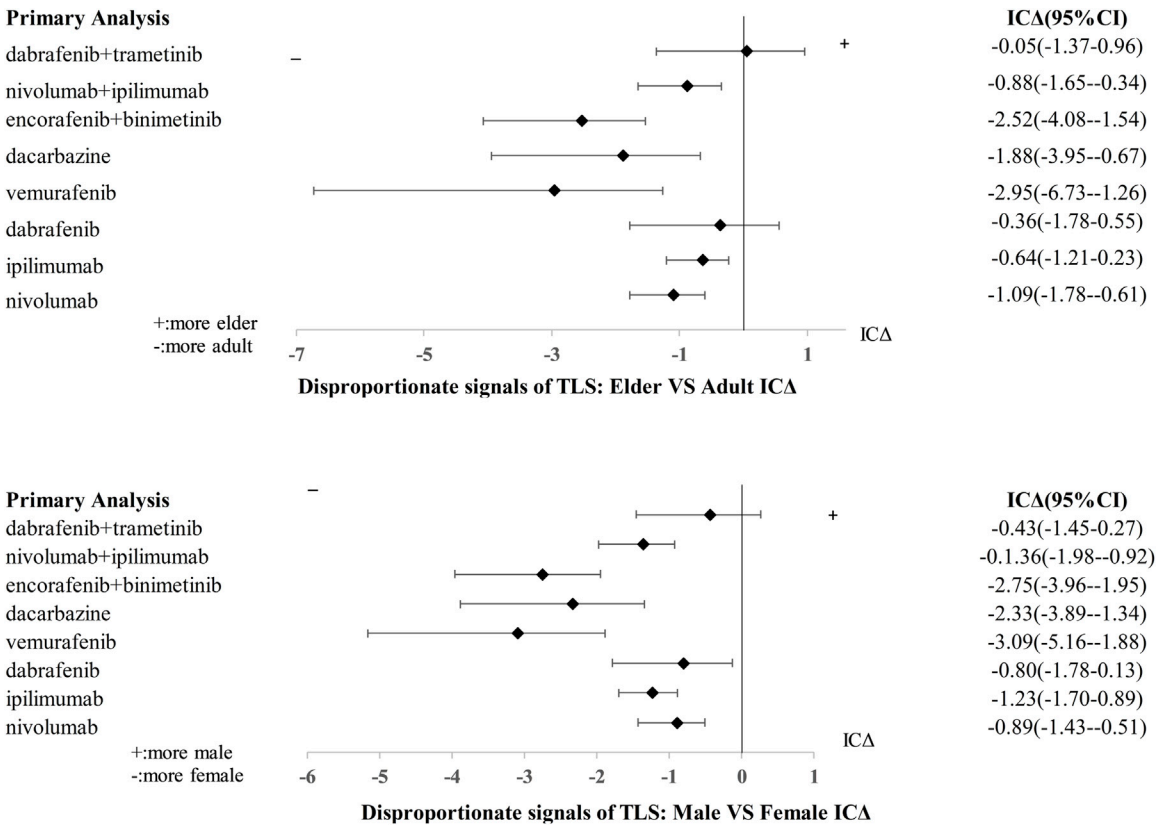


FIGURE 3
Subgroup analyses (age and sex) of TLS signals with different anti-cancer drugs.

TABLE 3 Time-to-onset analysis of TLS associated with anti-cancer drugs for MM in the FAERS database.

Categories	Binimetinib	Dabrafenib	Encorafenib	Ipilimumab	Nivolumab
Reports of TLS	19	18	19	54	41
Median days	2.0	2.0	2.0	21.5	22.0
Scale parameter α (95% CI)	1.10 (0.19–2.01)	0.97 (0.68–1.25)	0.97 (0.68–1.25)	30.79 (22.50–41.62)	30.60 (23.48–39.37)
Shape parameter β (95% CI)	0.85 (0.51–1.85)	0.60 (0.45–0.85)	0.60 (0.45–0.85)	0.93 (0.75–1.14)	1.28 (0.98–1.64)

α, scale parameter, represents the scale of the distribution function as the quantile in which 63.2% of AEs, occur. β, shape parameter, could be used to confirm. the distribution type: early failure type (β < 1), random failure type (95% CI, of β include 1), and wear-out type (β > 1).
95% CI, 95% confidence interval; AEs, adverse events; FAERS, US, food and drug administration adverse event reporting system; TLS, tumor lysis syndrome.

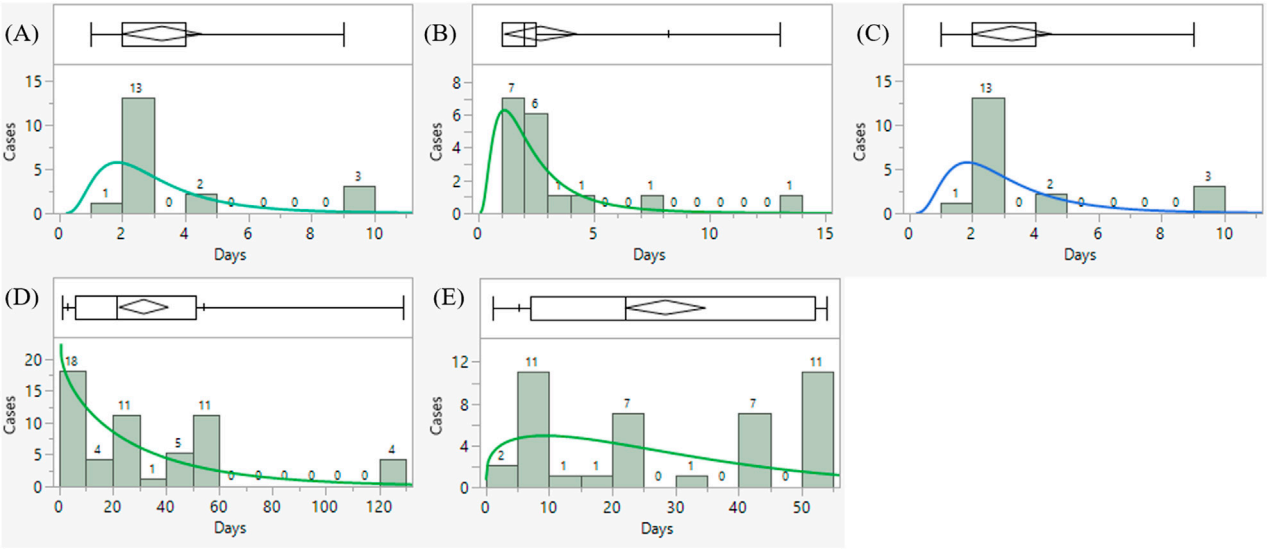


FIGURE 4
Time to onset analysis of tumor lysis syndrome associated with **(A)** binimetinib **(B)** dabrafenib **(C)** encorafenib **(D)** ipilimumab **(E)** nivolumab in the FAERS database (choose the best model after goodness-fit distribution test).

4 Discussion

This is the first pharmacovigilance study to investigate the disproportionate signals of TLS with the combination of encorafenib and binimetinib for the treatment of MM. We have identified three new key findings that provided additional information to the safe administration of the combination of encorafenib and binitenib in the treatment of malignant melanoma.

First, by exploring the FAERS database and performing a disproportionality analysis, we found that the disproportionate signals between TLS and two combinational therapies ("encorafenib and binimetinib", "nivolumab and ipilimumab") were strong, and much higher than other drugs in the FAERS database, including other anticancer drugs for the treatment of malignant melanoma. We verified the robustness of the signals through four sensitivity analyses to exclude confounding factors such as drug competition, exposure bias, and information bias. Our data suggested that the combination of encorafenib and binimetinib may significantly increase the signal of TLS compared to other anticancer drugs (e.g., chemotherapy or targeted therapy). Of note, 33 TLS cases with the combination of encorafenib and binimetinib were reported from 2019 to 2023, which showed a rapidly increasing reporting of TLS with this combination therapy. Previous research (Wang et al., 2021) already reported that the combination of nivolumab plus ipilimumab had higher TLS signals compared to monotherapy, which was consistent with our study. In the time-scan analysis (Figure 2), TLS signals with nivolumab, ipilimumab, nivolumab plus ipilimumab became insignificant in 2022. But TLS signals with the combination of encorafenib and binimetinib kept robust from 2019 to 2023. And the following sentences were added into the end of second paragraph of the discussion: "Considering that TLS have some typical symptoms, such as raised creatinine, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia and renal impairment. We compared the disproportionate signals of all preferred terms within the Standardised MedDRA Queries (SMQ, broad) associated with different regimens for the treatment of MM. We found that the combination of encorafenib and binimetinib had higher disproportionate signals of blood creatinine increased, hyperkalaemia and renal impairment compared to other regimens (Supplementary File S5). This is consistent with the disproportionate signal of TLS.

Second, we found that the combination of "encorafenib and binimetinib" had a shorter onset time than "nivolumab and

TABLE 4 Global assessment through adapted Bradford Hill Criteria.

Criteria	Description	Source/method
Strength of the association	Although IC is not a measure of risk, it shows a strong disproportionate signal in the disproportionate signal analysis	Disproportionate reporting of TLS with "encorafenib and binimetinib" in the FAERS database
Analogy	Other anti-cancer drugs (such as venetoclax) have also demonstrated this association	Literature
Biological plausibility/ empirical evidence	Not applicable	Not applicable
Consistency	Published two case reports studies support the potential association of TLS with "encorafenib and binimetinib"	Literature
Exclusion of biases/ confounders	The statistical disproportionality persisted and was strong after sensitivity analysis, excluding the influence of confounders	Disproportionality
Specificity	This study did not detect significant TLS signals with other two BRAF/MEK combinations (dabrafenib plus trametinib, or cobimetinib plus vemurafenib). A drug-specific effect (rather than a class-effect) was considered	Disproportionality
Temporal relationship	All TLS events with "encorafenib and binimetinib" manifested after the suspected drug was administered in both the pharmacovigilance analysis and published case reports	Time-to-onset analysis and literature
Reversibility	This criterion is of limited value here as there is no data on discontinuation and dechallenge in the FAERS database	Not applicable
Coherence	The reasoning about cause and effect as present in the aforementioned criteria	Literature

FAERS, US, food and drug administration adverse event reporting system; IC, information components; TLS, tumor lysis syndrome.
These items were not included in the original Bradford Hill Criteria.

ipilimumab" (median days, 2.0 days vs. 22.0 days). By searching the website of Drugbank, we found that the mean terminal half-life (t1/2) of binimetinib, encorafenib, nivolumab and is 3.5 h (28.5%), 3.5 h (17%), 20 days and 14.7 days, respectively. This may partly explain the difference of TLS latency between "encorafenib and binimetinib" and "nivolumab and ipilimumab".

Both "encorafenib and binimetinib" and "nivolumab and ipilimumab" have strong disproportionate signals of TLS, the shorter onset time of TLS with "encorafenib and binimetinib" is of great concern to patients and clinicians. Because encorafenib and binimetinib are orally administered while nivolumab and ipilimumab are intravenous injection. It would be more difficult to manage if TLS occur when patients orally administer the combination of encorafenib and binimetinib at home.

Third, through subgroup analysis, we found that people aged 25–65 years who were treated with "encolafenib and binimetinib" were more likely to have TLS compared with other age groups. Previous research (Guy et al., 2015) showed that the peak incidence of MM is around the age of 50. This may partly explain the difference of TLS signals in different ages. This study also identified that females were more likely to develop TLS with the co-treatement of encolafenib and binimetinib. Previous literature (Ji et al., 2013; Blum et al., 2011) showed that female gender was the most influential of all risk factors identified for TLS occurrence after flavopiridol treatment with an OR of 8.6 (95% CI: 2.6–27.7) because females displaying higher flavo-G exposure than males. According to the FDA approved drug labels, encorafenib is primarily metabolized by CYP3A4 (83%) and to a lesser extent by CYP2C19 (16%) and CYP2D6 (1%). The primary metabolic pathway is glucuronidation with UGT1A1 contributing up to 61% of the binimetinib metabolism. Males and females may have different metabolism capacity on encorafenib and binimetinib, which may affect the clearance of encorafenib and binimetinib in the body. This may partly explain the higher disproportionate signals of TLS in females. Further studies are needed to investigate the influence of age and gender on the occurrence of TLS associated with the combination of encorafenib and binimetinib. Further research is warranted to verify our findings.

This study has some limitations (Noguchi et al., 2021). Firstly, the reports in the FAERS database are heterogeneous (from both healthcare professionals and non-health care professionals), which may affect the quality of data. Secondly, reports from the FAERS could not provide more clinical information (for example, the stages of MM), which may affect the disproportionate signals. Thirdly, there is under-reporting bias, channel bias in the data from FAERS (Faillie, 2019). Therefore, it is suggested that future studies should use more comprehensive data sources, including clinical trials and observational studies, to further validate our findings.

5 Conclusions

In this study, we conducted a pharmacovigilance study on tumor lysis syndrome signaling in anticancer drug therapy for MM based on the FAERS database. The study found that among the treatments for MM, the commonly used treatment method—"encorafenib and binimetinib" is prone to tumor lysis syndrome (TLS)-related adverse reactions. Moreover, in focused analysis after excluding confounding factors, we not only corroborated this finding but also identified that the TLS onset time of "encorafenib and binimetinib (2.0 days)" was shorter than that of "nivolumab (22.0 days) and ipilimumab (21.5 days)". Subgroup analyses revealed that middle-aged patients, particularly women, are more likely to experience TLS when taking the combination of encorafenib and binimetinib. TLS is known to be a

serious complication associated with anticancer therapy. This study outlines the TLS profiles for common MM drugs for improved safety in clinical practice. TLS related indicators should be closely monitored in patients receiving anticancer therapy, and timely and effective interventions should be taken to reduce the risk of TLS. In addition, future studies should further explore the pathogenesis and prevention strategies of TLS to improve the quality of life and prognosis of patients.

Data availability statement

All data are publicly available on the website of AERSMine, a curated FAERS database: https://research.cchmc.org/aers/.

Ethics statement

No institutional ethics approval was required because this study utilized anonymized data from an open-access database. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board also waived the requirement of written informed consent for participation from the participants or the participants legal guardians/next of kin because data were collected from a publicly available database and do not require written informed consent.

Author contributions

SX: Writing–original draft, Writing–review and editing, Data curation, Formal Analysis. J-WX: Writing–original draft, Writing–review and editing, Data curation, Formal Analysis. K-XY: Writing–review and editing. YN: Writing–review and editing. MS: Writing–review and editing, Software. MY: Conceptualization, Funding acquisition, Resources, 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. The Hunan Natural Science Funds for Distinguished Young Scholars (No. 2022JJ10097). The Hunan Province Degree and Graduate Education Reform Research Project supported by Education Bureau of Hunan Province (2023JGYB041). The Central South University Education and Teaching Reform Research Project (2022jy166).

Acknowledgments

We appreciate the help of Prof. Emanuel Raschi. He put forward many useful advice to help us further improve 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1413154/full#supplementary-material

SUPPLEMENTARY FILE S1
Calculation methods of ROR, IC and IC delta.

SUPPLEMENTARY FILE S2
Raw data of subgroup analysis.

SUPPLEMENTARY FILE S3
Raw data of time to onset analysis.

SUPPLEMENTARY FILE S4
Fit of goodness results for parametric models in time-to-onset analsis.

SUPPLEMENTARY FILE S5
The disproportionate signals of all PT terms within the "tumour lysis syndrome" SMQ (broad) with different drug therapies for the treatment of malignant melanoma.

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frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 13 September 2024
DOI 10.3389/fphar.2024.1426777

OPEN ACCESS

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RECEIVED 02 May 2024
ACCEPTED 28 August 2024
PUBLISHED 13 September 2024

CITATION
Jin R, Liu C, Chen J, Cui M, Xu B, Yuan P and Chen L (2024) Exploring medication self-management in polypharmacy: a qualitative systematic review of patients and healthcare providers perspectives.
Front. Pharmacol. 15:1426777.
doi: 10.3389/fphar.2024.1426777

Exploring medication self-management in polypharmacy: a qualitative systematic review of patients and healthcare providers perspectives

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Purpose: Polypharmacy presents many challenges to patient medication self-management. This study aims to explore the self-management processes of medication in polypharmacy from the perspectives of both patients and healthcare providers, which can help identify barriers and facilitators to effective management.

Methods: A systematic review of qualitative studies was performed by searching seven databases: PubMed, Web of Science, Cochrane Library, Embase, CINAHL, PsycINFO, and MEDLINE, from their establishment until August 2024. The Critical Appraisal Skills Programme (CASP) tool was employed to evaluate the quality of the studies included. The extracted data were then analysed thematically and integrated into The Taxonomy of Everyday Self-management Strategies (TEDSS) framework.

Results: A total of 16 studies were included, involving 403 patients and 119 healthcare providers. Patient management measures were mapped into TEDSS framework, including categories such as medical management, support-oriented domains, and emotional and role management.

Conclusion: Enhancing patients' proactive health awareness, improving medication literacy, balancing lifestyle adjustments with medication therapy, dynamically reviewing and optimizing medications, strengthening patients' social support networks, and helping patients integrate medication management into their daily life are the key elements that can effectively assist patients in self-managing their medications. Future interventions to improve patient medication self-management ability should be designed for these issues.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42024524742.

KEYWORDS

polypharmacy, self-management, health system, qualitative, systematic review

1 Introduction

Polypharmacy, often defined as the use of multiple medications, has become increasingly prevalent worldwide and is now a significant public health concern (Donaldson et al., 2017). Factors such as the aging population, the rising burden of chronic diseases, and advancements in medical technology and diagnostic capabilities have led to a growing reliance on multiple medications in daily treatment regimens (elara et al., 2022). Globally, the prevalence of polypharmacy in the general population is approximately 37%, with higher rates observed in older individuals at 45% (Kim et al., 2024). Though polypharmacy is often defined as the use of five or more medications (Varghese et al., 2024; Nicholson et al., 2024), there is no consensus on its exact definition (Masnoon et al., 2017). The World Health Organization emphasizes that beyond numerical definitions, the focus should be on evidence-based practices to reduce inappropriate polypharmacy (Varghese et al., 2024).

Appropriate polypharmacy is crucial for managing complex health conditions, but inappropriate polypharmacy, characterized by the use of unnecessary or potentially harmful medications, can lead to significant adverse outcomes (Hoel et al., 2021). As the number of medications used increases, the risk of drug-related problems grows almost exponentially, including drug-drug and drug-disease interactions, adverse drug reactions, and potentially inappropriate medications (Wastesson et al., 2018). Healthcare systems often lack shared records, leading to patients receiving duplicate or interacting prescriptions from multiple providers, and sometimes additional medications to treat adverse reactions caused by other medications (Wang X. et al., 2023). The use of multiple medications also increases the risk of adverse drug events, such as falls (Roitto et al., 2023), weakness (Palmer et al., 2019), cognitive, physical, and emotional dysfunctions (Khezrian et al., 2019), and even rehospitalization (Prasad et al., 2024) and death (Chang et al., 2020), imposing a significant cost burden on healthcare systems (Hoel et al., 2021). Besides, The increase in the number of medications is associated with low medication management ability (Wastesson et al., 2018). The complexity of managing multiple medications, especially with different dosing schedules or special storage conditions (Albert et al., 2022), can lead to reduced medication literacy (Wang W. et al., 2023) and difficulty in self-management. The high economic cost of medications can be a barrier, particularly for those without adequate insurance coverage (Holbrook et al., 2021). The psychological stress from side effects or fear of interactions, as well as social pressures such as disrupted social schedules and social stigma, can also lead to patients skipping doses or stopping medication (Widyakusuma et al., 2023), resulting in incorrect usage, affecting the effectiveness of treatment.

Medication self-management is a complex and crucial process that involves a range of services aimed at improving clinical outcomes. These services include completing medication reviews and health assessments, monitoring treatment plans and the effectiveness and safety of therapies, as well as providing education and promoting self-management. This process goes beyond simple medication adherence (Cadel et al., 2021). Self-management encompasses three domains: medical, emotional, and role management (Lorig and Holman, 2003). Through extensive conceptual reviews and interviews with patients suffering from neurological disorders, Audulv et al. (Audulv et al., 2019) developed the Taxonomy of Everyday Self-management Strategies (TEDSS) framework. This framework aims to provide a structured understanding of the strategies patients use to manage their health in daily life. The TEDSS framework consists of five goal-oriented domains (internal, social interaction, activities, health behavior, and disease controlling) and two additional support-oriented domains (process and resource). These domains correspond to the traditional concepts of medical, emotional, and role management in self-management.

To meet a broader range of self-management needs, Cadel et al. (Cadel et al., 2020) refined the TEDSS framework based on analyses of attitudes and experiences of medication self-management among patients with spinal cord injuries and healthcare providers. These adjustments categorized the framework into medical management (disease controlling strategies and health behavior strategies), support-oriented domains (process strategies and resource strategies), and emotional and role management (activities strategies, internal strategies, and social interaction strategies). These refinements allow researchers to more comprehensively capture the diverse methods patients use to manage their medications in daily life. For instance, disease controlling strategies and health behavior strategies help patients effectively manage chronic conditions. Process strategies and resource strategies focus on how patients obtain and utilize necessary resources and implement these strategies. Additionally, activities strategies, internal strategies, and social interaction strategies address how patients fulfill their social roles, manage emotions, and engage in social interactions in their daily lives. This comprehensive framework helps to reveal the actual challenges and needs in patients medication self-management, providing healthcare providers with valuable insights to offer more targeted and supportive care.

In recent years, the phenomenon of polypharmacy has garnered widespread attention, and some qualitative studies on medication self-management have been conducted. However, the results of single qualitative studies can not comprehensively and accurately reflect the medication self-management in polypharmacy. Although some studies have synthesized the medication self-management experiences of polypharmacy among patients, these results tend to focus more on medical management, less on other aspects of self-management, and lacking the perspective of healthcare providers (Eriksen et al., 2020). As medication self-management research evolves, reviews need to be updated to better guide clinical practice. Therefore, the purpose of this systematic review is to utilize the TEDSS framework to gain an in-depth understanding of the barriers and facilitators influencing medication self-management, considering the perspectives of both patients and healthcare providers. The results of this comprehensive study may provide valuable information for designing and effectively implementing medication self-management interventions for patients with polypharmacy, potentially improving patients quality of life and reducing the burden of medication.

2 Methods

2.1 Study design

We adopted a systematic review as it allows for an in-depth understanding of multiple study outcomes, facilitates the formation

of novel theoretical or conceptual models, and provides substantiation for the creation, implementation, and evaluation of health interventions (Tong et al., 2012). This review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number CRD42024524742.

2.2 Search strategy

The search was carried out across seven databases, including PubMed, Web of Science, Cochrane Library, Embase, CINAHL, PsycINFO, and MEDLINE. The search period ranged from the establishment of each database to August 2024. Based on our research objectives, we identified relevant search terms for three key concepts: polypharmacy, self-management, and qualitative research. We used a search strategy that combined medical subject headings (MeSH) and free-text terms, with adaptations tailored to the characteristics of each database. The detailed search strategy for the databases is provided in Supplementary Appendix S1.

2.3 Inclusion and exclusion criteria

Following the principles of the SPIDER tool (Sample, Phenomenon of Interest, Design, Evaluation, Research type), we devised a sensitive and comprehensive search strategy (Methley et al., 2014). The samples included patients with multimorbidity and polypharmacy, as well as healthcare providers; Studies that focused solely on patient experiences or solely on healthcare provider experiences were also considered. We defined multimorbidity as the coexistence of two or more chronic diseases and polypharmacy as the use of five or more medications. The phenomenon of interest was the attitudes and experiences of patients who manage their medication regimens within the context of daily life and healthcare providers who implement interventions to promote patient medication self-management; The study design included ethnography, grounded theory, phenomenology, or narrative research; The evaluation consisted of patients' and healthcare providers' attitudes and experiences towards medication self-management; and the type of study was qualitative.

Studies were excluded if (1) patients were in the terminal stage of illness and receiving palliative care or had cognitive impairment, as they were unlikely to reflect the wider population's attitudes and experiences of medication self-management in daily life; (2) the type of study was reviews, case studies, editorials, conference abstracts, commentaries, or research protocols; (3) the full text of the study was not available; or (4) English was not the language of publication for the original research report.

2.4 Study selection

The studies retrieved in this research were imported into Endnote X9, and duplicate articles were removed. Two authors (RJ and CYL) independently screened the titles, abstracts, and full texts based on the inclusion and exclusion criteria to obtain the final included studies. Any disagreement was evaluated by another author (LC) and discussed to reach a consensus. The detailed flowchart is illustrated in Figure 1.

2.5 Data extraction and synthesis

Two authors (RJ and CYL) independently evaluated and extracted key data from each eligible study, including information on authors, year of publication, country, study aim, participants, number of medications, data collection and analysis methods, conceptual or theoretical framework, and main findings. The findings were used in a deductive process into the TEDSS framework, which is the framework thematic synthesis approach (Brunton et al., 2020). Participant citations from 16 eligible studies were imported into NVivo 14 software. These citations were coded by two authors (RJ and CYL) independently to develop a mutual understanding of the coding framework and themes. Any disagreements or uncertainties were evaluated by the full research team and discussed to reach a consensus.

2.6 Quality appraisal

This study assessed the methodological quality of the included studies using the Critical Appraisal Skills Programme (CASP) qualitative checklist (Eriksen et al., 2020). Two authors (RJ and CYL) independently conducted the assessment, and no studies were excluded based on methodological quality. Besides, the same two authors independently used the 'Confidence in the Evidence from Reviews of Qualitative research' (GRADE-CERQual) approach (Lewin et al., 2015) to assess the confidence in each finding. Disagreements were discussed and resolved with another author (LC) to reach a consensus.

2.7 Theoretical framework

As previously described, the findings of this study are related to the TEDSS framework (Cadel et al., 2020). The TEDSS framework, originally created by Audulv et al. (Audulv et al., 2019) for more general self-management, was adapted to comprehensively capture the diverse methods patients use to manage their medications in daily life and to reveal the actual challenges and needs in medication self-management. The improved TEDSS framework includes three domains: medical management (disease controlling strategies and health behavior strategies), support-oriented domains (process strategies and resource strategies), and emotion and role management (activities strategies, internal strategies, and social interaction strategies). In the Results section, we provide detailed explanations for each topic.

2.8 Rigour, trustworthiness, and reflexivity

We analysed quotes from participants to provide detailed explanations of the topic. Our team, consisting of academic

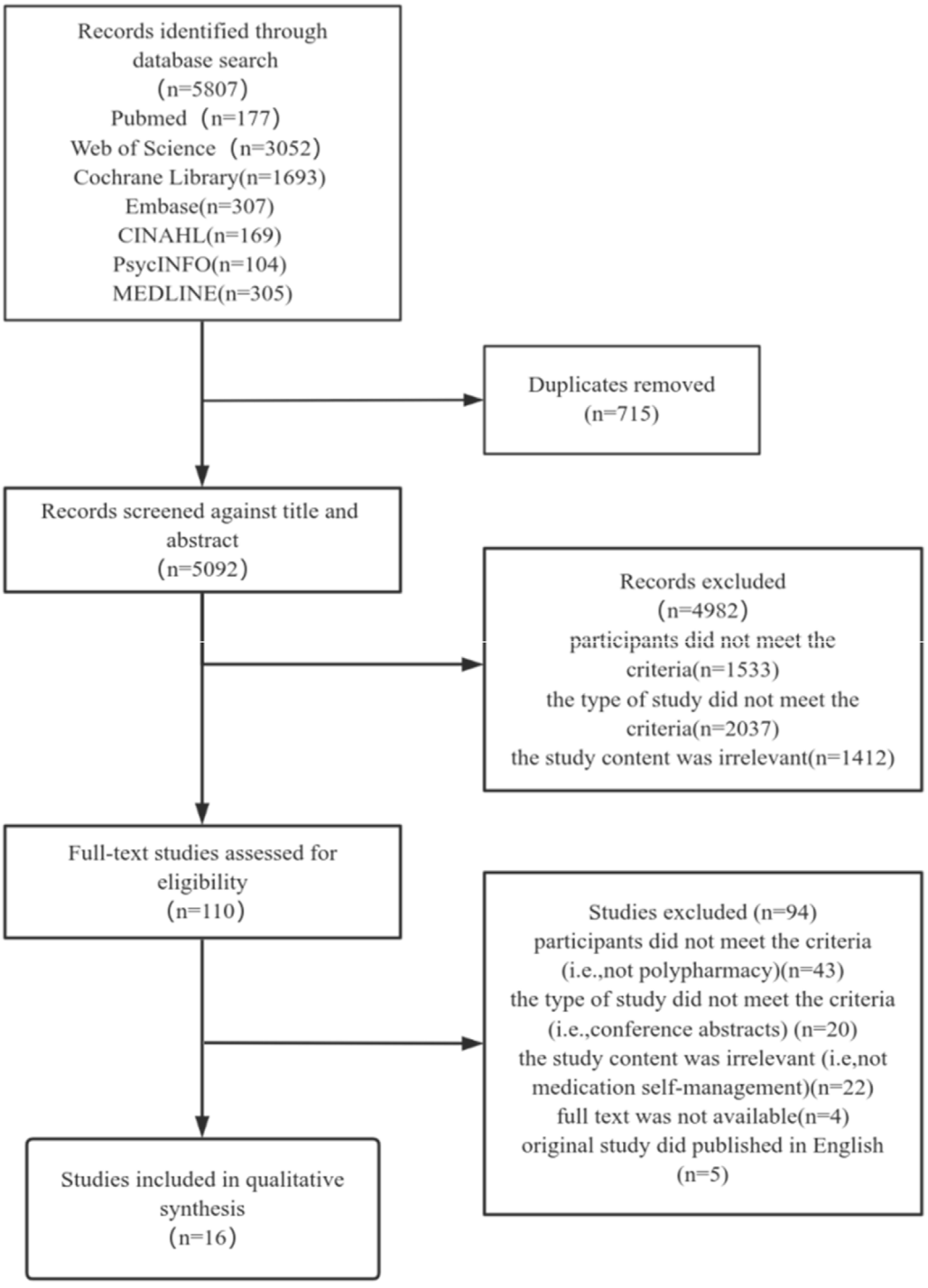

FIGURE 1
PRISMA flow diagram of the literature screening.

nurses, research assistants, and clinical experts trained in qualitative methods, spans different academic career stages and cultural backgrounds. This diversity significantly aids in reducing personal biases during the processes of literature screening, quality assessing, and result interpreting. Additionally, to address and resolve any disagreements, the team held regular meetings throughout the study. The authors (CYL, JHC, MJC, BX, PY, and LC) have extensive research experience and have previously published systematic reviews. BX, LC, and PY are clinical experts with rich clinical practice experience in promoting patient medication self-management. This review, part of a master's thesis, explored the barriers and facilitators to medication self-management in patients with polypharmacy, providing theoretical support and practical guidance for the development of interventions. Additionally, seven participants, including four patients and three healthcare providers (HCPs), reviewed the

TABLE 1 Study characteristics.

Author/ (year) Country	Study aim	Participants	Medication numbers	Data collection method (DC) and analysis (DA)	Conceptual/ Theoretical framework	Main findings
(Holmqvist et al., 2019) Sweden	explore and describe older persons' experiences of evaluation of their medication treatment	20 community-dwelling older persons (age 75–91 years)	mean (range): 12.7 (6-26)	DC: semi-structured interviews DA: inductive qualitative content analysis	the medication use model	Theme 1: Own role in the evaluation Theme 2: Views of evaluation received
(Fried et al., 2008) United States	examine the ways in which older persons with multiple conditions think about potentially competing outcomes in order to gain insight into how processes to elicit values regarding these outcomes can be grounded in the patient's perspective	66 participants aged 65 years and older	median (range): 7 (5-14)	DC: focus groups DA: constant comparison method	NA	Theme 1: Recognition of competing outcomes Theme 2: Understanding of the likelihood of outcomes Theme 3: Disease-specific versus global outcomes
(Schöpf et al., 2018) Germany	explore elderly patients' and general practitioners' (GPs') perceptions of communication about polypharmacy, medication safety and approaches for empowerment	6 patients at least 65 years old with polypharmacy; 3 GPs (general practitioners)	mean ± SD: 8.2 ± 2.6	DC: semi-structured interviews DA: a framework analytical approach	NA	Theme 1: differing medication plans: causes? Theme 2: dialogue concerning medication: whose responsibility? Theme 3: supporting patients' engagement: how?
(Tudball et al., 2015) Australia	how consumers residing in Australia experience and manage their multiple medicines while travelling	35 community dwelling participants, most aged over 50 years	range: 5-25	DC: face-to-face, narrative interviews DA: constant comparative method	NA	Theme 1: Planning for the trip Theme 2: Organising and packing medicines for the trip Theme 3: Maintaining usual routines while travelling Theme 4: Travelling overseas
(Williams et al., 2005) United Kingdom	explore attitudes and practices to medication regimens among patients already in receipt of multiple medications, and to assess whether a combined tablet would be perceived as advantageous	92 men and women aged >40 years	range: ≥6	DC: focus groups DA: a framework analytical approach	NA	Theme 1: Daily drug routines Theme 2: Problems with regimens Theme 3: Attitudes to a combined pill
(Hannum et al., 2021) United States	understand clinical team members' perceived barriers to medication safety in preparing older patients to return home and to identify potential redesign strategies that reduce ADEs throughout the transition	37 clinical team members representing 10 different professional roles involved in providing transitional care	NA	DC: semi-structured interviews DA: thematic analyses	Systems Engineering Initiative for Patient Safety (SEIPS)2.0 framework	Theme 1: Streamlining and coordinating clinical management of medication regimens across care settings to better prepare patients for the transition to home Theme 2: Building patient capacity and engagement in self-managing medications at home

(Continued on following page)

TABLE 1 (*Continued*) Study characteristics.

Author/ (year) Country	Study aim	Participants	Medication numbers	Data collection method (DC) and analysis (DA)	Conceptual/ Theoretical framework	Main findings
						Theme 3: Redesigning the transitional process to be more patient centered
(Cossart et al., 2022) Australia	examine medication-taking behaviors of kidney transplant recipients transplanted at 60 years of age or older	14 older adult kidney transplant recipients	median (min–max): 13 (10–26)	DC: semi-structured interviews DA: thematic analyses	The Theory of Planned Behaviour	Theme 1: Perceived Health Literacy Toward Medicines Theme 2: Support Networks Theme 3: Adjusting Health Expectations Theme 4: Motivators for Self-Care Theme 5: Medication Management Theme 6: Approaches to Medication Taking
(Previdoli et al., 2024) United Kingdom	examine in depth how older people with mild to moderate frailty manage their polypharmacy regimens at home	32 patients aged 65 years or older with mild or moderate frailty and taking five or more medicines	range: 5-15	DC: semi-structured interviews DA: reflexive thematic analysis	resilient healthcare framework	Theme 1: Managing many medicines is a skilled job I did not apply for Theme 2: Medicines keep me going, but what happened to my life? Theme 3: Managing many medicines in an unclear system Theme 4: the support with medicines I value and that makes my work easier Theme 5: My medicines are very familiar to me. There is nothing else I need (or want) to know or worry about
(Foley et al., 2022) Ireland	explore the experience of self-managing multimorbidity among older adults, with a focus on medication adherence	16 people with complex multimorbidity aged 65 years or older	mean (range): 13.2 (9-18)	DC: individual semi-structured interviews DA: reflexive thematic analysis	NA	Theme 1: Amplified burden Theme 2: Pathways towards relief
(Guilcher et al., 2019) Canada	explore healthcare providers' conceptualization of factors impacting medication adherence for persons with SCI/D	32 healthcare providers with varying clinical expertise	NA	DC: individual semi-structured telephone interviews DA: constant comparative	ecological model of medication adherence	Theme 1: Micro-level factors Theme 2: Meso-level factors Theme 3: Macro-level factors
(Vatcharavongvan and Puttawanchai, 2022) Thailand	explore how older patients with polypharmacy manage medications at home in a primary care unit (PCU)	19 patients (mean age = 69 years)	median (range): 6 (5-10)	DC: in-depth semi-structured interviews and observations DA: thematic content analysis	NA	Theme 1: Medication storage system Theme 2: Factors affecting medication adherence
(Hernandez, 2017) United States	explore the personalized meanings study participants ascribed to the experience of	15 NPs (nurse practitioners) with self-identified as caring for	NA	DC: narrative inquiry DA: thematic analysis	The metaphorical three-dimensional narrative inquiry space	Theme 1: Mastering the art of the puzzle Theme 2: It takes a village

(Continued on following page)

TABLE 1 (*Continued*) Study characteristics.

Author/ (year) Country	Study aim	Participants	Medication numbers	Data collection method (DC) and analysis (DA)	Conceptual/ Theoretical framework	Main findings
	managing polypharmacy in practice	geriatric patients taking multiple medications				Theme 3: Power in knowledge
(Dijkstra et al., 2022) Netherlands	explore how older people living at home self-manage their medication and what considerations and decisions underpin their medication self-management behaviour	60 patients with a median age of 86.5 (IQR 78–89)	median (IQR): 8 (6-11)	DC: semi-structured interviews DA: content analysis with a directed approach	three phases of medication self-management (initiation execution, and discontinuation)	Theme 1: The initiation phase Theme 2: The execution phase Theme 3: The discontinuation phase
(Vandermause et al., 2016) United States	examine the experiences of older adults with multiple chronic medical conditions when a new medication was added to their existing multiple medication regimen	15 patients aged 60 years and older, 5 or more medications plus a new prescription and 3 chronic medical diagnoses	mean ± SD: 11.9 ± 4.4	DC: In-depth hermeneutic interviews DA: hermeneutical analysis and content analysis	NA	Theme 1: Preserving Self: Living With Chronic Conditions and Being With Healthcare Providers Theme 2: Engaging Providers in Visioning Health
(Guilcher et al., 2020) Canada	explore the experiences of healthcare and service providers supporting medication therapy management	32 healthcare and service providers	NA	DC: semi-structured interviews DA: constant comparative analysis	NA	Theme 1: Professional contribution to medication therapy management Theme 2: medication therapy management barriers and enablers
(Jallow et al., 2024) United States	explore medication safety strategies used by community dwelling older adults aged 65 years and older who took five or more prescription medications	9 residents from the retirement community and 19 patients from 2 clinics with a median age of 75	mean ± SD: 7.7 ± 2.5	DC: semi-structured interviews DA: deductive thematic analysis	Systems Engineering Initiative for Patient Safety (SEIPS) 2.0 model	Theme 1: Collaborating With Prescribers Theme 2: Collaborating With Pharmacists Theme 3: Learning About Medications Theme 4: Safe Practices at Home

integrated themes and their recommendations were included in the determination of the final themes.

3 Results

3.1 Search results and study characteristics

A total of 5,807 records were identified. After removing duplicates and screening the titles and abstracts, 5,697 studies were excluded. At full text assessment, 16 studies were included. The study flowchart is shown in Figure 1.

Five studies were conducted in the United States, two studies each in the United Kingdom, Australia, and Canada, and one study each in Sweden, Germany, Ireland, Thailand, and Netherlands. A total of 403 patients and 119 HCPs were included. The data collection method was mainly interviews, twelve studies used interviews, one study combined interviews with observations, while two studies used focus groups and one study used narrative inquiry. Methodological analysis was mainly thematic analysis, six studies used this method, while four studies used constant comparison method, three studies used content analysis, two studies used framework analysis and one used hermeneutical analysis and content analysis. Table 1 shows the specific details of the 16 studies included.

3.2 Quality of studies included

The CASP tool assessment indicates that most of these studies (n = 12) demonstrate minor to moderate methodological limitations. These studies articulate clear objectives and employ qualitative methodologies appropriately and all of the studies put a clear statement of findings and were of value. While these studies

TABLE 2 Key supporting quotes.

Theme	Subtheme	Supporting quotes
Medical Management	Disease Controlling Strategies	"I have an idea of what each shape is. I knowm water pill is a little, pink pill. My blood pressure, is a long blue pill."
		"I do not have a printed medication list, but I have photos of the plastic pouches [of the MDD system] in my mobile phone. I always have my mobile phone and thus information of my medications. When I go to a physician, I show him the photo."
		"I fit something else that I can take that the insurance would cover, and it's the same medicine, maybe a generic or something, then I will see if they will prescribe that one instead of the one I have to pay out of pocket for that's more than what I can afford."
		"If they're not getting their refills or if they're not coming back on a regular basis, that's something that you do have to monitor or that's something that would signify that [the medication is] not working." (HCP)
		"So there are high-risk medications that we as case managers go. We need to make sure everything's onboard with this, that they're getting what they need to be done, like the levels done. Are they doing what they're supposed to be doing to make sure that the medication's effective for them? make sure that they're going to a clinic to get their blood tested. " (HCP)
		"I do not know where I can find an expiratory date, but I normally finish the remaining medications before taking newly received medications. I do not want to waste the medications."
		" [I kept medications] in a drawer. [Some] are hung on a bed because I believe the room is not hot and moist. Some medications should not be kept in a hot and moist room, should they? I organize them all myself. A doctor told me to keep them in a dry and cool location. "
		"Well, I suppose you need a few spatial skills to make sure you put them [medicines] in the right [compartment of the compliance aid], I mean and you need to understand the ones that are morning, and the ones that are evening. And I think you need to concentrate as well. "
		"So I always check the colors of the pills before I take the pills. I use eight pills, six white pills, a pink one and a yellow one. But that pill, the color has been changed, the pill was yellow but now it is white. I get confused because my system tells me to take six white pills each day."
		"... sometimes I fall asleep during the day. So, I have medications for 12 o'clock, but when I sleep at that time and wake up at let's say 12.30 o'clock, it is too late to take it. Someone told me to not take the medications when the intake moment has passed, so I do not take the pills."
		" [For] traumatic accidents, spinal cord injury and brain injury can go hand-in-hand [individuals with brain injuries sometimes have] difficulty remembering to take their medications [and might be] less likely to take their medications . . . forget to take [their medications or] think it does not matter if they take [their medications]." (HCP)
		"Well, they have said that it is good if you can stay under ten [blood sugar] One day we had nineteen and I understand that it is not good."
		"I have been trying to convince my doctor that I do not need the cholesterol medication any longer, because it has zapped me of my strength, and it is debilitating."
		"Because I know that when I got blood pressure medications then, then the doctor said 'If there is anything that you feel then, that you have not felt before, because you are taking this medication, you will have to let us know' But I have never felt that."
		"My neighbor has diabetes. Once his medications ran out. He asked me for medications. I had plenty of them, so I gave him ten packages approximately 100 pills. He was delighted and thanked me for the medication."
		"I throw it in the garbage bin. The medications will be disposed of in the garbage bin in the pharmacy, so I may do that at home as well."
	Health Behavior Strategies	"... so I've noticed that there is one medication, and I forgot the name, but it is one that they have to take and they're not able to eat their meal after. And one of the things that impacts them taking that one on a regular basis is that they have to wait a certain amount of time before they're able to eat and I think it's like 2 hours or so. So, I guess the activities that they have to conform to, or the conditions while taking their medication." (HCP)

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TABLE 2 (*Continued*) Key supporting quotes.

Theme	Subtheme	Supporting quotes
		"I worked hard on my diet-kept track."
		"I would like to be a bit more active. I would like to get this all over, and feel this is not a burden anymore, I'd like to get back to my routine. I used to get up every morning and walk on a treadmill. I used to clean up the backyard."
Support-Oriented Domains	Process Strategies	"But he did not say anything last Friday. So it is happy and pleased. It must be."
		"... whether they actually see a benefit or not and sometimes with some medications, it's clear that you see benefits. For instance, if you take your medications for spasticity, then you really see it. But sometimes if you actually prescribe something that they do not necessarily see the direct benefits, then it's hard for them to be compliant unless they really understand what that's for." (HCP)
		"Expectations are a big thing. Specifically, like if they are taking something for a medication like a pain medication where you can see the results or you're expecting a change and you are able to notice that, it's a lot different than if you're treating like hypertension where, you know, they cannot really see the results and so, the expectations of what they are going to get out of the medication." (HCP)
		"More medicines means older and a declining condition, whether or not it's true."
		"I want to get off, reduce the Xanax that I'm taking, but that's for the stress and everything that I've just been through. So I have not done that because I've tried like breaking the pill in half, and my stomach is just rolling. So i take the other half and it settles down. But eventually, I will get off of it."
		"I just did nae like taking them cos in case I had side effects or that but I would nae take tablets, aspirin or anything. I would rather go about with a sore head until it cleared itself but nowadays. (laughing)"
		"Well for the amount I have to take, I do not know about these guys, but I take quite an amount of tablets, and do they not fight against one another? I mean is there not chemicals in one that's going to be fighting against another?"
		"... they want to know more and they want to be educated more, but sometimes where they get their education, their resources are not, are not appropriate sites." (HCP)
		"So, if you do not know why you are taking something, it's very difficult to think, 'okay, well I need to take this." (HCP)
		"... do not usually include patients with spinal cord injuries. So, it's hard to know if there needs to be any adjustments made for them because the data is not there." (HCP)
		"... you know, recognizing that for the average primary care practitioner, they are going to have a very small number of these people and so, to expect that they, by themselves, can maintain a level of clinical expertise necessary or appropriate to the complexity or the specifics of the type of health problems and medication issues that spinal cord patient experience, I think that's not reasonable." (HCP)
		"... because I'm not like primarily focused on the SCI patients, I do not know that much about specifics that should be addressed. So, I probably do not provide education that might be more specific or tailored to them just because I'm unaware of that information and where to find it." (HCP)
		"Yeah, it was overwhelming. And it was like in one ear and out the other. I could not concentrate on what they [doctors] were saying."
		"I can't read the text, the letters are too small. My daughter in law reads aloud the leaflets for me."
		"I tell the doctor that my back hurts. He says, okay, take this. I say, what's it for? He says, it helps with the pain. I say, okay, thank you. I take the medicine [ask no further questions]."
		"They'll send an information sheet, and so I read that very thoroughly. If I have any questions about it, I'll ask my doctor when I see him."
		"I think it's probably easier taking the lot together. Yeah. Because if you were taking them in ones I'd say you'd be forgetting them half the time. you'd be missing them."

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TABLE 2 (*Continued*) Key supporting quotes.

Theme	Subtheme	Supporting quotes
		"... the [medication] for the thyroid. This one I would like to leave out. The daughter has said: Just do not take them. Then I said: I know, I have already taken that for years. And leaving them out, I do not know. I will talk to the GP, that at least one or two."
		"I made the decision to stop taking statin because I feel better. Living is more important. if you said to me, right you can have pain free now for the next year and a really nice time and then you will die, I would say, I'll take it."
		"I had terrible trouble because if you take your tablets at 8 o'clock in the morning, at 8 o'clock at night you do not know where you're going to be anyway, and I'd be in bed and I'd think, oh, forgot my tablet. Soit was the chemist actually, who was going through them, and he said: You can have one that you just take once a day. So, that makes that a lot easier for me, because it's just once a day."
		"I think number one [for medication adherence] would be like the frequency. So, I think people can take things once a day, but I think you are really pushing it when you are asking them to take things twice and three times a day. The other thing that I find is like the actual volume of pills. So, when I can I will also look for opportunities to combine medications so that there would be less pill burden." (HCP)
		"The longer the person has [the] injury, the more insight they have into their body and you have to give credit. I could say once they are, you know, more medically stable, you really need to listen to them and listen to how they want to live their life and how you can complement their life with the medication to control the spasms, to control the pain at the right time so that they can have a meaningful life." (HCP)
	Resource Strategies	"I know nothing about this. I mean, you have to bow to the knowledge that the doctor has. You got to believe that, in some way, it helps."
		"No, but I have a little in me that they know what to do. I trust them."
		"I remember all medications because I take them every day. I know which medications have to be taken before a meal in the morning, and I take them before breakfast."
		"We're navigators in trying to help them to keep their things in order, but we do not want to do it for them. We want to make them as independent as possible. So I'll sit there and say, Okay, now, take the paper he gave you and okay, he made that change. Now take that pill and put it in a box and let me see you. Because we want them to do it and not us do it for them." (HCP)
		"... like to be involved in the decision making and I think if you involve them, they are actually probably more likely to accept the therapy and be adherent." (HCP)
		"I think it's important to understand what the medications are for, and you know, things, things that they could cause. And I just find it interesting."
		"My vision and hearing are not that good. I cannot read labels. My niece writes instructions in big letters. Sometimes, she reads the labels. She tells me to take these medications after breakfast. I need her help. She does not organize them every day. Medications from PCU are put in baskets. one for morning and the other for the evening."
		"I just think that the young ones, the children or whoever takes care of you, should influence you. I know that from my daughters, who say: Now you are going to the doctor and also tell him that and so on. Perhaps that is less the case with some people who are totally alone or so on. So, one sometimes needs a bit of a push. (laughing)"
		"... now that I got this plan from the doctor's office on how they intended to do it. It is the first time they have reported what they have been thinking. And how they have planned to manage it."
		"Yes, but it's as different as night and day [to see the same physician instead of different ones] because then you can just pick up where you left off instead of having to go over everything from the beginning, everything that has happened and so on."

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TABLE 2 (*Continued*) Key supporting quotes.

Theme	Subtheme	Supporting quotes
		"... she said 'You should take this pill' and I had no idea what it was. She could have sat down [bedside] and said that this one is for this and that and so on, they do not have time for that."
		"If you go and take blood tests, then you ought, at least, to get some kind of result, one would think. Because the doctor, he gets the test results, but I do not."
		" [I have not had a review] for the last 2 years, because you cannot see a GP. You cannot get to speak to anybody."
		"If you feel put off by somebody, you're not going to feel free to ask questions or ask them to do something for you. But the one, the pharmacy I'm going to now, they are very good about talking to me about my medicines and will answer any question that I might have."
		" [Caregivers] may get confused and give the wrong [medications]." (HCP)
		"It is so important for the patient's family, or significant other, or significant friend, to be aware of the geriatric patient. Be aware and notice if the patient is unable to put medications in order or take them every day." (HCP)
		" [creating a] family atmosphere [with the patient and their caregivers to create] this background bond . . . [so they] do not feel scared to be honest with you." (HCP)
		"With this population, if it's the inability of them sometimes to maybe get into the pharmacy so that they are not getting the one-on-one counselling, so they can fall through the cracks. So, someone, you know, everybody just assumes it's easier just to keep sending the medication [medication delivery] versus anyone going out having the discussion with them about it are big barriers [to supporting patients with SCI/D with their medications]." (HCP)
		"I rely on either the specialist provider and reach out to them if I've got questions or our local pharmacist who can also access other pharmacists, for instance, who might be in particular clinics where they are providing care to a lot of spinal cord patients." (HCP)
		"... we have support through PCVC (personal computer video conferencing) support that they do not have to necessarily come in in-person or virtual visits." (HCP)
		"You trust a patient who can accurately tell their medications more than one who reads it from a list and then the list is changed three times because of a doctor or another doctor or a nurse." (HCP)
		"The time of the doctors, for example, patient has 10, 20 medications. The nurses, they do not have really time. You will see if you will audit not all patient is done the [medication reconciliation], or sometimes the patient does not know and the family does not know or they're not a [hospital] patient, so they will not know." (HCP)
Emotional and Role Management	Activities Strategies	"I place the pills beside the toothbrush. It reminds me every morning and evening to take the pills."
		"So no matter where I go I'd always make sure that the tablets, they'd be the definite the one thing I would never go without are my medication."
		"I will get it open and leave it open, and that's the way I know I've taken it."
		"And I cannot remember what it was, but something was going on and the [alarm] went off, and I thought, 'I must take those tablets' I think somebody was here. And so, I sort of said 'Oh they're going to go in a minute, I'll take them as soon as they're gone' and, and they did not go!"
		"And you know, you carry your bag wherever you go. So you know if you sit down. if you go out and you have lunch out, you know that you've got to take your pill at lunchtime."
		"You have to have, well I had little tricks to prompt me. It used to be feed the cat, take my warfarin, pour a glass of wine. see then, if there was a night when we did not have a wine, I'd forget my tablets."
		"I find it's the best way. So when I get them in the chemist they have them in, do you know these blister packs? So they're all in the one. So I take them all then together."

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TABLE 2 (*Continued*) Key supporting quotes.

Theme	Subtheme	Supporting quotes
		"... well I had capsules, it's not for high blood pressure it's for acid and eh you know they're in silver-backed and you're to try and get the corner and pull them and I cannot, they're annoying for me God knows what they'd be like for an 80-year-old."
		"The last time I travelled, I actually ran out of medication, which was terrifying, I realised that I was about to run out of it about a week before I was going to run out. So I then worked out a routine, where I reduced the dosage to one-quarter of what I'd been taking and took that every day, instead of taking what I should have been taking."
		"I went to Tamworth and was supposed to only be there for the day. The job went wrong and I was there for 3 days. I went to a doctor, he would not prescribe the medication. I went to the emergency room at the hospital. Because of the lithium, they then referred me to mental health and a psychiatrist came down. But it took about four and a half hours out of my day to actually go and do that."
		"I'm going away for 8 weeks next year. So I've already checked online the websites for the embassies, consulates, whatever, for the different countries I'm going to, to find out what I can take in; what I need to have a letter from my doctor about; whether I need to have everything in the packaging it came in. I'm checking whether certain over the counter medications or alternatives are available in the countries that I'm going to, so that I do not have to travel with so much."
	Internal Strategies	"I cannot stop taking these medications. Sugar and blood pressure go up and down all the time. Without medications, I cannot control them."
		"I like it [organising and managing my medicines], I really like doing it, you know, it makes me feel good that I'm capable and I can do it and I know why."
		"That becomes a problem particularly on a plane where you have to get up into the overhead lockers, get your bag out, get them out. People look at you, ask for a glass of water and take them and then it becomes awkward with the Novo-Pens. You roll the pen in your hand one way and roll it in the other way and then shake it up and down and then test it to see that it's coming out. You look like you're taking a major drug lot. Then you put it in and do it. That is an effort in a plane."
		"Well to be honest with you, if I had a choice I would prefer not to have to be taking the medication at all, do you know. But with my conditions, like, I do have no choice."
	Social Interaction Strategies	"There's no colour, race, anything. It's just everybody's a big family. It is, it really is. I've met some beautiful people."
		"I've got another friend, whose daughter had a double lung transplant many years ago, so again, she understands completely what's going on with me. If you're talking to somebody who knows exactly what you're talking about, it does make a difference."

10.3389/fphar.2024.1426777

except one overlooked the relationship between researcher and participants. Additional information can be found in Supplementary Appendix S2.

3.3 Confidence in review findings

The GRADE-CERQual approach assessment indicates that the majority of the finding statements demonstrate moderate or high confidence. Additional information can be found in Supplementary Appendix S3.

3.4 Findings

From the 16 studies included, we extracted 320 citations and categorized them using the TEDSS model to describe the self-management of medication. Following and Table 2 are some of the key exemplary citations.

3.4.1 Theme 1 medical management (77/320)

3.4.1.1 Subtheme 1: disease controlling strategies (71/320)

In disease controlling strategies, close collaboration between patients and healthcare providers is essential to enhance patients' ability to self-manage their medications and effectively control the disease in combination with non-pharmacological treatment. This involves the patient's understanding and consent to use the medication, timely acquisition and replenishment of medication, careful review and verification of medication, proper storage of medication, correct medication usage, and continuous monitoring and managing the medication efficacy and side effects, as well as the appropriate handling of leftover medication.

3.4.1.1.1 Understanding and consent to medication use

Patients typically obtain medication information through education from healthcare providers or medication lists, leading to their understanding and consent to use the medication. However, some patients may be reluctant to learn about the details of their medications, only remembering the shape and color, and relying entirely on healthcare providers for prescriptions. This can hinder their ability to participate in decision-making. Additionally, some patients may stop taking medication due to an overemphasis on side effects, which can reduce adherence. Therefore, healthcare providers should ensure that patients are fully informed about their medications to enhance their ability to manage them effectively.

> "When I pick up the prescription, I'll do like any normal person, I'll read the instructions for taking the medication. When you get the medication, they tell you all about it. They give you a sheet." (Jallow et al., 2024)

> "Yeah no, well I do not even consider that [when asked about understanding each different medicine]. I've got to take them. That's it. Full stop . . . You know, I have not got the knowledge about the pills so . . . so in other words, I'm trusting that they're giving me the right stuff and I'll go with that." (Cossart et al., 2022)

> "Miconazole (vaginal) cream, no I will not use it. I have read the patient information leaflet and I am scared of getting side effects." (Dijkstra et al., 2022)

> "I mean, sometimes they need all those medications, but they're understanding of what their medicines are and they're understanding of how to take them, why they take them, and what they're for, is really lost. They do not have good insight into what they're taking." (HCP) (Hannum et al., 2021)

3.4.1.1.2 Timely acquisition and replenishment of medication

Most patients recognize the importance of timely acquisition and replenishment of medication. Patients often use methods like taking photos of their medications or keeping personal records to provide a medication history. However, some may hide parts of their medication history (such as over-the-counter medications) or rely entirely on the healthcare system, which can lead to incomplete or inaccurate medication records, especially when interacting with different healthcare systems. Additionally, some patients prefer to use medications with lower out-of-pocket costs. Healthcare providers should assess patients' medication acquisition practices to evaluate their management abilities, and consider the costs involved, such as transportation and time, and explore innovative ways to reduce these costs.

> "One thing is you always have to kind of make sure you're going to have your prescription and get it in on time and have your tablets, There's that to taking all this medication." (Foley et al., 2022)

> "I do not bring a medication list with me to the physician, because all information about my medication is in their computer." (Dijkstra et al., 2022)

> "I would say with the elderly population they're on very limited incomes, so we have to be really mindful of that, and many times they'll come in here and we'll tweak their medications change it just a bit. Very confusing to an elderly person." (HCP) (Hannum et al., 2021)

3.4.1.1.3 Careful review and verification of medication

The dual communication between healthcare providers reviewing medications and patients verifying them is crucial for achieving optimal treatment outcomes and reducing inappropriate polypharmacy. However, some patients rely entirely on healthcare providers without verifying their medications, and may even take expired drugs. Some patients, having experienced medication errors, placed greater emphasis on verifying their medications.

> "Our pharmacy technicians right now are assisting with getting appropriate medication lists. So sometimes at the discharge point, the provider realizes that the medication list is wrong, and they're trying to send out the right medication list, and so they want to make sure they have the old and the new to compare and write a good instruction sheet for the patient. Because if you do not tell them what to stop and you just tell them to start, they have some conflicting information. So our technicians help with

> that and they'll [also] help to get those medications filled at our outpatient pharmacy for them, and then bring them to the bedside. So they leave with the meds in hand." (HCP) (Hannum et al., 2021)

> "No, I do not check the medications [interviewer: 'No, you do not check the correctness?']. No, the pharmacy sends the medications and then well I assume that the medications are correct." (Dijkstra et al., 2022)

> "Once, I received the wrong medication by the pharmacy; since then, I always check the correctness." (Dijkstra et al., 2022)

> "I never take expiration dates into account, and I did not know that the dates are described on the medication packages." (Dijkstra et al., 2022)

3.4.1.1.4 Proper storage of medication

Medications that are not stored according to recommended temperature, light, and humidity conditions, or that are not properly kept in their original packaging, can have reduced therapeutic effectiveness. Many patients are unaware of the correct storage methods, or they prioritize convenience over proper storage, neglecting the necessary conditions. Additionally, healthcare providers often do not provide detailed instructions on proper storage. It is also crucial to remind patients to keep medications out of reach of pets and children.

> "I do not know where I have to store the medications. I do not know anything about rules. I store all pills of my wife, so the MDD system (including furosemide, metoformine, sotalol, spironolactone, and enalapril maleate, [interviewer's note]) and the other medications (tiotrus tiotropium, [interviewer's note]), in the fridge. For me it is a logical place, so I store all the medications in the same place." (Dijkstra et al., 2022)

> "I keep medications in the bedroom and hang some on a bookshelf. Medications taken in the morning are kept in the kitchen both before and after a meal. There is a dining table there in the kitchen." (Vatcharavongvan and Puttawanchai, 2022)

> "My role is to take it regularly and [make sure] she [cat, does not] get into my medicine. I have to keep it out of sight." (Jallow et al., 2024)

3.4.1.1.5 Correct medication usage

Taking medications as prescribed is crucial for effective disease management. Healthcare providers note that some patients may intentionally or unintentionally not adhere to medication due to physical disabilities or cognitive misunderstandings. Additionally, some patients may be unsure about the correct way to take their medications, or what to do if they miss a dose. Others may self-administer over-the-counter medications to supplement their treatment without considering potential drug interactions, which can pose risks. Therefore, it is important to provide personalized assessment and guidance to these patients.

> "I do not know the rules, I stir all pills in a glass of water and when they are mixed, I drink the water." (Dijkstra et al., 2022)

> "I did not know there could be interactions between my medications of my physicians and the OTC medications. I do not ask the pharmacist or the seller of OTC medications if it is safe for me to use it." (Dijkstra et al., 2022)

> "[I focus on improving] fine motor skills to pick up pills physically opening pill boxes." (HCP) (Guilcher et al., 2019)

3.4.1.1.6 Monitoring and managing medication efficacy and side effects

Patients with polypharmacy often suffer from several chronic conditions, necessitating close attention to continuous monitoring and managing medication efficacy and side effects. This allows for dynamic adjustments to medications based on the patient's symptoms. It is important to note that some patients, particularly the elderly, may not recognize side effects, while others may have misconceptions about side effects, leading them to stop or alter their medications on their own. To address this, healthcare providers should inform patients in advance about potential side effects and encourage open communication to facilitate dynamic medication adjustments as needed.

> "But they will keep track on me for five years now, with two blood samples every year. To see how it is then." (Holmqvist et al., 2019)

> "That is when, if you get side effects. Or you cannot notice it. That one has received ... too much? ... And one does not know. ... Side effects, it may be so different with that. Because you may feel slightly strange. It may be for other reasons. ... So, it's not given that it's the drugs either. That bothers me so." (Holmqvist et al., 2019)

> "If you have side effects, you do not have a choice. You just stop taking the medication because it could lead to something else happening." (Fried et al., 2008)

> "Well, often [the] side effects most people get are expected and a normal consequence, like if someone's on gabapentin for neuropathic pain, and they feel some fatigue within the first few days, I will ask them - I will reassure them that that's expected and it will likely improve. If it does not, then I'm willing to make a dose adjustment, change medications or stop that therapy altogether." (HCP) (Guilcher et al., 2020)

3.4.1.1.7 Appropriate handling leftover medication

It is important to address how patients store leftover medication. Some patients keep unused medications for future use but often neglect to check details such as expiration dates, which can lead to adverse outcomes. Additionally, some patients may share their medications with others without proper guidance, potentially resulting in serious consequences.

> "I used to share metformin with my nephew, and he got severe diarrhea. After that, I never shared medications with anyone again." (Vatcharavongvan and Puttawanchai, 2022)

> "I use remaining medications first. I do not look at an expiratory date. [I look at] the date I received the medications and use the older ones first." (Vatcharavongvan and Puttawanchai, 2022)

3.4.1.1.8 Combing non-pharmacological treatment

In addition to medication treatment, healthcare providers also recommend assessing the patient's condition and considering their preferences to incorporate non-pharmacological treatments, such as acupuncture, to improve symptoms.

> "So, not even just medications based, but things like acupuncture, other kind of techniques that can be done. So, I think that something like pain is a very difficult problem to solve and we should be trying as many different things as we can." (HCP) (Guilcher et al., 2020)

3.4.1.2 Subtheme 2: health behavior strategies (6/320)

In health behavior strategies, patients should actively adjust their lifestyle to enhance the effectiveness of medication and maximize health benefits. Some patients need to be aware of the potential interactions between medications and food, adjusting their dietary habits to align with medication timing and mitigate risks. Regular exercise is also important for improving physical condition and mood, which can, in turn, enhance the effectiveness of medications. Additionally, maintaining a positive mindset and seeking psychological support can further strengthen patients' management capabilities. Proper sleep management is essential to reduce stress and fatigue during the treatment process. Although these adjustments may cause inconvenience or impatience for patients, they are crucial for managing and improving health and supporting the overall effectiveness of medication. Healthcare providers should offer personalized recommendations based on the individual needs of each patient.

> "Yeah, I keep moving, I keep doing you know, doing what I have to do. And going, going for a walk, I think that really helps. I'm sure, I'm absolutely certain exercise makes me feel better but yeah I, I, I feel quite tired." (Cossart et al., 2022)

> "... because we have to be at the pathology and then the clinic, you know by half past six in the morning, every single day for nearly a month it's like, you just spend your whole time trying to work yourself out. You're really not mentally capable of taking in anymore." (Cossart et al., 2022)

> "You have to take it first thing in the morning, you have to stand up or at least sit upright, you cannot eat or drink for half an hour after you've done it, half an hour to an hour, and you have to be careful." (Previdoli et al., 2024)

3.4.2 Theme 2: support-oriented domains (185/320)

3.4.2.1 Subtheme 1: process strategies (97/320)

In process strategies, patients need to develop proper belief of medication use, identify and address any abnormalities during the medication process, and optimize their medication strategies by acquiring accurate information. Healthcare providers should ensure that the medication plans they develop and implement align with the overall treatment goals and consider the patient's needs for medication adjustment and optimization to achieve the best possible treatment outcomes.

3.4.2.1.1 Developing proper medication belief

Many patients may adjust or even stop their medication on their own due to a lack of understanding of the medication's mechanism, concerns about or experiences with side effects, not perceiving significant benefits, believing they have improved when symptoms lessen, resistance to long-term medication use, or due to the cost of medications. Additionally, some patients do not proactively monitor their health and rely entirely on healthcare providers, which can hinder effective treatment and potentially worsen their condition. This underscores the importance of the need for patients to establish proper medication belief.

> "For a while, I thought I would just cut my pill in half because I live away from the pharmacist." (Jallow et al., 2024)

> "I'm worried now what have I. What's the cause of this, you know? And is it that the medications need to be changed to accommodate what's wrong with me?" (Foley et al., 2022)

> "I do not use the furosemide anymore. I do not have any problems with urinating anymore. I did not ask the physician if I could stop using the medications." (Dijkstra et al., 2022)

> "If there is anything that is wrong. Then, they will contact you. At once. Therefore, I trust that." (Holmqvist et al., 2019)

> "If the injury is minor then it's not totally affecting their daily life, they may only use the medication when things get a little worse. Even though they may be supposed to take it on a daily basis. If it's not bothering them, they may not [take it]. Yeah, so the less severe the injury is, the more prone, they are to not adhering, essentially." (HCP) (Guilcher et al., 2019)

3.4.2.1.2 Acquiring accurate medication information

Healthcare providers, especially primary care providers, need further education to recognize reliable information sources and enhance their knowledge base through multidisciplinary collaboration. Utilizing community resources and strengthening coordination among healthcare providers is essential to offer patients accurate information. When providing education, it is important to consider the patient's cultural background and needs, selecting appropriate methods of instruction. Additionally, helping patients gain more social support and encouraging family involvement in managing the patient's treatment are crucial.

> "I think my role as a nurse practitioner impacting the identification and management of polypharmacy in the geriatric population is really on a community level. I think my impact is really on providing the community, patients, students, and other disciplines [information] about Beers Criteria, aging and the toll on the body, and education." (HCP) (Hernandez, 2017)

> "I have to explain in detail. And I tell them, 'The paper that you have from our hospital, that's the one I'm going to be teaching you on.' And then sometimes we get into this struggle with patients because they'll say, 'Well, I just saw my doctor yesterday or two weeks ago and he put me on medication [for fluid retention],' which is a fluid pill. 'He put me on that and now you guys tell me to stop it, so what do I do?' I'm like, 'Well, go by the most recent summary, which is what we - what I'm going over is they want you to stop it. But now, however, you need to see your primary care right away.'" (HCP) (Hannum et al., 2021)

> "Maybe it's the educational level of the person. If it's really, really, rudimentary level then it's a little bit - can be a little bit tough, you know, to reinforce certain ideas." (HCP) (Guilcher et al., 2020)

> "I think it would help to have, obviously more social support for these patients through case management and social work." (HCP) (Hannum et al., 2021)

Some patients obtain medication information through various channels such as medication lists, package inserts, consultations with doctors or friends, and the internet. However, when being educated, patients may encounter information overload or incorrect information, leading to omissions or misunderstandings. Additionally, some patients do not actively seek information and make decisions on their own, or they may have misconceptions about the medication, which can negatively impact the safety and effectiveness of their treatment.

> "I read about them. I just google them. Any time I get a new medicine, like headache medicine, I google it, and I find out what it does, what you can take with it or what you cannot take with it." (Jallow et al., 2024)

> "I prepared a medicine list, and I listed what I was concerned about health-wise for me [to ask the provider during visits]." (Jallow et al., 2024)

> "Yes, some things one remembers, but it can be like stuffing too much information in, so to say. When you sit and go through a list like this, you know, and you concentrate, there may be something that gets lost, you know." (Holmqvist et al., 2019)

> "I do not ask no questions because I figure the doctor knows what he's doing." (Schöpf et al., 2018)

3.4.2.1.3 Rational medication adjustment and optimization

Many patients wish to adjust their current medication regimens, seeking to control their condition with fewer doses or fewer types of medication. However, they have concerns about the potential risks of such adjustments and therefore desire comprehensive medication review and optimization. Some patients suggest using combination medications to reduce the complexity of management, but this approach may also pose challenges in monitoring and making necessary adjustments.

> "I do sometimes wish I were not taking as many tablets, but while ever it's keeping me going, I'll take them. [laughs] Is the side effects better than, you know, what you're taking them for? That sort of thing goes through me head sometimes." (Previdoli et al., 2024)

> "Do you know when you're years on a tablet too I think it's, it was time to assess them. That's my belief anyway. I was years going in there and it was the same ding dong, get a prescription, give him a prescription, and you take them and there were some of them now, some of them were bad anyway. I was too long on them anyway." (Foley et al., 2022)

> "Well perhaps, I've heard talk about maybe where you're on two or three different tablets getting a tablet that contains, one tablet that contains the three drugs that you're on. That would make matters easier for a lot of people, especially people that are on these drugs because they are long term so they're not going to change very often. So that's one way that would help." (Williams et al., 2005)

> "I do not honestly think so because there are different heart tablets and different cholesterol tablets and it is difficult enough to find the one that suits you rather than suddenly finding that they put two together and you cannot find one that suits you. If they were asking for a recommendation then I would say no." (Williams et al., 2005)

Healthcare providers should align with the patient's treatment goals, encouraging active participation in the decision-making process. They should comprehensively weigh the benefits and risks of medication adjustments and conduct dynamic medication reviews. Additionally, healthcare providers should enhance coordination and communication among themselves to optimize medication use, avoid inappropriate prescriptions, and ensure that patients receive the safest and most effective treatment plan.

> "I think in the longer term it probably also, depends on the patients' goals for themselves and whether they start valuing quality of care over quantity, or yeah, quality of life versus quantity of life, especially if their condition is starting to deteriorate. Sometimes they may not want to continue certain medications because of their long terms goals." (HCP) (Guilcher et al., 2019)

> "... in terms of I guess how inconvenient it is like if it's something they were taking every four hours, you kind of have to stop whatever you're doing to take the medication versus if you can give them something that's long-acting that you only take twice a day." (HCP) (Guilcher et al., 2019)

> "Later on now in my career, I've taken on a different type of feeling about my approach. I understand that managing polypharmacy is an art as much as it is a science. You have to balance quality of life, risks and benefits, when prescribing medications to the older adult. I do not feel the need to fix everything." (HCP) (Hernandez, 2017)

> "It's not cut and dry. I will identify patients with polypharmacy, but at the same time going through all of the medications and why they were put on the medication is such a web. You see that someone is on medications for legitimate issues, heart problems, high blood pressure, but then you have to step back and look at are we treating symptoms of other medications. Did you go to the urologist for incontinence because of the diuretic you were placed on for your blood pressure? It's a scenario that gets repeated a lot." (HCP) (Hernandez, 2017)

3.4.2.2 Subtheme 2: resource strategies (88/320)

In resource strategies, patients need to actively exercise their initiative by expressing their needs and participating in medical decision-making to ensure that their preferences and requirements are fully considered. Additionally, patients should develop the ability to identify and effectively utilize social support networks, which can aid them in making more informed decisions during complex treatment processes. This approach ensures that their medication management is closely aligned with their personal treatment goals, ultimately leading to the best possible treatment outcomes.

3.4.2.2.1 Exercising initiative

Most patients are able to exercise their initiative, actively participating in the treatment process to maintain a level of autonomy. Healthcare providers also emphasize the importance of patients having a proactive health mindset, strengthening their management capabilities through improved communication and involvement in decision-making. However, some patients tend to adopt a passive approach, being reluctant or unable to actively engage in the treatment process, thereby not fully realizing their self-management potential.

> "Yes, as I was about to say. The responsibility must be mine almost. That I alert them if it would fail." (Holmqvist et al., 2019)

> "I have no problem, it's a very simple operation. I've never questioned with my GP as to whether it should change, I'm in the hands of the professionals." (Previdoli et al., 2024)

> "A lot of patients, particularly the older-old have a mentality of I just do whatever my provider tells me. They do not question the different specialties adding other medicines. It is up to me in primary care to be the gate keeper and inform the patient and their families." (HCP) (Hernandez, 2017)

3.4.2.2.2 Utilizing social support networks

Social support networks refer to the collection of social relationships and resources that individuals can rely on in their daily lives. In the context of medication management, patients can enhance their self-management capabilities by effectively utilizing these networks to gain emotional support, informational assistance, and practical help. However, some patients may face challenges when leveraging social support networks, such as concerns about burdening caregivers, not receiving thorough evaluation or accurate information support, and experiencing a lack of coordinated communication.

> "Thankfully, I had my daughter. She came in every day. And she was in on all the conversations [about how to pack and take medicines]." (Cossart et al., 2022)

> "When I have a problem, for example a side effect, then I go to the general practitioner." (Dijkstra et al., 2022)

> "I do not want my son to help me because I can do it myself. I do not want to disturb him." (Vatcharavongvan and Puttawanchai, 2022)

> "I asked the doctor on my recent visit 'Aren't you going to check my bones' I said. However 'No,' she said, 'they had not said anything from there [the hospital]'. You know, when you get old, they withdraw all such assessments." (Holmqvist et al., 2019)

> "I'm finding that difficult. It's between three lots, both consultants and the surgery and, yeah, and it's difficult for them because, you know, it's changing each time, and I phone the surgery and say, 'I know my prescription needs to change because I was told that at the consultation', and they say, 'No, we have not got a letter from them, we cannot change it'." (Previdoli et al., 2024)

Healthcare providers should assess patients' social support networks, identifying existing resources and potential gaps, and provide targeted assistance to help patients build and strengthen these networks. This could involve establishing trust, collaborating with community resources, promoting multidisciplinary cooperation, enhancing coordination, and innovating support delivery methods. Additionally, by offering education and training, the capacity and knowledge of caregivers can be improved, ensuring they are able to effectively support the patient's treatment process and ultimately enhance the patient's treatment outcomes.

> "... it can be you know, very overwhelming, I find. Particularly affecting sort of you know, sort of my clients who are males and they're in their 30s, 40s even 50s who [prior to] their spinal cord injury had, you know, little to no interaction with the healthcare system. And now, you know have major healthcare needs. I find, you know for a lot of them, they kind of struggle in the beginning in terms of wrapping their head around it. I find for people who have been connected with the healthcare system longer, it's sort of not as jarring." (HCP) (Guilcher et al., 2019)

> "Polypharmacy always gets sticky. I think mismanagement of pharmaceuticals is the main problem that most of my patients encounter. I think it takes a very skilled clinician to be able to piece everything together; piece all the specialists' work together; piece all the transitions of care together." (HCP) (Hernandez, 2017)

> "And sometimes it's important to address their non or informal caregivers on motivational speaking. The patient may be depressed, for example, or they may be unwilling to take their medication, in which case it is important for people in

> their life to help them stay motivated in order to adhere to the optimum medication therapy regimen." (HCP) (Guilcher et al., 2019)

3.4.3 Theme 3: emotional and role management (58/320)

3.4.3.1 Subtheme 1: activities strategies (24/320)

In activities strategies, patients need to integrate medications into their daily routines and use various methods to remind themselves to take their medications on time. Some patients may also need to handle complex packaging issues. Actively participating in meaningful activities is another key component of these strategies, which includes ensuring that treatment is not interrupted during outings, thereby allowing patients to manage their medication process more flexibly and effectively.

3.4.3.1.1 Integrating medication into daily life

Most patients recognize the importance of taking their medication on time and use methods such as setting alarms, choosing strategic storage locations, checking pillbox status, relying on memory, and establishing fixed habits to remind themselves to take their medication. However, some patients, particularly younger ones, may forget to take their medication due to unexpected events like social gatherings, while elderly patients might forget due to memory decline. Additionally, some patients encounter difficulties in opening medication packaging, which can disrupt their medication process.

> "You have to have a bit of a routine when you have so many things." (Foley et al., 2022)

> "I have a timer that I set every time I finish my meal. And when that timer dings, then I take my medication." (Jallow et al., 2024)

> "Well, it's a lifestyle thing. I'm not always home for breakfast. I'm not always home for lunch. I'm not always home for dinner. I might want to go out and meet someone. Going out or I am sleeping in later than I normally would because I've been out the night before or, heaven forbid, I do not wake up at home. but you do not have your medication there. It's one of those things, it's lifestyle based, it does not fit in with a young person's lifestyle." (Tudball et al., 2015)

> "I take them with my lunch. And when I do that I forget to take them entirely if I do not leave them on the table in the morning." (Foley et al., 2022)

> "I have problems with opening packages every day because of my arthrosis in both my hands. I found a way to handle this situation. I decided to prepare the intake for a whole week on one day a week. Then the pain is just once per week." (Dijkstra et al., 2022)

3.4.3.1.2 Planning for outings

Patients usually prepare their medications in advance once travel plans are confirmed, ensuring that their treatment is not interrupted during the trip. However, unexpected events such as sudden changes in itinerary, lack of access to luggage, insufficient medication supply, or time zone differences can cause difficulties with medication management, thereby disrupting the normal medication routine.

> "So, if I go away on holidays [or a work trip], I have to think, 'Do I have enough of my main medication to cover the period I'm going to be away? Will I be able to get them if I take my scripts, will I be able to get them where I'm going, or do I have to go and get more now? Do I have to go and get new scripts?' I'll take a couple of days extra, just in case there's a change in plans." (Tudball et al., 2015)

> "I rarely miss medications, especially when I stay at home. The exception is when I go out; I sometimes forget to take medications with me." (Vatcharavongvan and Puttawanchai, 2022)

> "So a bit of a business, when I go to the Czech Republic, which I do every year, again visiting grandchildren and family, adjusting the time shift with the medicine is a bit of an issue. But I just work out what seems to be reasonable, stick somewhere in the middle." (Tudball et al., 2015)

3.4.3.2 Subtheme 2: internal strategies (31/320)

In internal strategies, patients should learn to identify and manage negative emotions related to medication use and maintain a positive mindset to minimize the impact of these emotions on their treatment. The complexity of managing multiple medications may cause psychological distress, but most patients cope with these challenges by focusing on the benefits of treatment and diverting their attention to other activities.

> "You look at all the bottles up there and you just shake your head." (Vandermause et al., 2016)

> "If I am afraid of side effects or if I do not take medicines, I may have complications from diseases. I have to accept that fact. Take them. If there will be side effects, let them be. I am not worried at all." (Vatcharavongvan and Puttawanchai, 2022)

> "And suddenly it's almost like you've regained your whole life, you can go out, you can go on holidays. You can go out for lunch with your friends and walk the length of the Shopping Centre. I mean it's, it's just amazing I'm telling you. Anybody who says it's not a good thing, they're not doing it right." (Cossart et al., 2022)

> "Yeah, I think it's always in the back of mind. I do not care, anybody who's had a transplant must think that, and I do think that. But I do not dwell on it." (Cossart et al., 2022)

3.4.3.3 Subtheme 3: social interaction strategies (3/320)

In social interaction strategies, patients should actively maintain and develop social connections to restore their social functioning. Patients may choose to engage in selective social interactions, preferring to communicate with others who share the same condition, in order to gain encouragement and advice, thereby further facilitating the success of their treatment.

> "If you're talking to somebody who knows exactly what you're talking about, it does make a difference." (Cossart et al., 2022)

4 Discussion

This systematic review of 16 qualitative studies was to explore the process of medication self-management in polypharmacy from the perspectives of patients and healthcare providers, and to analyse the complex factors affecting medication self-management, which were mapped into the TEDSS framework (Cadel et al., 2020). The study found that while most patients could incorporate medication management into their routine self-care practices, there were still issues to be improved in medical management, support-oriented domains and emotion and role management.

Polypharmacy has become an increasingly common issue in modern healthcare, with a growing number of patients requiring long-term use of multiple medications to manage various conditions (Tang et al., 2022). As the number of medications increases, medication management becomes more complex, necessitating higher levels of medication literacy and personalized management strategies. However, a study by Plaza-Zamora et al. (Plaza-Zamora et al., 2020) found that only 34% of community pharmacy clients have adequate medication literacy. This finding aligns with the significant lack of rational medication knowledge among the elderly population (Mei et al., 2024). Additionally, research by Funk et al. (Funk et al., 2021) revealed that 76.7% of households store at least one medication improperly, consistent with our findings that many patients struggle to properly follow complex medication regimens. Due to insufficient medication information and beliefs, some patients even adjust or discontinue their medications on their own. These studies highlight the necessity of enhancing medication education and information provision in polypharmacy management to improve medication literacy, ensuring that patients not only understand the function of their medications and provide accurate medication history but also have the ability to access, correctly verify, store, and use them promptly, while effectively monitoring and managing the efficacy and side effects of the medications.

There is a close relationship between health behavior strategies and medication management. Research indicates that behaviors such as obesity and smoking are risk factors for polypharmacy (Piao et al., 2024). By adopting a healthy lifestyle, such as a balanced diet and regular exercise, patients can sometimes enhance the effectiveness of their medications and reduce their dependence on them (Gillies et al., 2007; Zhang et al., 2023; Koren et al., 2024). On the other hand, medication use may require patients to adjust their lifestyle to avoid potential side effects and adverse reactions. For instance, some medications might necessitate dietary adjustments to prevent drug-food interactions from affecting efficacy (Niederberger and Parnham, 2021; D'Alessandro et al., 2022). Therefore, healthcare providers should offer personalized guidance and ongoing support to help patients find the optimal balance between lifestyle adjustments and medication therapy. In this way, patients can not only manage their medications more effectively but also reduce the risk of adverse reactions and improve their overall health.

It is noteworthy that as modern healthcare systems increasingly shift responsibility onto patients and their social support networks, this shift, although intended to enhance patients' self-management capabilities, may also increase their burden (May et al., 2014). Without adequate support and guidance, this burden could lead to poor management, resulting in suboptimal healthcare outcomes and an increase in healthcare service demand and costs. Consequently, polypharmacy management now requires a higher level of expertise from healthcare providers. To achieve minimally disruptive medicine, dynamically conducting medication reviews and optimization is particularly crucial (May et al., 2009). To this end, various tools need to be developed that assist healthcare providers (Fellenor et al., 2021; Urbańczyk et al., 2023) and patients (Dimitrow et al., 2023) in reviewing current medications, identifying those who might benefit from deprescribing interventions, and reducing the incidence of inappropriate prescriptions. This approach not only helps lower associated costs but also alleviates the daily burden on patients, thereby improving their quality of life.

A robust social support network can provide patients with essential emotional support, informational support, and practical assistance, thereby encouraging proactive health engagement and enhancing their self-management capabilities (Dhand et al., 2016). Many patients wish to adjust their current medication regimens, seeking to control their condition with fewer doses or fewer types of medication. Healthcare providers should assess patients' social support networks and consider patients' life needs, treatment goals, economic circumstances (Woodward et al., 2024), and personal preferences (Limenh et al., 2024) to offer personalized support and guidance to help patients build and strengthen their support systems. Additionally, healthcare providers should engage in education and training programs to improve their own health literacy, gain stronger medication knowledge, and enhance clinical judgment (Lüthold et al., 2024). By implementing effective resource allocation, promoting pharmacist integration, fostering multidisciplinary collaboration, and utilizing electronic medication verification tools (based on web or mobile applications), healthcare providers can improve coordination and deliver better services to patients (Ciudad-Gutiérrez et al., 2023; Naseralallah et al., 2023).

With the continuous advancement of technology, more and more innovative tools are being developed to help patients integrate medication management into their daily lives, effectively reducing the risk of forgetting medications (Kini and Ho, 2018). Such as smart pillboxes, medication reminder apps, and digital health monitoring systems. Travel is important for maintaining a positive mental state (Ybanez-Blomstrom et al., 2008), but it is crucial to develop a medication plan for patients during travel. This not only enhances their convenience and comfort but also strengthens their ability to handle emergencies. This includes strategies for managing time zone differences, insufficient medication supplies, unexpected trips, and missed doses, allowing patients to better manage their medication therapy while traveling and avoid health complications due to unexpected situations (Tudball et al., 2015). Additionally, focusing on psychological counseling is a key factor in improving patients' quality of life. Teaching psychological counseling methods can help patients better manage their emotions when facing illness and treatment pressures, restore social functions, and improve overall health and life satisfaction (van Agteren et al., 2021).

5 Strengths and limitations

This study presents the first systematic review of the medication self-management process in polypharmacy from the attitudes and experiences of patients and healthcare providers, following a strict protocol and the ENTREQ guidelines to ensure a thorough, transparent, and repeatable review process. The study adopted the most common definition of polypharmacy, which facilitates the generalization and extension of the results. The studies included were evaluated using the CASP quality assessment checklist and were generally perceived to be of high quality, enhancing our reliance on their outcomes. In addition, we invited three healthcare providers and four patients to review the comprehensive themes, and their suggestions were incorporated into the determination of the final themes. This process not only helped to validate the research team's analytical results, ensuring consistency with real-world situations, but also enriched our thematic analysis, making the results more comprehensive and targeted. The study helps in designing interventions that are more tailored to patient needs and supporting health policy making.

Despite its strengths, this systematic review has some significant limitations. The majority of the included studies are from high-income countries, revealing a gap in research from low and middle-income countries. Thus, interpreting these findings requires particular care, especially regarding low and middle-income countries. Additionally, this study only included English language articles, likely missing other relevant research that conforms to the criteria, and thus might have introduced some bias. The findings include insufficient details about emotional and role management, making it difficult to thoroughly analyse patients' strategies in these areas. Finally, the professional backgrounds of the authors may have an impact on the conclusions of this review.

6 Conclusion

This study used the TEDSS model as a framework to analyse medication self-management process in polypharmacy from the perspectives of patients and healthcare providers and found that patients still have problems to improve in medical management, support-oriented domains and emotion and role management. Enhancing patients' proactive health awareness, improving medication literacy, balancing lifestyle adjustments with medication therapy, dynamically reviewing and optimizing medications, strengthening patients' social support networks, and helping patients integrate medication management into their daily life are the key elements that can effectively assist patients in self-managing their medications. Future research should focus on developing effective intervention strategies to further enhance self-management abilities. The insights gained from this study can help design specific interventions tailored to patients' needs.

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

RJ: Writing–review and editing, Writing–original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. CL: Writing–review and editing, Writing–original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. JC: Writing–review and editing, Writing–original draft, Visualization, Software, Resources, Methodology, Investigation, Formal Analysis, Data curation. MC: Writing–review and editing, Writing–original draft, Visualization, Software, Resources, Methodology, Investigation, Formal Analysis, Data curation. BX: Writing–review and editing, Validation, Supervision, Formal Analysis, Data curation. PY: Writing–review and editing, Validation, Supervision, Formal Analysis, Data curation. LC: Writing–review and editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal Analysis, Data curation, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study is sponsored by Jiangsu Provincial Department of Science and Technology. The project is a social development project of Jiangsu Province, with the project number: BE2022668.

Acknowledgments

We thank the patients and healthcare providers who reviewed the initial themes and provided valuable feedback.

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.2024.1426777/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 November 2024
DOI 10.3389/fphar.2024.1458600

OPEN ACCESS

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RECEIVED 02 July 2024
ACCEPTED 31 October 2024
PUBLISHED 14 November 2024

CITATION
Peng H, Ou Y, Zhang R, Wang R, Wen D, Yang Q and Liu X (2024) Monitoring vancomycin blood concentrations reduces mortality risk in critically ill patients: a retrospective cohort study using the MIMIC-IV database.
Front. Pharmacol. 15:1458600.
doi: 10.3389/fphar.2024.1458600

Monitoring vancomycin blood concentrations reduces mortality risk in critically ill patients: a retrospective cohort study using the MIMIC-IV database

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Background: The incidence and mortality of severe Gram-positive cocci infections are particularly high in intensive care units (ICUs). Vancomycin remains the treatment of choice for severe infections caused by Gram-positive cocci, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Some guidelines recommend therapeutic drug monitoring (TDM) for critically ill patients treated with vancomycin; however, there is currently a lack of evidence to support that TDM improves the mortality rates of these patients. Therefore, we designed this cohort study to compare the impact of monitoring vancomycin blood concentrations on mortality rates in critically ill patients and to provide evidence to support this routine clinical practice.

Methods: Data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-IV database for a retrospective cohort analysis of critically ill patients receiving intravenous vancomycin treatment. The primary outcome was the 28 day mortality rate. The propensity score matching (PSM) method was used to match the baseline characteristics between patients in the TDM group and the non-TDM group. The relationship between 28 day mortality and vancomycin TDM in the critically ill cohort was evaluated using Cox proportional hazards regression analysis and Kaplan-Meier survival curves. Validation of the primary outcomes was conducted by comparing the PSM model and the Cox proportional hazards regression model. The robustness of the conclusion was subsequently verified by subgroup and sensitivity analyses.

Results: Data for 18,056 critically ill patients who met the study criteria were collected from the MIMIC-IV database. Of these, 7,451 patients had at least one record of vancomycin blood concentration monitoring, which we defined as the TDM group. The TDM group exhibited a 28 day mortality rate of 25.7% (1,912/7,451) compared to 16.2% in the non-TDM group (1,723/10,605). After PSM, 4,264 patients were included in each of the TDM and non-TDM groups, with a 28 day mortality rate of 20.0% (1,022/4,264) in the TDM group and 26.4% (1,126/4,264) in the non-TDM group. Multivariate Cox proportional hazards analysis revealed a significantly lower 28 day mortality risk in the TDM group when compared to the non-TDM group (adjusted hazard ratio [HR]: 0.86; 95% confidence interval [CI]:

0.79, 0.93; $p < 0.001$). Further PSM analyses (adjusted HR: 0.91; 95% CI: 0.84, 0.99; $p = 0.033$) confirmed the lower risk of mortality in the TDM group. Kaplan-Meier survival analysis revealed a significantly higher survival rate at 28 days for the TDM group (log-rank test, $p < 0.001$). Subgroup analysis results indicated that patients with sepsis, septic shock, estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2, undergoing renal replacement therapy, using vasoactive drugs, on mechanical ventilation, and those with higher severity scores (Acute Physiology Score III ≥40, Oxford Acute Severity of Illness Score ≥30, Simplified Acute Physiology Score II ≥ 30) significantly benefited from monitoring vancomycin blood concentrations. The results remained unchanged excluding patients staying in ICU for less than 48 h or those infected with MRSA.

Conclusion: This cohort study showed that monitoring vancomycin blood concentrations is associated with a significantly lower 28 day mortality rate in critically ill patients, highlighting the importance of routinely performing vancomycin TDM in these patients.

KEYWORDS

vancomycin, therapeutic drug monitoring, critically ill patients, mortality, mimic iv

1 Introduction

Severe infections caused by Gram-positive cocci are prevalent in intensive care units (ICUs), with reported incidence rates ranging from 16.1% to 50% (Vincent et al., 2009; Baykara et al., 2018; Martin et al., 2003; Chen et al., 2023; Tang et al., 2023). In particular, Gram-positive cocci have been isolated from respiratory specimens in more than 50% of cases with ventilator-associated pneumonia (Yoshimura et al., 2022). These infections are often accompanied by high mortality (Hanberger et al., 2011; van Hal et al., 2012). For instance, bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has a 30 day mortality rate of 28%–30.5% (Wang et al., 2010; Yaw et al., 2014). Vancomycin, a glycopeptide antibiotic, has demonstrated efficacy against severe infections caused by Gram-positive cocci, including MRSA (Jeffres, 2017). Furthermore, it has been the treatment of choice for MRSA for decades and remains one of the most frequently used antibiotics in ICUs (Magill et al., 2014). However, due to a narrow therapeutic window, significant inter-individual pharmacokinetic (PK) variability, and dose-dependent nephrotoxicity, some guidelines recommend therapeutic drug monitoring (TDM) for critically ill patients or those with severe MRSA infections treated with vancomycin (Ye et al., 2016; He et al., 2020; Reuter et al., 2022; Abdul-Aziz et al., 2020; Rybak et al., 2020).

In a narrow sense, vancomycin TDM focuses on adjusting dosage based on blood drug concentration measurements, primarily trough levels, to ensure effective treatment while minimizing risk of toxicity. Trough levels, the lowest drug concentration before the next dose, are recommended by the 2009 clinical guideline to be maintained between 10 and 20 mg/L to balance efficacy and toxicity (Rybak et al., 2009). More broadly, vancomycin TDM includes both trough concentration monitoring and the area under the concentration-time curve (AUC), which offers a more comprehensive assessment of drug exposure and correlates better with both efficacy and toxicity. As a result, AUC monitoring has been increasingly incorporated into TDM standards, enabling more precise dose adjustments and individualized treatment strategies, as seen in the 2020 guideline (Rybak et al., 2020). Trough concentration monitoring offers the advantages of simplicity and quick results, as it involves direct measurement. In contrast, traditional AUC monitoring requires multiple blood samples at different time points, followed by nonlinear curve fitting, making it impractical in clinical settings due to the need for repeated sampling (Yamada et al., 2023). Currently, clinical practice primarily uses the peak-trough two-point method and Bayesian software for AUC estimation. The two-point method involves collecting peak and trough concentrations within a dosing interval, followed by calculating AUC using a first-order equation (Meng et al., 2019). The Bayesian method uses a population PK model combined with 1-2 blood concentration measurements to estimate AUC(Rybak et al., 2020; Turner et al., 2018). Thus, regardless of the method, AUC monitoring requires at least 1-2 blood concentration measurements, making blood concentration monitoring essential for accurate AUC estimation. Therefore, as long as blood concentration measurements are available, it is possible to determine if a patient underwent vancomycin TDM, whether through trough level or AUC monitoring.

Emerging evidence supports a specific relationship between nephrotoxicity and both trough concentration (van Hal et al., 2013; Bellos et al., 2020) and the AUC to the minimum inhibitory concentration (AUC/MIC) (Aljefri et al., 2019; Abdelmessih et al., 2022) during the treatment of serious infections caused by *Staphylococcus aureus*, particularly MRSA. Although vancomycin TDM can effectively reduce the incidence of nephrotoxicity, trough concentrations do not appear to predict clinical efficacy accurately (Lodise et al., 2008; Steinmetz et al., 2015; Prybylski, 2015). A previous systematic review, incorporating data from over 2,000 patients with invasive MRSA infections, found no significant difference in all-cause mortality between patient groups with trough concentrations >10 mg/L compared to those with levels ≥15 mg/L (Steinmetz et al., 2015). Similarly, a previous meta-analysis that included more than 1,600 patients with *Staphylococcus aureus* bacteremia demonstrated that trough concentrations >15 mg/L did not correlate with reduced rates of treatment failure, duration of bacteremia, or mortality (Prybylski, 2015). It is generally believed that the AUC/MIC ratio is superior to

trough concentration in predicting survival outcomes and clinical cure, while this ratio only shows moderate levels of sensitivity and specificity (Lodise et al., 2008; Dalton et al., 2020; Tsutsuura et al., 2021). The multicenter prospective PROVIDE study further elucidated the relationship between initial vancomycin exposure and clinical treatment failure rates in adult patients with MRSA bacteremia, highlighting that higher AUC/MIC ratios do not necessarily translate into a reduced risk of treatment failure but are linked to an increased incidence of acute kidney injury (Lodise et al., 2020). There is still a clear lack of robust data correlating AUC with mortality; furthermore, the available evidence on the impact of vancomycin TDM on mortality rates is highly limited (Flannery et al., 2021; Briassoulis and Briassoulis, 2022). This highlights the necessity for further rigorous studies to clarify these relationships and optimize vancomycin TDM strategies in clinical settings.

In ICUs, vancomycin is predominantly administered empirically by clinicians based on the severity of infection, the prevalence of local pathogens, and patterns of antibiotic resistance without results generated by pathogen culture (Jones et al., 2020; Cowley et al., 2019). This practice has generated clinical debate about whether routine TDM of vancomycin is necessary for all critically ill patients (Darko et al., 2003). In particular, we need to know whether routine TDM can reduce the mortality rate of these patients. Although some guidelines advocate the use of TDM during vancomycin therapy in critical settings, these recommendations are based on limited clinical and safety data and do not consider the costs associated with vancomycin TDM. Currently, there is insufficient evidence to evaluate the impact of this practice on mortality and cost-effectiveness (Ye et al., 2016; He et al., 2020; Reuter et al., 2022; Abdul-Aziz et al., 2020; Rybak et al., 2009). In the updated 2020 vancomycin TDM guideline, the Therapeutic Drug Monitoring Committee of the Chinese Pharmacological Society reported that despite recommendations for TDM in critically ill patients, these were classified as low-quality evidence due to the lack of supportive data (He et al., 2020). Some previous studies reported that routine vancomycin TDM may consume significant time and healthcare resources, and may potentially lack cost-effectiveness (Jeffres, 2017; Darko et al., 2003). Consequently, in the present study, we utilized a large dataset from the MIMIC-IV database to investigate the impact of monitoring vancomycin blood concentrations on mortality rates in critically ill patients. Our hypothesis was that monitoring vancomycin blood concentrations would reduce mortality. If our hypothesis is proven, our findings would provide the most direct evidence to support the routine implementation of vancomycin TDM in critically ill patients.

2 Materials and methods

2.1 Data source

The Medical Information Mart for Intensive Care IV (MIMIC-IV) database, hosted at PhysioNet, is a publicly accessible, single-center repository that includes data relating to 730,141 ICU admissions at the Beth Israel Deaconess Medical Center in the United States, spanning from 2008 to 2019 (Johnson et al., 2023). Researcher Huaidong Peng (certification number: 59679596) and colleagues utilized the database to extract a wide range of clinical data, including patient demographics, vital signs, laboratory tests, comorbidities, severity of illness scores, therapeutic interventions, and specifics regarding vancomycin administration and TDM information. The use of the MIMIC-IV database was authorized by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Our study was conducted in accordance with the Declaration of Helsinki, and due to the anonymization of participant data and its standardized format, additional approval from the ethics committee was deemed unnecessary.

2.2 Study population

All patients recorded in the MIMIC-IV database were considered eligible for inclusion in this study. For those with multiple ICU admissions, only the data from their first ICU stay were analyzed. We included patients who began intravenous vancomycin treatment either before or after ICU admission. Vancomycin TDM was defined as having at least one blood vancomycin concentration measurement during the ICU stay, irrespective of whether it was a trough, peak, or random concentration. Patients receiving vancomycin TDM during their ICU hospitalization were designated as the experimental group (the TDM group), while those administered vancomycin without subsequent TDM formed the control group (the non-TDM group). Additionally, the analysis was limited to adult patients aged 18 years and older. The patient enrollment process for this study is depicted in Figure 1.

2.3 Covariates and outcome

We used Structured Query Language to systematically extract patient data from the database. The extracted data included a range of variables: basic demographic details for hospital admission registration such as gender, age, and race; vital signs, including heart rate, mean arterial pressure, respiratory rate, temperature, and SpO2; laboratory tests, including white blood cell count (WBC), hemoglobin, hematocrit, platelets, creatinine, blood urea nitrogen (BUN), finger glucose, potassium, and bicarbonate; comorbidities, including hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), liver disease, diabetes, renal disease, and malignant cancer; severity of illness scores, including the Acute Physiology Score (APS) III, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score, Charlson Comorbidity Index, and Oxford Acute Severity of Illness Score (OASIS); therapeutic interventions such as renal replacement therapy (RRT), vasoactive drugs, and mechanical ventilation; and vancomycin administration and TDM information. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which adjusts for serum creatinine while accounting for the patient's gender, age, and creatinine levels (Inker et al., 2021).

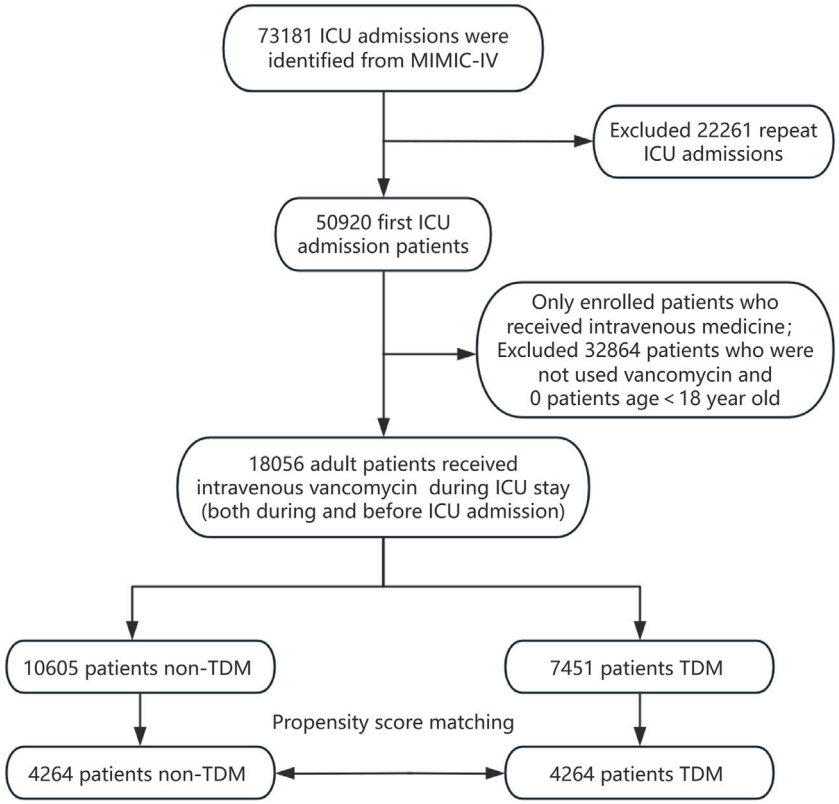

FIGURE 1
Flow chart depicting the enrollment process for patients.

The primary outcome of this study was 28 day mortality. Secondary outcomes included ICU mortality, hospital mortality, 60 day mortality, and 90 day mortality.

2.4 Statistical analysis

We addressed missing data using K-Nearest Neighbors imputation (Faisal and Tutz, 2022), detailed information relating to missing data is provided in Supplementary Table 1. Continuous variables are reported as either mean ± standard deviation or median with interquartile range (IQR), while categorical variables are reported as frequency (percentage). The conformity of continuous variables to the normal distribution was tested using the Shapiro-Wilk test or Kolmogorov-Smirnov test. For continuous variables that conformed to a normal distribution, we used the Student's t-test to compare means. For non-normally distributed continuous variables, the Wilcoxon's rank-sum test was applied. For categorical variables, we used Pearson's chi-squared test or Fisher's exact test, as appropriate.

Cox proportional hazards regression analyses were used to investigate the independent association between vancomycin TDM and 28 day mortality, yielding hazard ratios (HRs) and 95% confidence intervals (CIs). Survival distributions were estimated by Kaplan-Meier analysis, and differences were assessed by the log-rank test. To balance baseline characteristics between the TDM and non-TDM groups, we implemented propensity score matching (PSM) using a 1:1 nearest neighbor matching algorithm with a caliper width of 0.1. The variables listed in Table 1 were used to generate the propensity score. The primary outcome was further validated using the PSM model, which applied the estimated propensity scores as weights. The results were then compared to those derived from the Cox proportional hazards regression model.

All statistical analyses were conducted using R statistical software, version 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software, version 1.9 (https://www.clinicalscientists.cn/freestatistics/). A two-tailed test approach was adopted, and $p < 0.05$ was considered statistically significant.

2.5 Subgroup analysis and sensitivity analysis

To evaluate the robustness of our findings, we conducted subgroup analyses stratified by gender, age, race, sepsis, septic shock, eGFR, RRT, the use of vasoactive drugs, mechanical ventilation, APS III, OASIS, and SAPS II. Furthermore, to delineate independent associations, we performed distinct sensitivity analyses. Sensitivity analysis was performed after excluding patients with ICU hospitalization time less than 48 h or diagnosed with MRSA infection. These analyses aimed to ensure the reliability and applicability of our results across diverse patient groups and clinical scenarios.

TABLE 1 Baseline characteristics of the patients enrolled from the MIMIC-IV database.

Patient characteristic	Before PSM				After PSM			
	Total (n = 18,056)	Non-TDM group (n = 10,605)	TDM group (n = 7,451)	SMD	Total (n = 8,528)	Non-TDM group (n = 4,264)	TDM group (n = 4,264)	SMD
Gender [male, n (%)]	10,599 (58.7)	6,220 (58.7)	4,379 (58.8)	0.002	4,844 (56.8)	2,422 (56.8)	2,422 (56.8)	<0.001
Age (years)	66.0 ± 16.0	67.2 ± 15.5	64.4 ± 16.6	0.178	66.1 ± 16.4	66.2 ± 16.4	66.1 ± 16.5	0.006
RACE [white, n (%)]	11,939 (66.1)	7,251 (68.4)	4,688 (62.9)	0.115	5,509 (64.6)	2,737 (64.2)	2,772 (65)	0.017
Vital signs								
Heart rate (bpm)	87.4 ± 16.1	85.8 ± 15.0	89.7 ± 17.2	0.242	88.5 ± 16.6	88.7 ± 16.5	88.2 ± 16.7	0.03
MAP (mmHg)	76.3 ± 10.1	76.0 ± 9.8	76.7 ± 10.5	0.064	76.5 ± 10.6	76.5 ± 10.7	76.5 ± 10.4	0.004
Respiratory rate (/min)	19.9 ± 4.1	19.4 ± 3.9	20.7 ± 4.3	0.329	20.3 ± 4.2	20.4 ± 4.3	20.3 ± 4.1	0.019
Temperature (°C)	37.5 ± 0.8	37.4 ± 0.8	37.7 ± 0.9	0.294	37.6 ± 0.9	37.6 ± 0.9	37.6 ± 0.9	0.008
Spo2(%)	96.9 ± 2.5	96.9 ± 2.6	96.8 ± 2.4	0.049	96.8 ± 2.6	96.7 ± 2.9	96.8 ± 2.4	0.028
Laboratory tests								
WBC($\times10^9$)	14.4 (10.3, 19.6)	14.3 (10.3, 19.0)	14.8 (10.5, 20.3)	0.081	14.4 (10.2, 19.8)	14.5 (10.1, 19.7)	14.4 (10.3, 19.9)	0.011
Hemoglobin (g/L)	9.8 ± 2.1	9.8 ± 2.1	9.8 ± 2.2	0.022	9.8 ± 2.2	9.8 ± 2.2	9.8 ± 2.2	0.007
Hematocrit (%)	29.7 ± 6.3	29.5 ± 6.1	29.9 ± 6.6	0.067	29.8 ± 6.5	29.9 ± 6.6	29.8 ± 6.5	0.015
Platelets ($\times10^9$)	161.0 (111.0, 228.0)	157.0 (113.0, 220.2)	169.0 (108.0, 237.5)	0.074	169.0 (112.0, 238.0)	168.0 (112.0, 236.0)	170.0 (112.0, 240.0)	0.004
eGFR (mL/min/1.73 m^2)	61.2 (34.4, 88.0)	67.9 (42.9, 89.9)	50.7 (24.6, 83.6)	0.347	51.8 (27.7, 82.1)	52.9 (29.7, 82.7)	50.8 (25.1, 81.4)	0.075
BUN(mg/dL)	22.0 (15.0, 36.0)	19.0 (14.0, 30.0)	26.0 (17.0, 45.0)	0.398	25.0 (16.0, 41.0)	25.0 (16.0, 41.0)	24.0 (16.0, 41.0)	0.021
Glucose (finger,mg/dL)	132.0 (115.5, 159.5)	130.4 (116.4, 152.8)	135.9 (114.0, 170.0)	0.047	134.0 (113.6, 167.2)	135.2 (115.0, 169.0)	133.0 (112.3, 165.5)	0.021
Potassium (mmol/L)	3.9 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	0.108	3.9 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	0.007
Bicarbonate (mmol/L)	21.0 ± 4.9	21.4 ± 4.5	20.3 ± 5.3	0.222	20.6 ± 5.2	20.6 ± 5.4	20.7 ± 5.1	0.007
Comorbidity diseases, n(%)								
Hypertension	11,448 (63.4)	6,922 (65.3)	4,526 (60.7)	0.094	5,269 (61.8)	2,623 (61.5)	2,646 (62.1)	0.011
Congestive heart failure	5,250 (29.1)	2,933 (27.7)	2,317 (31.1)	0.076	2,675 (31.4)	1,344 (31.5)	1,331 (31.2)	0.007
COPD	4,654 (25.8)	2,619 (24.7)	2035 (27.3)	0.06	2,322 (27.2)	1,185 (27.8)	1,137 (26.7)	0.025
Liver disease	2,554 (14.1)	1,134 (10.7)	1,420 (19.1)	0.237	1,374 (16.1)	704 (16.5)	670 (15.7)	0.022
Diabetes	4,428 (24.5)	2,623 (24.7)	1805 (24.2)	0.012	2068 (24.2)	1,034 (24.2)	1,034 (24.2)	<0.001
Renal disease	3,707 (20.5)	1875 (17.7)	1832 (24.6)	0.17	2058 (24.1)	1,044 (24.5)	1,014 (23.8)	0.016
Malignant cancer	2,526 (14.0)	1,427 (13.5)	1,099 (14.7)	0.037	1,373 (16.1)	699 (16.4)	674 (15.8)	0.016
Sepsis	14,053 (77.8)	7,227 (68.1)	6,826 (91.6)	0.612	7,481 (87.7)	3,780 (88.6)	3,701 (86.8)	0.056
Septic shock	8,236 (45.6)	3,786 (35.7)	4,450 (59.7)	0.496	4,212 (49.4)	2,137 (50.1)	2075 (48.7)	0.029
Severity of illness scores								
CCI	6.0 (4.0, 8.0)	5.0 (4.0, 7.0)	6.0 (4.0, 8.0)	0.09	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	0.022
SOFA score	5.0 (3.0, 8.0)	5.0 (3.0, 7.0)	6.0 (4.0, 9.0)	0.454	6.0 (3.0, 8.0)	5.0 (3.0, 8.0)	6.0 (3.0, 8.0)	0.034

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics of the patients enrolled from the MIMIC-IV database.

Patient characteristic	Before PSM				After PSM			
	Total (n = 18,056)	Non-TDM group (n = 10,605)	TDM group (n = 7,451)	SMD	Total (n = 8,528)	Non-TDM group (n = 4,264)	TDM group (n = 4,264)	SMD
APS III	50.0 (35.0, 71.0)	42.0 (31.0, 59.0)	63.0 (46.0, 84.0)	0.737	54.0 (40.0, 73.0)	54.0 (40.0, 75.0)	55.0 (41.0, 72.0)	0.049
SAPS II	39.9 ± 15.0	37.9 ± 14.3	42.8 ± 15.4	0.335	41.4 ± 15.4	41.7 ± 16.0	41.1 ± 14.9	0.04
OASIS	34.9 ± 9.6	32.6 ± 8.9	38.3 ± 9.5	0.619	36.0 ± 9.1	36.2 ± 9.2	35.8 ± 9.1	0.042
Therapy, n(%)								
RRT	928 (5.1)	260 (2.5)	668 (9)	0.284	470 (5.5)	229 (5.4)	241 (5.7)	0.012
Mechanical ventilation	10,423 (57.7)	5,174 (48.8)	5,249 (70.4)	0.453	4,981 (58.4)	2,492 (58.4)	2,489 (58.4)	0.001
Vasoactive drug	10,034 (55.6)	5,407 (51)	4,627 (62.1)	0.226	4,484 (52.6)	2,248 (52.7)	2,236 (52.4)	0.006
Infectious pathogen, n (%)								
MRSA	1,307 (7.2)	541 (5.1)	766 (10.3)	0.195	672 (7.9)	329 (7.7)	343 (8)	0.012
Details of first administration of vancomycin in ICU								
Accumulated dose(g)	2.0 (1.25, 4.0)	2.0 (1.0, 3.0)	4.0 (2.0, 6.0)	0.843	2.75 (1.875, 4.0)	2.0 (1.5, 4.0)	3.0 (2.0, 4.125)	0.071
Medication time(d)	2.7 (1.7, 6.0)	2.0 (1.2, 3.1)	5.2 (2.7, 10.0)	0.624	3.0 (1.7, 6.1)	2.5 (1.2, 5.3)	3.5 (2.1, 6.6)	0.087

MAP, mean arterial pressure; Spo2, percutaneous arterial oxygen saturation; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CCI, charlson comorbidity score; SOFA, score, sequential organ failure score; APS III, acute physiology score III; SAPS II, simplified acute physiology score II; OASIS, oxford acute severity of illness score; RRT, renal replacement therapy; MRSA, methicillin-resistant *Staphylococcus aureus*.

3 Results

3.1 Patient characteristics

A total of 18,056 patients who received intravenous vancomycin were enrolled in our cohort from the MIMIC-IV database. The mean age of the patients was 66.0 ± 16.0 years, and 58.7% were male (n = 10,599). The overall 28 day mortality rate was 20.1% (3,635/18,056). Of these, 7,451 patients (41.3%) underwent at least one round of vancomycin blood concentration monitoring, while 10,605 (58.7%) patients did not (Table 1). Table 1 presents the clinical information of both the non-TDM and TDM groups before and after PSM. When considering all enrolled patients, those in the TDM group were older, had higher WBC counts, lower eGFR levels, higher BUN levels, and a higher proportion of comorbidities such as heart failure, COPD, liver disease, and kidney disease when compared to the non-TDM group (all $p < 0.001$). The incidence of sepsis and septic shock was higher in the TDM group, and all five severity scores were higher than those in the non-TDM group (all $p < 0.001$). Additionally, there was a higher proportion of patients with definitive MRSA infections, as well as more patients requiring RRT, mechanical ventilation, and vasoactive drug treatment (all $p < 0.001$). These data suggest that patients in the TDM group were in more severe condition than those in the non-TDM group.

After performing PSM, the characteristics of 4,264 patients were successfully matched between the two groups. The standardized mean differences (SMD) of all variables after PSM were less than 10%, indicating good quality of the matched samples (Table 1). After minimizing the interference of confounders through PSM, monitoring vancomycin blood concentrations was identified as the main factor.

3.2 Primary outcome

Table 2 presents the mortality data arising from our analysis. According to the MIMIC-IV database, the 28 day mortality rate for critically ill patients treated with vancomycin was 20.1% (3,635/18,056). Notably, the 28 day mortality rate in the TDM group was 25.7% (1,912/7,451), which was significantly higher than 16.2% (1,723/10,605) in the non-TDM group ($p < 0.001$). After PSM, the overall 28 day mortality rate was 25.2% (2,148/8,528). However, within the matched cohort, the 28 day mortality rate of the TDM group was significantly lower than that of the non-TDM group (20.0% vs 26.4%, $p = 0.009$).

3.3 Secondary outcomes

ICU mortality, hospital mortality, 60 day mortality, and 90 day mortality, all showed patterns that were similar to the 28 day mortality results (Table 2). After PSM, all of these mortality metrics shifted from being higher in the TDM group than the non-TDM group before PSM to being significantly lower in the TDM group after PSM, with all differences were significant ($p < 0.05$).

TABLE 2 Primary outcome and secondary outcomes of the study.

Outcomes	Matching	Total	Non-TDM group	TDM group	*p*
28 day mortality	before PSM, n (%)	3,635/18,056 (20.1)	1723/10,605 (16.2)	1912/7,451 (25.7)	<0.001
	after PSM, n (%)	2,148/8,528 (25.2)	1,126/4,264 (26.4)	1,022/4,264 (20.0)	0.009
ICU mortality	before PSM, n (%)	2,309/18,056 (12.8)	1,053/10,605 (9.9)	1,256/7,451 (16.9)	<0.001
	after PSM, n (%)	1,355/8,528 (15.9)	757/4,264 (17.8)	598/4,264 (14.0)	<0.001
hospital mortality	before PSM, n (%)	3,088/18,056 (17.1)	1,401/10,605 (13.2)	1,687/7,451 (22.6)	<0.001
	after PSM, n (%)	1828/8,528 (21.4)	994/4,264 (23.3)	834/4,264 (19.6)	<0.001
60 day mortality	before PSM, n (%)	4,359/18,056 (24.1)	2066/10,605 (19.5)	2,293/7,451 (30.8)	<0.001
	after PSM, n (%)	2,544/8,528 (29.8)	1,324/4,264 (31.1)	1,220/4,264 (28.6)	0.014
90 day mortality	before PSM, n (%)	4,739/18,056 (26.2)	2,241/10,605 (21.1)	2,498/7,451 (33.5)	<0.001
	after PSM, n (%)	2,753/8,528 (32.3)	1,411/4,264 (33.1)	1,342/4,264 (31.5)	0.110

TABLE 3 Association between TDM and 28 day mortality using Cox proportional hazards regression analysis.

	Adjusted HR	95% CI	*p*-value
Model 1	1.59	(1.49 ~ 1.70)	<0.001
Model 2	1.67	(1.56 ~ 1.78)	<0.001
Model 3	1.18	(1.10 ~ 1.27)	<0.001
Model 4	1.13	(1.05 ~ 1.21)	0.001
Model 5	0.91	(0.84 ~ 0.98)	<0.001
Model 6	0.84	(0.78 ~ 0.90)	<0.001
Model 7	0.68	(0.63 ~ 0.73)	<0.001
Model 8	0.86	(0.79 ~ 0.93)	<0.001

Adjusted covariates: Model 1 = Vancomycin TDM, only; Model 2 = Model 1+(Gender, Age, Race); Model 3 = Model 2+(Heart rate, MAP, respiratory rate, Temperature, and SpO2)+(WBC, hemoglobin, Hematocrit, Platelets, Creatinine; BUN, finger glucose, Potassium, and Bicarbonate); Model 4 = Model 3+(Hypertension, Congestive heart failure, COPD, liver disease, Diabetes, Renal disease, and Malignant cancer); Model 5 = Model 4+(RRT, vasoactive drug, Mechanical ventilation, and MRSA); Model 6 = Model 5+(Sepsis, Septic shock); Model 7 = Model 6+(CCI, SOFA, score, APS III, SAPS II, OASIS); Model 8 = Model 7+(Accumulated dose, Medication time).

TABLE 4 The association between vancomycin TDM and 28 day mortality, as determined by analyses incorporating multiple models.

	HR	95% CI	*p*-value
Crude analysis.Unmatched	1.59	(1.49 ~ 1.70)	<0.001
Multivariable.adjusted[a]	0.86	(0.79 ~ 0.93)	<0.001
PropensityScore.Matched[b]	0.85	(0.78 ~ 0.92)	<0.001
PropensityScore.adjusted[c]	0.91	(0.84 ~ 0.99)	0.033

[a]HR, from a multivariable Cox proportional model adjusted for all covariates in Table 1.
[b]HR, from a multivariate Cox proportional hazards model with the same strata and covariates matched according to the propensity score.
[c]HR, from a multivariable Cox proportional hazards model with the same strata and covariates, with additional adjustment for the propensity score.

3.4 Association between vancomycin TDM and 28 day mortality

In extended multivariable Cox regression models, we made adjustments using various covariates, and the changes in the HRs are detailed in Table 3. After incorporating all covariates, multivariate Cox proportional hazards regression analysis revealed an adjusted HR of 0.86 (95% CI: 0.79, 0.93; $p < 0.001$), indicating a significant reduction in hazard. This finding was consistent with the post-matched cohort results, where PSM (adjusted HR: 0.91; 95% CI: 0.84, 0.99; $p = 0.033$) showed that monitoring vancomycin blood concentrations was significantly associated with reduced 28 day mortality among critically ill patients (Table 4). This robust statistical evidence highlights the

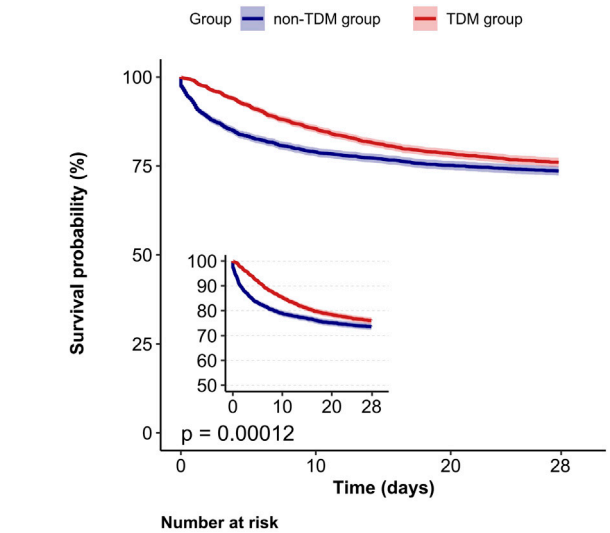

FIGURE 2
Kaplan-Meier survival curves for 28-day mortality in critically ill patients from the TDM group and the non-TDM group.

efficacy of vancomycin TDM in improving survival outcomes in this vulnerable patient population.

A Kaplan-Meier survival curve also demonstrated that the TDM group had a lower 28 day mortality rate (log-rank test: $p < 0.001$; Figure 2). Results from the 60 day and 90 day survival curves were consistent with those from the 28 day results (detailed results are available in Supplementary Images 1, 2).

3.5 Subgroup analysis

Next, we stratified our cohort into various demographic and clinical subgroups based on gender, age, race, sepsis, septic shock, eGFR, RRT, the use of vasoactive drugs, mechanical ventilation, APS III, OASIS, and SAPS II. The impact of monitoring vancomycin blood concentrations on 28 day mortality was investigated and the results were visualized as a forest plot (Figure 3). Subgroup analyses indicated a general negative correlation between monitoring vancomycin blood concentrations and 28 day mortality among critically ill patients. The results showed lower 28 day mortality in several subgroups, including males (HR: 0.76; 95% CI: 0.67, 0.85), females (HR: 0.85; 95% CI: 0.75, 0.97), patients younger than 65 years (HR: 0.63; 95% CI: 0.54, 0.74), those aged 65 years or older (HR: 0.90; 95% CI: 0.81, 1.00), White individuals (HR: 0.81; 95% CI: 0.72, 0.90), non-White individuals (HR: 0.79; 95% CI: 0.69, 0.91), patients with sepsis (HR: 0.79; 95% CI: 0.73, 0.87), those with septic shock (HR: 0.73; 95% CI: 0.66, 0.82), patients with eGFR <15 mL/min/1.73 m^2 (HR: 0.51; 95% CI: 0.41, 0.65), those with eGFR between 15 and 60 mL/min/1.73 m^2 (HR: 0.76; 95% CI: 0.68, 0.86), patients undergoing RRT (HR: 0.46; 95% CI: 0.32, 0.65), those receiving vasoactive drugs (HR: 0.73; 95% CI: 0.65, 0.81), those on mechanical ventilation (HR: 0.79; 95% CI: 0.71, 0.88), and patients with APS III scores ≥40 (HR: 0.77; 95% CI: 0.70, 0.84), OASIS scores ≥30 (HR: 0.77; 95% CI: 0.70, 0.84), or SAPS II scores ≥30 (HR: 0.78; 95% CI: 0.71, 0.85). However, interactions were identified between age, septic shock, RRT, vasoactive drugs, vasoactive drugs, APS III, OASIS, and SAPS II (p for interaction <0.05) (Figure 3).

3.6 Sensitivity analysis

There were 18,056 patients in the entire cohort. After excluding 6,058 patients whose ICU stay was less than 48 h, 11,998 patients remained for final analysis. Our findings indicated that vancomycin TDM was associated with a lower risk of 28 day mortality (multivariable Cox proportional model, adjusted HR: 0.87; 95% CI: 0.79, 0.95; $p = 0.002$). Furthermore, after excluding 1,307 patients with positive microbiological cultures for MRSA infection, the association between vancomycin TDM and 28 day mortality remained significant (multivariable Cox proportional model, adjusted HR: 0.84; 95% CI: 0.78, 0.92; $p < 0.001$) (Table 5).

4 Discussion

In this large retrospective cohort study, we found that patients in the TDM group exhibited more severe conditions and a higher 28 day mortality rate compared to those in the non-TDM group. After balancing the baseline characteristics of patients between the two groups using PSM, the mortality rate in the TDM group was lower than that in the non-TDM group. After including all covariates, the multivariate Cox model suggested that vancomycin TDM is a protective factor that can reduce the 28 day mortality rate among critically ill patients. Both the Cox proportional hazards regression analysis model and the PSM model corroborated this finding. Kaplan-Meier survival curves identified a lower 28 day mortality rate in the TDM group. Collectively, these results demonstrated that monitoring vancomycin blood concentrations was associated with a lower 28 day mortality rate in critically ill patients.

Typically, the severity of illness in critically ill patients correlates positively with both the duration of ICU admission and mortality rate (Knaus et al., 1991). In patients treated with vancomycin, increased disease severity not only prolongs hospitalization but also increases the need for TDM (Abdul-Aziz et al., 2020; Wong et al., 2014). Consequently, critically ill patients undergoing vancomycin TDM may exhibit higher mortality rates due to their more severe condition, while those not undergoing TDM, reflecting milder conditions, may present lower mortality rates. Our findings corroborate this hypothesis. If vancomycin TDM indeed mitigates the risk of mortality in critically ill patients, the severity of the underlying conditions might obscure these beneficial effects. Our analysis using multivariate Cox proportional hazards regression and PSM model robustly demonstrated that, after adjusting for covariates reflecting disease severity, monitoring vancomycin blood concentrations was associated with a significant reduction in the 28 day mortality rate in critically ill patients. Although monitoring drug concentrations alone does not constitute a complete TDM process, it is a fundamental component of TDM.

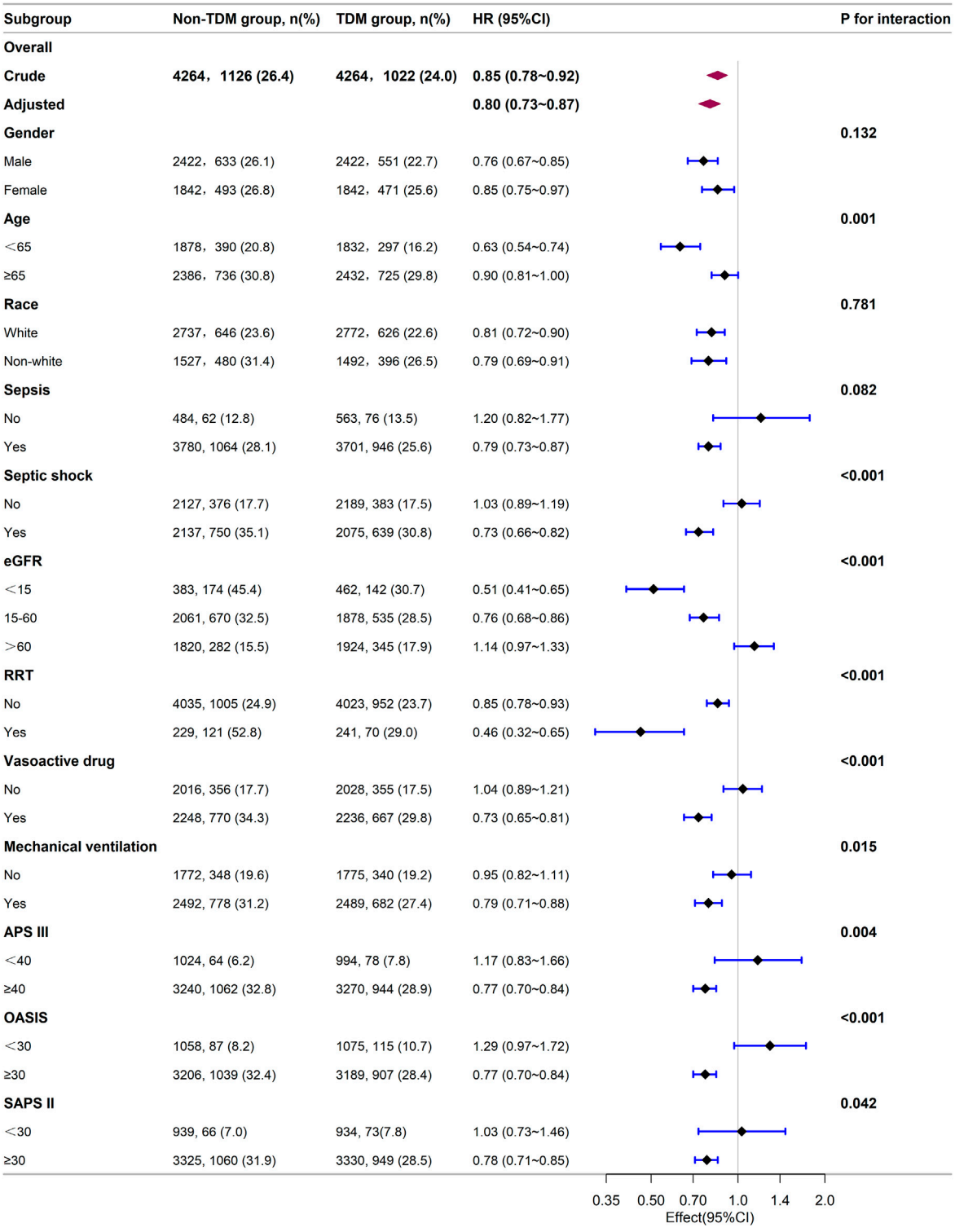

FIGURE 3
Subgroup analysis of the relationship between vancomycin TDM and 28-day mortality, as visualized by a forest plot.

It provides the basis for individualized vancomycin dosing, allowing clinicians to optimize therapy based on patient-specific PK and PD characteristics. Drug concentration monitoring enables timely dose adjustments, achieving therapeutic levels, reducing toxicity, and improving patient outcomes. Therefore, drug concentration monitoring represents an essential part of TDM and significantly reflects the application of TDM in clinical practice.

It is pertinent to note that only a limited number of studies have investigated the clinical outcomes of vancomycin dose adjustments under TDM guidance compared to those without such interventions

TABLE 5 Sensitivity analysis of the relationship between vancomycin TDM and 28 day mortality.

Sensitivity	Matching	28 day mortality,n (%)				Correlation analysis		
		Total	Non-TDM group	TDM group	P	HR	95%CI	P
Model 1 (n = 11,998)	before PSM	2,591/11,998 (21.6%)	864/5,255 (16.4%)	1727/6,743 (25.6%)	<0.001	0.87[a]	0.79~0.95	0.002
	after PSM	1,418/6,052 (23.4%)	764/3,026 (25.2%)	654/3,026 (21.6%)	<0.001	0.90[b]	0.81~1.00	<0.001
Model 2 (n = 16,749)	before PSM	3,318/16,749 (19.8%)	1,607/10,064 (16.0%)	1711/6,685 (25.6%)	<0.001	0.84[a]	0.78~0.92	<0.001
	after PSM	1956/7,892 (24.8%)	1,054/3,946 (26.7%)	902/3,946 (22.9%)	<0.001	0.89[b]	0.82~0.97	0.009

Model 1: Excluded those who ICU, stay was less than 48 h; Model 2: Excluded those who had positive microbiological cultures of MRSA.
[a]HR, from a multivariable Cox proportional model adjusted for all covariates in Table 1.
[b]HR, from a multivariable Cox proportional hazards model with the same strata and covariates, with additional adjustment for the propensity score.

(Ye et al., 2013; Fernández de Gatta et al., 1996; Iwamoto et al., 2003; Liu et al., 2024; Welty and Copa, 1994; Marella et al., 2020; Cardile et al., 2015). Predominantly, these investigations were derived from small-scale, single-disease studies, and non-randomized controlled trials. For instance, Machado et al. (2017) investigated the effect of antimicrobial TDM, including agents such as imipenem, meropenem, piperacillin, and vancomycin, on the prognosis of burns patients but found no evidence of prognostic improvement. A systematic review and meta-analysis investigated the advantages of vancomycin TDM and demonstrated a significant improvement in clinical efficacy (HR: 2.62; 95% CI: 1.34, 5.11; p = 0.005) and a marked reduction in nephrotoxicity (HR: 0.25; 95% CI: 0.13, 0.48; $p < 0.0001$), albeit without mortality data (Ye et al., 2013). In another study, Fernández de Gatta et al. (1996) found that vancomycin TDM reduced nephrotoxicity in patients with hematological malignancies; however, the sample sizes analyzed in this study were small. Another retrospective analysis of 184 MRSA infections, classified into TDM and non-TDM groups, did not report mortality outcomes (Iwamoto et al., 2003). A previous study by Huanhuan et al. compared patients with postoperative intracerebral hemorrhage who received TDM to those who did not; the analysis found no significant differences between the two groups in terms of 14 day mortality rate and the length of hospital stay (Liu et al., 2024). Welty et al. further reported that vancomycin TDM was associated with a lower incidence of nephrotoxicity, a shorter treatment duration, a reduced total dose, and a shorter hospital stay, but not mortality rates (Welty and Copa, 1994). In another study, Marella et al. compared the efficacy of vancomycin TDM in critically ill adult patients undergoing extracorporeal membrane oxygenation and found no significant difference in mortality rates between the TDM group (62.3%) and the non-TDM group (68.4%) (Marella et al., 2020). Cardile et al. found that TDM successfully achieved the initial target trough concentration of vancomycin for Gram-positive cocci infections more rapidly, particularly for MRSA infections; however, there was no significant difference between the groups in terms of treatment failure and in-hospital mortality rates (Cardile et al., 2015). To our knowledge, our present study is the first to use large-scale data to confirm that monitoring vancomycin blood concentrations can significantly reduce mortality rates in critically ill patients when compared to the administration of vancomycin without monitoring. The strength of our study lies in the provision of detailed mortality data, a large sample size, and consistent results.

Vancomycin TDM provides substantial benefits for critically ill patients in several key aspects. First, attaining therapeutic levels of vancomycin in ICUs remains a significant challenge. Previous evidence indicated that 40%–55.8% of ICU patients do not attain adequate initial trough concentrations post-administration, potentially leading to therapeutic failure (Mahmoodian et al., 2016; Obara et al., 2016; Alshehri et al., 2020; Bakke et al., 2017). The implementation of TDM for vancomycin enables clinicians to tailor pharmacotherapy more precisely, ensuring the timely attainment of therapeutic targets (Bakke et al., 2017; Truong et al., 2018; Flannery et al., 2020) and enhancing the likelihood of treatment success (Ye et al., 2013; Shahrami et al., 2016). Many studies have investigated the relationship between mortality rates and trough concentrations or AUC/MIC within a specific range (Alshehri et al., 2020; Li et al., 2022; Chen et al., 2024). If the trough concentrations or AUC/MIC ratios fall outside of these therapeutic ranges, dose adjustments can be effectively employed to align with established targets, thereby mitigating the risk of mortality (Steinmetz et al., 2015; Casapao et al., 2015; Lodise et al., 2014). Furthermore, both trough concentrations and AUC can predict potential nephrotoxicity. When high trough concentrations or AUC are detected, adjustments in dosage and administration can prevent drug-related nephrotoxicity (Hall et al., 2024; Ishigo et al., 2024), thereby reducing patient mortality (Aljefri et al., 2019; Abdelmessih et al., 2022; Li et al., 2022; Chen et al., 2024). Although TDM increases medical costs, dosage adjustment remains cost-effective for some critically ill patients (Ye et al., 2016; Fernández de Gatta et al., 1996). These considerations clearly demonstrate the necessity of implementing vancomycin TDM in critical care settings.

Our subgroup analysis showed that patients diagnosed with sepsis or septic shock had better survival outcomes from monitoring vancomycin blood concentrations compared to those without such diagnoses. Patients receiving RRT, vasopressor drugs, or mechanical ventilation showed significantly greater survival benefits from monitoring vancomycin blood concentrations compared to those who did not. Compared to patients with eGFR ≥60 mL/min/1.73 m^2, those with eGFR <60 mL/min/1.73 m^2 gained survival benefits from monitoring vancomycin blood concentrations, especially those with eGFR <15 mL/min/1.73 m^2, while patients with eGFR ≥60 mL/min/1.73 m^2 did not show survival benefits. Additionally, patients with higher severity scores (APS III ≥40, OASIS ≥30, SAPS II ≥ 30) benefited from vancomycin TDM, while those with lower severity scores did not. These findings suggest that only critically ill patients with severe conditions benefit from monitoring vancomycin blood

concentrations. This indicates that monitoring vancomycin blood concentrations is especially important for critically ill patients, probably because precise dosing is necessary to balance efficacy and toxicity in severe cases. These findings are crucial for guiding clinical decisions regarding the implementation of TDM in critically ill patients receiving vancomycin.

Due to time constraints, a short ICU stay might preclude the possibility of conducting vancomycin TDM, even if it is needed. When excluding patients with an ICU stay of less than 48 h, our findings mirrored those of the entire cohort, further confirming the survival benefits of monitoring vancomycin blood concentrations for critically ill patients. Previously, most research on precise clinical guidance relating to vancomycin TDM focused on infections caused by MRSA (Steinmetz et al., 2015; Lodise et al., 2020; Bakke et al., 2017; Casapao et al., 2015; Lodise et al., 2014), whereas vancomycin was often used empirically in ICU settings (Cowley et al., 2019; Chow et al., 2020; Bostwick et al., 2019). To investigate the impact of monitoring vancomycin blood concentrations on mortality during empirical use, we excluded those with confirmed MRSA infections. Our results demonstrated clear survival benefits for severely ill patients without confirmed MRSA infection.

This study has several limitations that need to be considered. First, as a retrospective study, the non-randomized grouping of patients introduced inherent baseline disparities. To address potential selection and ascertainment biases, we used PSM to mitigate these disparities. However, residual confounding factors might have influenced prognostic outcomes for critically ill patients. Second, although our findings indicated that monitoring vancomycin blood concentrations reduced mortality in critically ill patients, our analysis did not consider cost-effectiveness. This leaves the economic feasibility of routine implementation for all critically ill patients uncertain. Third, monitoring vancomycin blood concentrations is not equivalent to completing the full TDM process; it merely represents a foundational step. Furthermore, due to the limitations of our data sources, we were unable to determine which patients underwent AUC monitoring and which only had trough levels measured. Moreover, it is unclear who led the TDM implementation, who interpreted the results, and how the treatment regimen was adjusted based on the monitoring results. Additionally, blood concentration monitoring may serve as a surrogate marker for overall higher quality of care, and the influence of other unknown variables on patient outcomes cannot be excluded. Fourth, due to the complex clinical scenarios of critically ill patients and the prevalence of infections, a definitive causal relationship between monitoring vancomycin blood concentrations and patient outcomes in critical care settings has yet to be established. Therefore, our findings should be interpreted with caution.

5 Conclusion

This cohort study showed that monitoring vancomycin blood concentrations is associated with a significantly lower 28 day mortality rate in critically ill patients, with greater survival benefits observed in those with more severe conditions, underscoring the importance of routine vancomycin TDM in these 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

The studies involving human subjects were approved, and the requirement for additional ethical approval was waived by the Clinical Research Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University. This waiver was granted because the MIMIC-IV database had already received ethical approval from the institutional review boards (IRBs) at Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The studies were conducted in accordance with local legislation and institutional requirements. Additionally, the ethics committee/institutional review board waived the requirement for written informed consent from participants or their legal guardians/next of kin, as the studies adhered to local legal and institutional guidelines and the database does not contain protected health information.

Author contributions

HP: Data curation, Formal Analysis, Investigation, Validation, Writing–original draft, Methodology, Writing–review and editing, Project administration, Visualization. YO: Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing–original draft, Project administration, Software. RZ: Project administration, Validation, Visualization, Data curation, Writing–original draft, Formal Analysis, Investigation, Methodology. RW: Supervision, Writing–original draft, Methodology. DW: Supervision, Writing–review and editing, Methodology. QY: Supervision, Writing–review and editing, Data curation, Methodology, Project administration, Software, Validation. XL: Supervision, Writing–review and editing, Data curation, Methodology, Project administration, Resources, Validation, Funding acquisition.

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 Medical Scientific Research Foundation of Guangdong Province (No. B2024150), Guangzhou Health Science and Technology Project (No. 20251A011077) and the Hospital Pharmacy Research Foundation of Guangdong Province (No. 2023KJ16).

Acknowledgments

The authors express their deep gratitude to all the researchers who built and maintained the MIMIC IV database.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1458600/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 05 December 2024
DOI 10.3389/fphar.2024.1427772

OPEN ACCESS

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RECEIVED 04 May 2024
ACCEPTED 20 November 2024
PUBLISHED 05 December 2024

CITATION
Montané E, Sanz Y, Martin S, Pérez-Mañá C, Papaseit E, Hladun O, De la Rosa G and Farré M (2024) Spontaneous adverse drug reactions reported in a thirteen-year pharmacovigilance program in a tertiary university hospital. *Front. Pharmacol.* 15:1427772. doi: 10.3389/fphar.2024.1427772

Spontaneous adverse drug reactions reported in a thirteen-year pharmacovigilance program in a tertiary university hospital

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Objectives: We aimed to assess the characteristics of adverse drug reactions (ADRs) collected in a university hospital.

Methods: A retrospective analysis of ADRs spontaneously reported in the Hospital Pharmacovigilance Program database (RutiRAM) over a 13-year period was conducted. The analysis included a description of ADRs [System Organ Class (SOC)] and their seriousness, the drugs involved [level 1 of the Anatomical Therapeutic Chemical (ATC) Classification System], drug-drug interactions, medication errors, drugs 'under additional monitoring', positive rechallenge, and the 'pharmacovigilance interest' of ADRs. An ADR was considered of 'pharmacovigilance interest' when it was serious, and/or produced sequelae, and/or affected the paediatric population, and/or when the suspected drug was 'under additional monitoring'. Additionally, an exploratory analysis for bivariate associations through an automated method was performed.

Results: A total of 2,148 spontaneous ADRs were registered in the RutiRAM database, with 92.5% recorded by medical doctors. The mean age of cases was 59.2 years (SD 20.9), range 1 day–99 years; 5.7% were paediatric, 46.2% adults, and 48.1% elderly. The drugs most often involved were anti-infectives (ATC group J), mainly amoxicillin-clavulanic acid. 'Blood system disorders' were the most frequent SOC ADRs, and skin rashes were the most frequent ADRs. The 63.2% of ADRs were considered of 'pharmacovigilance interest'. Almost half of ADRs were hospital-acquired, and these were related to medication error; serious ADRs were related to drug-drug interactions and elderly patients, and involved drugs 'under additional monitoring' were related to younger ones.

Conclusion: This is the first study to overview of ADRs reported in an HPVP over more than a decade. Almost two-thirds of the ADRs collected in the RutiRAM database are of sufficient quality to be classified as 'pharmacovigilance interest', and thus can contribute to signal detection and the issuing of drug alerts by

pharmacovigilance systems. Analysing ADRs in hospitals contributes to patient safety by implementing relevant actions to prevent medication errors or ADRs, some of which can be applied to other centres.

KEYWORDS

pharmacovigilance, postmarketing drug safety, adverse drug reaction, spontaneous reporting systems, patient safety

1 Introduction

Adverse drug reactions (ADRs) are unwanted results of pharmacological therapy. ADRs worsen the quality of life of patients, increase hospital admissions, lengthen hospital stays, increase mortality, and represent a considerable economic burden for health systems (Pirmohamed et al., 2004; Montané and Castells, 2021; Sultana et al., 2013; Davies et al., 2009).

The definition of ADRs has evolved over time. The first and globally recognized definition was proposed by the World Health Organization (WHO) (World health organization technical report series, 1972); but in the last decade, a new European legislation on pharmacovigilance appeared, which is currently in force and has broadened the definition of ADR to 'A response to a medicinal product which is noxious and unintended', which includes off-label use, medication errors, drug abuse, and drug misuse (Commission directive 2010, 2010). The WHO has defined pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine/vaccine related problems' (World Health Organization, 2024).

The primary approach in pharmacovigilance to generate signals or alerts and to identify emerging safety concerns is through the spontaneous reporting of suspected ADRs. Its key benefits encompass its simplicity and cost-effectiveness, but the most acknowledged drawbacks involve underreporting and the inability to calculate incidence rates (Pal et al., 2013). Underreporting results in reduced method sensitivity, often leading to delays in signal detection (Hazell and Shakir, 2006). Priority ADR notifications include cases related to recently marketed medications that require further follow-up, events not previously documented, serious ADRs, and those that impact the paediatric patients (Guidelines for Detecting & Reporting Adverse Drug Reactions, 2014).

The major pharmacovigilance systems for the collection of spontaneous ADRs available worldwide are the Food and Drug Administration's Adverse Event Reporting System (FAERS) (from the USA), European Medicines Agency's (EMA) network system for reporting and evaluating suspected ADRs called Eudravigilance (from the European Union), the Japanese Adverse Drug Event Report (JADER) database, and the global database of individual case safety reports Vigibase (from the members of the WHO program for international drug monitoring) (The European network of centres for pharmacoepidemiology and pharmacovigilance guide on methodological standards in pharmacoepidemiology, 2024). The characteristics of the reported ADRs may vary in different countries and regions due to demographic and genetic characteristics of the population, and the patterns of drug consumption (Leporini et al., 2017). In Spain, the Spanish Pharmacovigilance System monitors medicine safety. Its main goal is to ensure medicines are safe and to identify, assess, and minimize potential risks. It operates under the European pharmacovigilance framework, coordinated by the Spanish Agency for Medicines and Medical Devices (AEMPS). There are 17 autonomous pharmacovigilance centres that contribute data to the national database (FEDRA), through spontaneous reports from physicians, pharmacists, nurses, and other healthcare providers, as well as patients and citizens. Hospitals report ADRs either individually or centrally through an Hospital Pharmacovigilance Program (HPVP) reporting their collected cases to the autonomous pharmacovigilance centre. Where they exist, the content of the HPVP may differ from one hospital to another, but they share the same objectives: detecting, quantifying, and preventing ADRs to increase patient safety.

Considering that the regulatory framework establishes pharmacovigilance as an activity of shared responsibility among all agents involved, such as hospitals, participation through their Pharmacovigilance Program is necessary for monitoring serious and even fatal ADRs, among others (Guideline on good pharmacovigilance practices GVP, 2017). Preliminary data from low-income countries have been published, but little is reported about data from tertiary care hospitals and their pharmacovigilance programs in high-income countries (Jha et al., 2009; Geer et al., 2016; Kaur et al., 2020; Lobo et al., 2013; Alsbou et al., 2015).

The aims of the present study were to determine the characteristics of ADRs in patients registered in the Hospital Pharmacovigilance Program database over a 13-year period and to assess their quality according to 'pharmacovigilance interest'.

2 Methods

We followed the STROBE Statement to report the study sections and their contents (Vandenbroucke et al., 2007).

2.1 Study setting

The Germans Trias i Pujol Hospital is a tertiary care hospital with 734 beds for a population of about 850,000 people living in the Barcelonès Nord I Maresme area of Barcelona, in Catalonia, Spain.

The study was approved by the Research Ethics Committee of the Germans Trias i Pujol Hospital in 2019 and was conducted in 2023.

The HPVP at Germans Trias i Pujol Hospital was formally established in 2006, although some pharmacovigilance activity had been carried out previously. The main pharmacovigilance activities of this HPVP are to detect, quantify, and prevent ADRs as much as

possible to increase inpatient safety. Currently, the detection of ADRs is powered by spontaneous notifications from healthcare professionals made through the hospital's electronic yellow card. The registered ADRs come from any patient who is seen in the hospital, such as patients attending the emergency department, hospitalized patients, and outpatients followed up by hospital specialists. Suspected ADRs notifications, reported by different healthcare professionals, namely, medical doctors, nurses, medical students, and pharmacists of the hospital, are prospectively collected. A spontaneous report of an ADR includes the following minimal information: patient identification data, name of the suspected drug or drugs, description of the adverse reaction, and identification data of the reporter. Clinical pharmacologists are charged with collecting all the detailed data from electronic health record required for the yellow card. The Drug Safety Committee of the hospital accurately evaluates all the suspected ADRs. When the cases are considered possible, probable, or definite causality attribution according to the Spanish pharmacovigilance algorithm, the ADRs are included in the hospital registry named 'RutiRAM database'. Incomplete ADR outcomes are annually updated until January 31 of the following year.

2.2 Study design

We conducted a retrospective analysis of all ADRs reported by health professionals at the Germans Trias i Pujol Hospital and registered in the RutiRAM database over 13 years, between 1 January 2010, and 31 December 2022.

2.3 Study population

All ADRs recorded in the RutiRAM database were selected and included in the study. The included cases were previously reported to the Spanish Pharmacovigilance System, except those in which the patient was included in a clinical trial, because these ADR reports follow a specific notification system.

2.4 Variables

The following information was extracted for each ADR from the registry: year reported, healthcare reporter, origin of the ADR, age and sex of the patient, type and system organ class related to the ADR, type and number of drugs involved, drugs 'under additional monitoring', drug-drug interaction, type of interaction, medication error, seriousness of the ADR, 'pharmacovigilance interest' of the ADR, positive rechallenge of involved suspected drug, and outcome of the ADR.

2.4.1 Variable definitions and classifications

ADRs: descriptive terms of reactions were classified by the System Organ Classes (SOC) according to the MedDRA dictionary (Medical Dictionary for Regulatory Activities) (MedDRA Maintenance and Support Services Organization, 2023).

ADR origin: the origin of the ADRs was classified as hospital-acquired when the reaction occurred during hospitalization, in the emergency department, or in the area where patients receive treatments. ADRs that occurred in outpatient clinics or led to hospital admission were classified as non-hospital-acquired ADRs.

Age groups of the population: three groups were defined: paediatric (until 17 years old), adults (18–64 years), and elderly (65 years or more).

Drug classes: suspected drugs were classified according to the categories of the Anatomical Therapeutic Chemical (ATC) classification System (level 1) (WHO Collaborating Centre for Drug Statistics Methodology, 2024).

Nonprescription drugs: suspected nonprescription drugs were illegal drugs, herbal medicines, or dietary supplements, which are not classified in the ATC Classification System, therefore they were analysed separately.

Drug-drug interaction: if a drug-drug interaction was suspected a review of the literature was done to document the interaction. Drug-drug interactions were classified as either pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions were defined as those in which drugs influence each other's pharmacologic effect, and were evaluated if they were synergistic or antagonistic. Pharmacokinetic interactions were defined as those in which a drug could result in the increase or the decrease of plasma drug concentrations (Cascorbi, 2012).

Drugs 'under additional monitoring': drugs were classified as being or not 'under additional monitoring'. 'Additional monitoring' is a term denoted by the EMA to medicines that are more intensively monitored than others (Medicines under additional monitoring, 2024). This is generally because there is less safety information available, for example, because the medicine has been recently marketed or there is limited data on its long-term use. A drug with additional follow-up is a drug that had an inverted black triangle (▼) on the package leaflet. A drug was denoted as 'under additional monitoring' if it was included in the EMA's list of medicines 'under additional monitoring' according to the year in which the ADR occurred (List of medicines under additional, 2024).

Healthcare reporters: healthcare professionals were classified as doctors, pharmacists, nurses, and medical students. Nursing assistants and radiology technicians were included in the nurses group. Medical students from the Germans Trias i Pujol Teaching Unit (Autonomous University of Barcelona) do their internships at the hospital, and during the fifth year they have a voluntary learning activity that consists of identifying and collecting suspected ADRs.

Medication error: a medication error was defined according to the National Coordinating Council for Medication Error Reporting and Prevention: 'medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use (About Medication Errors, 2024).

'Pharmacovigilance interest': an ADR was considered of pharmacovigilance interest when it was serious, and/or produced sequelae, and/or affected the paediatric population, and/or when the suspected drug was 'under additional monitoring' (Montané and Santesmases, 2020).

Rechallenge: a positive rechallenge was considered when following an adverse reaction that had been resolved by withdrawal of the suspected drug, the drug was re-administered and the same ADR reappeared (Stephens, 1983; Girard, 1987).

Seriousness of ADRs: a serious ADR was defined according to the International Conference on Harmonization (ICH) guideline E2D which encompasses ADRs that are fatal, life-threatening, requiring hospital admission or prolongation of hospital stay, causing persistent or significant disability/incapacity, congenital anomaly/congenital defect or medically important. The remaining cases were defined as non-serious ADRs (European Medicines Agency, 2004).

Time periods: ADRs were grouped in two periods, the first from 2010 to 2016, and the second from 2017 to 2022.

2.5 ADR causality assessment

The Drug Safety Committee of the Hospital was composed of clinical pharmacologists, one of them being a senior specialist in pharmacovigilance, and specialised nurses. It was responsible for assessing the causality attribution of all reported ADRs in the HPVP. Each reported case was evaluated in detail by clinical pharmacologists using the modified Karch and Lasagna algorithm, that is used by the Spanish Pharmacovigilance System (Aguirre and García, 2016). This algorithm assesses the following five items: temporal relationship between the onset of the drug and onset of the reaction, knowledge of the reaction in the literature, the clinical effect of withdrawal and rechallenge to the drug involved, assessment of alternative causes, and background clinical factors that may have contributed to the onset of the reaction (Aguirre and García, 2016). ADRs have been included in the RutiRAM database if the Drug Safety Committee scored their causality attribution as 'possible', 'probable', or 'definite'.

2.6 Statistical analysis

For descriptive analysis, we used the number of cases and percentages for categorical variables; median and range for ordinal variables; and mean and standard deviation (SD) for continuous variables. ADRs by SOC and involved drugs by ATC were compared between two periods (2010–2016 vs. 2017–2022) using Chi-square or the Exact Fisher Test. Characteristics of serious and non-serious ADRs were compared using Chi-square Test.

Statistical analysis was performed using the SPSS statistical software package for Windows, version 29.0 (SPSS Inc., Chicago, IL, USA).

2.6.1 Exploratory data analysis

A thorough automated method for exploratory data analysis (AutoDiscovery, Butler Scientifics, Barcelona, Spain) was conducted to evaluate bivariate associations with the ADR origin, ADR seriousness and drugs 'under additional monitoring'. The suitable statistical approach was chosen based on the type of data and the distribution of the variables in each case, as assessed by AutoDiscovery. The statistical methods utilized were:

a) Spearman's Rank Correlation: for numerical variable pairs.
b) Variance Analysis: for categorical (factor) and numerical (response) variable pairs, specifically: ANOVA one-way: when the response fits the normal distribution (D'Agostino/Pearson test); U Mann-Whitney: when the response does not fit the normal distribution and the factor has exactly two categories; and Kruskal–Wallis: when the response does not fit the normal distribution and the factor has more than two categories.
c) Cramer's V Contingency Index: for categorical variable pairs.

This procedure was implemented in each potential subgroup of the dataset, created based on previously selected stratification factors (demographics, characteristics of the ADR and features of the drugs). Subgroups or associations having a sample size of fewer than 5, a sample size that is less than 1% of the total, or a significance level α (two-sided test) of 0.05 or higher were automatically discarded.

Due to the nature of this multi-test approach, a False Discovery Rate (FDR) correction method (Benjamini–Hochberg, 5% false discovery rate) was applied, providing a new *p*-value threshold of 0.0004 for highly significant results.

Lastly, expert evaluation of the recorded findings, particularly highly significant results, was undertaken to identify the most pertinent outcomes related to the initial objectives.

3 Results

During the 13-year study period, a total of 2,148 spontaneous ADRs cases were recorded in the RutiRAM database. The number of ADRs recorded annually ranged from 79 to 230, with an average of 165 ADRs per year. Of the ADRs, 92.5% (1,987/2,148) were reported by medical doctors, 3.1% (67/2,148) by nurses, 2.6% (55/2,148) by pharmacists, and 1.8% (39/2,148) by medical students.

These 2,148 suspected ADRs occurred in 1,905 patients (198 patients had two ADRs each, 35 patients presented three ADRs, eight patients had four ADRs, one patient had five ADRs, and another six ADRs). The mean age of cases was 59.2 years (SD 20.9), ranging from 1 day to 99 years (median 63 years), of which 53.3% (1,145/2,148 cases) were males. The distribution of ADRs by age group was: 5.7% were paediatric (122/2,148), 46.2% were adults (993/2,148), and 48.1% were elderly (1,033/2,148).

In 1.8% of ADRs (38/2,148 cases), they occurred in patients included in clinical trials.

3.1 Characteristics of ADRs

The most frequent ADR classified by SOC were blood and lymphatic system disorders (18.4%, 394/2,148 cases) and immune system disorders (14.1%, 302/2,148 cases) (Table 1). Generalized skin rash or erythema was the most frequent ADR (11.5%, 247/2,148 cases). The remaining most frequent types of ADRs are detailed in Table 2.

Of the total, 55.8% (1,198/2,148 cases) of ADRs were serious, 171 of which were fatal ADRs (8%, 171/2,148). A total of 47.5% (1,020/2,148 cases) of reported ADRs were hospital-acquired. A

TABLE 1 Distribution of adverse drug reactions (ADRs) by organ and systems classification (SOC).

Organ and systems classification (SOC)[a]	N (%)
Blood and lymphatic system disorders	394 (18.4)
Cardiac disorders	87 (4.0)
Congenital, familial and genetic disorders	6 (0.3)
Ear and labyrinth disorders	3 (0.1)
Endocrine disorders	67 (3.1)
Eye disorders	8 (0.4)
Gastrointestinal disorders	66 (3.1)
General disorders and alterations at site of administration	10 (0.4)
Hepatobiliary disorders	201 (9.4)
Immune system disorders	302 (14.1)
Infections and infestations	229 (10.7)
Traumatic injuries, intoxications and complications of therapeutic procedures	44 (2.0)
Metabolism and nutrition disorders	79 (3.7)
Musculoskeletal disorders	47 (2.2)
Neoplasm benign, malignant and unspecified	10 (0.5)
Nervous system disorders	145 (6.8)
Pregnancy, puerperium and perinatal conditions	2 (0.1)
Psychiatric disorders	18 (0.8)
Renal and urinary disorders	64 (3.0)
Reproductive system and breast disorders	5 (0.2)
Respiratory, thoracic and mediastinal disorders	50 (2.3)
Skin and subcutaneous tissue disorders	287 (13.3)
Vascular disorders	24 (1.1)
Total	2,148 (100)

[a]Medical Dictionary for Regulatory Activities (MedDRA®).

total of 1,358 ADRs (63.2%, 1,358/2,148) were considered ADRs of quality.

The evolution percentage of serious ADRs over time showed values of around 50% (ranging from 42% to 60%) except in 2011, 2015, and 2016, which were >60% (Figure 1).

3.2 Characteristics of suspected drugs

The median number of suspected drugs was 1.0 (ranging from 1 to 10). In 33.5% of ADRs (719/2,148 cases) there was more than one suspected drug involved: two drugs in 473 ADRs (22%, 473/2,148), three in 173 ADRs (8.1%, 173/2,148), four in 46 ADRs (2.1%, 46/2,148), and five or more in 27 ADRs (1.3%, 27/2,148). In 18.3% of ADRs (393/2,148) a drug-drug interaction was considered the cause of ADR; 93.9% of these were pharmacodynamic (369/393) and 6.9% (27/393) were pharmacokinetic interactions. The ADRs caused by pharmacodynamic interactions were mainly infections (38.2%, 141/369) related to antineoplastics and/or immunosuppressants drugs. In 240 ADRs (11.2%, 240/2,148) a drug 'under additional monitoring' was involved. In 134 ADRs (6.2%, 134/2,148) a positive rechallenge with the suspected drug was reported. Medication errors were observed in 4.4% of ADRs (95/2,148 cases).

In total, there were 3,170 suspected drugs involved in 2,148 ADRs; 27.2% of involved drugs (863/3,170) were classified in the ATC category J (Anti-infectives for systemic use) and 20.9% (663/3,170) in the category L (Antineoplastic agents and immunomodulators) (Table 3). There were 514 different involved drugs, being the most frequently reported amoxicillin-clavulanic acid (5.3%, 114/2,148 cases) and metamizole (4.9%, 105/2,148 cases) (Table 4). In 13 patients (12.4%, 13/105), metamizole was suspected of causing agranulocytosis or neutropenia, and in four of these reports it was the suspected drug concomitantly with beta-lactam antibiotics. Nonprescription drugs, including herbal medicines, dietary supplements, or illegal drugs were implicated in 20 ADRs (0.93%, 20/2,148). (Table 5).

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TABLE 2 Distribution of the most frequent Adverse Drug Reactions (ADRs) type reported and their most frequent involved drugs.

ADR[a] and most frequent involved drugs	Number of ADRs	%
Generalized erythema Antibiotics/metamizole/iodinate contrasts	247	11.5
Acute hepatitis Antibiotics (mainly amoxicillin-clavulanic acid)/statins (mainly atorvastatin)	97	4.5
Cerebral haemorrhage Acenocoumarol and/or AAS	87	4.1
Cholestasis Antibiotics (mainly amoxicillin-clavulanic acid)	39	1.8
Elevation of liver function tests Antibiotics/statins (mainly atorvastatin)	38	1.7
Agranulocytosis Beta-lactam antibiotics and/or metamizole	51	2.4
Renal failure Vancomycin/NSAID	48	2.2
Pseudomembranous colitis Beta-lactam antibiotics	46	2.1
Pneumonia Monoclonal antibodies and corticosteroids	46	2.1
Thrombocytopenia Enoxaparin	39	1.8
Angioedema Miscellaneous	38	1.8
Leukopenia Beta-lactam antibiotics	31	1.4
Infusion reaction Monoclonal antibodies/amphotericin B	29	1.3
Anaphylaxis Beta-lactam antibiotics/metamizole	28	1.3
DRESS syndrome Allopurinol/antibiotics/metamizole	27	1.3
Hematoma soft parts Enoxaparin	27	1.3
Localized erythema Antibiotics (mainly ciprofloxacin)	26	1.2
Anaphylactic shock Metamizole/beta-lactam antibiotics	26	1.2
Pancytopenia Antibiotics/antineoplastics	26	1.2
Hypophosphatemia Iron carboxymaltose	26	1.2
Pneumonitis Monoclonal antibodies (mainly rituximab)	25	1.2
SIADH syndrome (inadequate secretion of ADH syndrome) Selective serotonin reuptake inhibitors and diuretics	20	0.9
Total ADRs	2,148	100

[a]ADRs, reported for more than 19 cases.

Types of ADRs, reported for more than four cases (number of ADRs): eosinophilia (18), drowsiness (17), long QT, syndrome (16), septic shock (15), pancreatitis (15), hypersensitivity reaction (14), bronchospasm (14), generalized erythema (14), encephalopathy (14), hyponatremia (13), flu infection (13), upper gastrointestinal bleeding (12), haematuria (10), hypopotassaemia (10), digoxin poisoning (10), hypoglycaemia (9), convulsion (9), acute generalized exanthematic pustulosis (9), diarrhoea (8), atrioventricular block (8), cytomegalovirus reactivation (7), rectorrhagia (7), hyperpotassaemia (7), internal hematoma (7), herpes zoster infection (6), malignant neuroleptic syndrome (6), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (6), lactic acidosis (6), red man syndrome (6), rhabdomyolysis (5), autoimmune hepatitis (5), toxic epidermal necrolysis (5), infusion lumbar pain (5), hepatic failure (5), leukocytoclastic vasculitis (5), erythema multiforme (5), and hyperglycaemia (5).

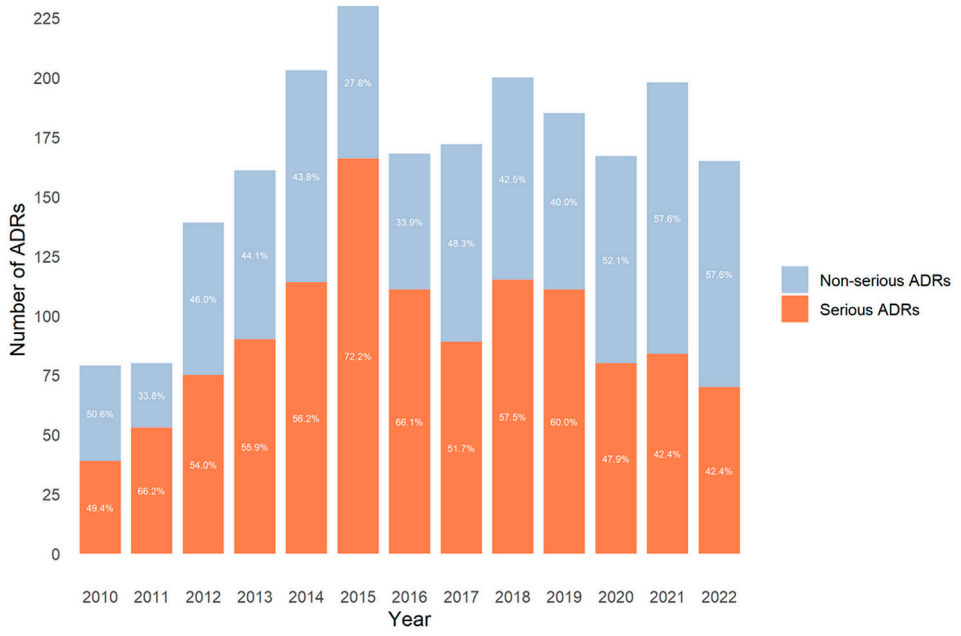

FIGURE 1
Distribution of the number of reported adverse drug reactions (ADRs) and seriousness by year.

TABLE 3 Distribution of the Anatomical Therapeutic Chemical (ATC) classification system of involved drugs.

ATC category	Therapeutic area	N	%
A	Alimentary tract and metabolism	132	4.2
B	Blood and blood forming organs	350	11.0
C	Cardiovascular system	316	10.0
D	Dermatological	11	0.3
G	Genito-urinary system and sex hormones	10	0.3
H	Systemic hormonal preparations, excluding sex-hormones and insulins	143	4.5
J	Anti-infectives for systemic use	863	27.2
L	Antineoplastic and immunomodulating agents	663	20.9
M	Musculo-skeletal system	126	4.0
N	Nervous system	447	14.1
P	Antiparasitic products, insecticides and repellents	17	0.5
R	Respiratory system	34	1.1
S	Sensory organs	2	0.1
V	Various	56	1.8
	Total	3,170	100

3.3 ADR outcome

The 81.8% of ADRs (1,758/2,148 cases) fully recovered, 2.7% of ADRs (57/2,148) had some sequelae, and in 11.1% of ADRs the patient died (239/2,148), of which 8% were drug-related death (DRD) (171/2,148) (in the remaining patients (68/2,148) the ADR was not the cause of the death). Additionally the 2.7% of ADRs (57/2,148) were ongoing and in 1.7% (37/2,148) the outcome was unknown when the data were extracted.

TABLE 4 The most frequent involved drugs in adverse drug reactions (ADRs).

Drugs[a]	Number of ADRs	%
Amoxicillin-clavulanic acid	114	5.3
Metamizole	105	4.9
Acenocoumarol	78	3.6
Acetylsalicylic acid	76	3.5
Enoxaparin	73	3.4
Prednisone	68	3.2
Vancomycin	55	2.6
Ceftriaxone	52	2.4
Levofloxacin	49	2.3
Omeprazole	47	2.2
Methotrexate	43	2.0
Piperacillin-tazobactam	43	2.0
Ciprofloxacin	41	1.9
Meropenem	39	1.8
Methylprednisolone	36	1.7
COVID-19 vaccine	36	1.7
Rituximab	36	1.7
Furosemide	34	1.6
Dexketoprofen	33	1.5
Infliximab	31	1.4
Mycophenolate acid	30	1.4
Total ADRs	2,148	100

[a]Drugs involved in at least 30 ADRs.

Drugs involved in more than four cases (number of ADRs): Cotrimoxazole (29), iron carboxymaltose (29), amiodarone (28), clopidogrel (28), tacrolimus (28), cefepime (26), enalapril (26), iomeprol (26), atorvastatin (25), ibuprofen (25), clindamycin (22), hydrochlorothiazide (22), cyclosporine (20), spironolactone (20), allopurinol (19), dexamethasone (19), sodium heparin (19), azathioprine (18), cyclophosphamide (18), nivolumab (18), cloxacillin (17), fentanyl (17), simvastatin (17), quetiapine (16), rifampicin (16), adalimumab (15), morphine (15), paracetamol (14), tocilizumab (14), tramadol (14), ceftazidime (13), cefuroxime (13), linezolid (13), paclitaxel (13), cefuroxime (12), cytarabine (12), digoxin (12), isoniazid (12), leflunomide (12), metformin (12), amikacin (11), phenytoin (11), propofol (11), sertraline (11), voriconazole (11), beta-lactams (10), cisplatin (10), dabigatran (10), diuretic (10), docetaxel (10), doxorubicin (10), fingolimod (10), gabapentin (10), gentamicin (10), olanzapine (10), ondansetron (10), pembrolizumab (10), rocuronium (10), valproic acid (10), azithromycin (9), diltiazem (9), haloperidol (9), lorazepam (9), mirtazapine (9), natalizumab (9), oxcarbazepine (9), vincristine (9), apixaban (8), cefotaxime (8), diclofenac (8), hydroxychloroquine (8), immunoglobulin (8), liposomal amphotericin B (8), metronidazole (8), risperidone (8), salbutamol (8), amoxicillin (7), bisoprolol (7), bortezomib (7), capecitabine (7), cetuximab (7), citalopram (7), everolimus (7), iodixanol (7), metoclopramide (7), remdesivir (7), torasemide (7), zoledronic acid (7), alprostadil (6), bictegravir/emtricitabine/tenofovir alafenamide (6), clonazepam (6), doxycycline (6), etanercept (6), fluoxetine (6), foscarnet (6), hydralazine (6), ionidated contrast agent (6), isotretinoin (6), lenalidomide (6), levetiracetam (6), lidocaine (6), losartan (6), sunitinib (6), alteplase rtpa (5), bendamustine (5), clomethiazole (5), durvalumab (5), etoposide (5), fluconazole (5), imatinib (5), itraconazole (5), lamivudine (5), naproxen (5), paroxetine (5), pemetrexed (5), ribavirin (5), ritonavir (5), trazodone (5), triamcinolone (5), valsartan (5).

3.4 Comparison of the characteristics of ADRs according to time periods

The number of ADRs reported during the 2010–2016 period was similar to those reported during the 2017–2022 period (1,060, 49.3% vs. 1,088, 50.7%; $p = 0.5600$).

The ATC of the drugs involved in ADRs was similar between the two periods, except for category L drugs, which were higher in the 2017–2022 period (16.9% vs. 24.8%; $p < 0.0001$) and category C drugs, which were lower in the second period (11.5% vs 8.4%; $p = 0.003$) (Figure 2).

The SOC of reported ADRs was similar between the two periods, except for those corresponding to 'Immune system disorders' and 'Skin and subcutaneous tissue disorders', which were higher in the 2017–2022 period (6.6% vs.12.4%; $p < 0.0001$, and 11.7% vs.14.8%; $p = 0.0359$; respectively), and for those corresponding to 'Infections and infestations' and 'Blood and lymphatic system disorders', which were lower in the 2017–2022 period (12.6% vs.8.8%; $p = 0.0052$, and 10.2% vs. 8.9%, $p = 0.0001$; respectively) (Figure 3).

3.5 Comparison of ADRs characteristics according to seriousness

Comparing of ADRs characteristics according to seriousness of ADRs showed that serious ADRs occurred in older patients (median

TABLE 5 Characteristics of adverse drug reactions (ADRs) involving herbal medicines, dietary supplements or illegal drugs.

	Product	ADR	Concomitant suspected drug	Seriousness
Herbal medicines	Aloe vera	Acute hepatitis	Interferon beta	Serious
	Colloidal gold	Acute hepatitis	None	Serious
	Copalchi	Cholestasis	None	Non serious
	Fucus + copalchi	Acute hepatitis	None	Serious
	Goji berries	Hyperpotassaemia	Enalapril	Serious
	Hedera	Tachycardia and urticaria	Ibuprofen	Serious
	Melissa officinalis	Somnolence	None	Serious
	Matcha green tea	Acute hepatitis	None	Serious
	Red yeast rice	Autoimmune hepatitis	None	Serious
Dietary supplements	Chlorine dioxide	Haemolytic anaemia	None	Serious
	Collagen + magnesium	Rhabdomyolysis and hepatitis	None	Serious
	Herbalife	Cholestasis	Atorvastatin	Non serious
	Oxid nitric	Myalgia	None	Serious
	Spascupreel	sudden death	None	Serious (death)
	Valentus Slimroast Optimum	Agranulocytosis	Naproxen/hydrochlorothiazide	Serious
	X-treme	Arthralgia	None	Serious
Illegal drugs	Cocaine	Vasculitis	None	Non serious
	Cocaine	Agranulocytosis	None	Serious
	Cocaine	Thrombotic microangiopathy	Ciprofloxacin/ustekinumab	Serious
	Cocaïne + heroin + amphetamine	Acute hepatitis	Paracetamol	Serious

age, 66 vs. 59 years, $p < 0.0004$) (Figure 4), drug-drug interactions were more frequently implicated (25.7% vs. 8.9%, $p < 0.0002$), as well as medication errors (4.9% vs. 3.7%, $p < 0.001$). On the other hand, serious ADRs were less often hospital-acquired (36.7% vs. 61.1%, $p < 0.001$), had fewer positive rechallenges (4.3% vs. 8.5%, $p < 0.0002$) and involved drugs 'under additional monitoring' less frequently (8.5% vs. 9.7%, $p = 0.002$) (Table 6).

3.6 Exploratory data analysis

Comparisons according to the origin of ADRs showed that hospital-acquired ADRs were more frequently related to error medication (6.5% vs. 2.4%, $p < 0.0002$) and to serious ADRs (67.2% vs. 43.1%, $p < 0.0002$). On the other hand, hospital-acquired ADRs were less related to drug-drug interactions (13.8% vs. 22.3%, $p < 0.0002$) and to drugs 'under additional monitoring' (3.6% vs. 13.9%, $p < 0.0002$), and less produced infections SOC (5.1% vs. 15.6%, $p < 0.0002$).

Comparisons according to ADRs with drugs 'under additional monitoring' involved (Figure 5) showed that patients with these ADRs were younger (median age 55 vs. 63 years, $p < 0.0004$). On the other hand, ADRs with a drug 'under additional monitoring' were less frequently related to the immune system disorder SOC (5.7% vs. 11.3%, $p < 0.0004$).

4 Discussion

Some medical institutions have developed ADR and medication error surveillance systems that are part of the HPVP, integrating pharmacovigilance into clinical practice and collaborating with the national pharmacovigilance system. In general, data on hospitals reporting ADRs to Pharmacovigilance Systems are scarce (Hazell and Shakir, 2006). In our centre, the number of suspected cases of ADR detected by HPVP is far from what would be expected based on the estimated incidences of ADR in the hospital setting (European Comission, 2024). There is clear underreporting as only a small proportion of the ADRs that occur are reported. According to the incidence described in the literature and considering that about 20,000 patients are admitted to the hospital each year, it is expected that approximately 1,000 patients will be admitted for an ADR and 1,000 patients will present an ADR during their hospital stay per year. Given that the RutiRAM database recorded an average of 165 ADR notifications per year, which represents 8.2% of the expected ADRs per year, there is a clear underreporting of ADRs; nevertheless, these results are similar to those described in other studies (Hazell and Shakir, 2006). On the other hand, healthcare professionals regularly report suspected ADRs to the HPVP as a sign of their commitment to pharmacovigilance. Regarding the profile of these healthcare professionals, in our study the reports were mostly submitted by physicians; in

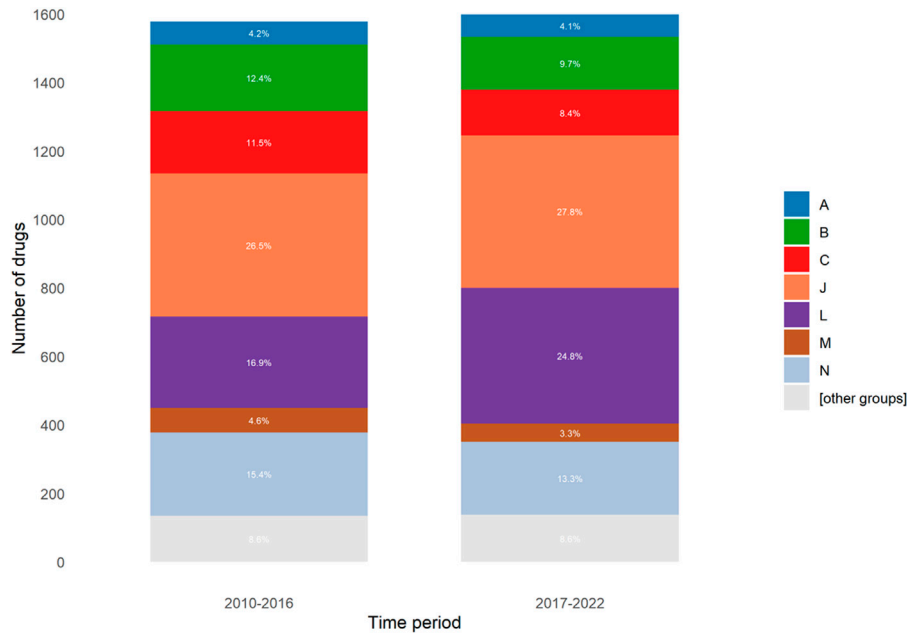

FIGURE 2
Distribution of involved drugs according to ATC classification for each period.

contrast to other pharmacovigilance programs wherereports were mostly made by pharmacists or nurses (Pérez-Ricart et al., 2019; Molina-Castiella and Napal-Lecumberri, 1999; Abu Esba et al., 2021). This could be explained by the fact that the HPVP in our hospital is designed and implemented by physicians who are specialised in clinical pharmacology. In any case, the most relevant aspect is that the participation of different categories of health professionals enriches the Pharmacovigilance Program because each group will observe different kinds of drug related problems (The importance of pharmacovigilance, 2002). Unlike other pharmacovigilance systems, patients did not participate in the reporting of ADRs in our HPVP.

The age of patients reported in our study and the slightly high prevalence of males were similar to those in another study (Pérez-Ricart et al., 2019; Brodsky et al., 2014). The most frequent ADR, as classified by SOC, was Blood and lymphatic system disorders and Immune system disorders, differing from data in other pharmacovigilance studies (Aagaard et al., 2012); where Skin and subcutaneous tissue disorders are globally the most frequently ADR reported, probably due to the fact that these ADRs come from primary healthcare settings, which are included in pharmacovigilance systems (Leporini et al., 2017; Brodsky et al., 2014; Marques et al., 2014), or due to their easier recognition by healthcare professionals (Pérez-Ricart et al., 2019).

On the other hand, 'Antibacterials for systemic use' (ATC code J) and/or 'Antineoplastic agents' (ATC code L) were the therapeutic subgroups mainly implicated in our study and several pharmacovigilance studies (Leporini et al., 2017; Pérez-Ricart et al., 2019; Molina-Castiella and Napal-Lecumberri, 1999; Brodsky et al., 2014). In contrast, these data differ from a previous study conducted in our hospital focusing on drug-related deaths, where the most frequently implicated therapeutic drugs were 'Antineoplastic agents' (ATC code L) and those of 'Blood and blood forming organs' (ATC code B) (Montané et al., 2018). The most frequently involved drugs in ADRs were amoxicillin-clavulanic acid and metamizole, both highly consumed in our country in primary care and in hospitalized patients. None of them are considered critical drugs by the EMA (The first Union list of, 2023); thus, they do not require any special supervision, unlike anticoagulants, for example, that must be carefully selected, monitored, and evaluated (O'Donnell, 2012). However, it is important to mention that recently, the EMA conducted a reassessment of the safety of metamizole due to cases of agranulocytosis and established risk minimization measures (EMA recommends measures to minimise, 2024). Thus, we would like to point out that metamizole was involved in 13 cases of agranulocytosis.

More than half of the reported ADRs were serious, and specifically 8% were DRD. These proportions are higher than in other studies probably due to reporting bias, since in our hospital's HPVP we encourage reporting DRDs because it is a topic of interest to us and we have published results from previous studies (Montané et al., 2018; Arellano et al., 2021). In addition, in studies of pharmacovigilance system data, the ADRs registered are generally milder than those reported in hospitals, since primary healthcare is usually the main reporting institution (Molina-Castiella and Napal-Lecumberri, 1999).

Almost two-thirds of the ADRs were considered of 'pharmacovigilance interest' because they met the priority reporting criteria of pharmacovigilance systems (Guidelines for Detecting & Reporting Adverse Drug Reactions, 2014); this could be considered as an indicator of high-quality of the ADRs registered in RutiRAM database. In support of this idea, we have identified that the paediatric cases included in RutiRAM generated drug safety alerts from the

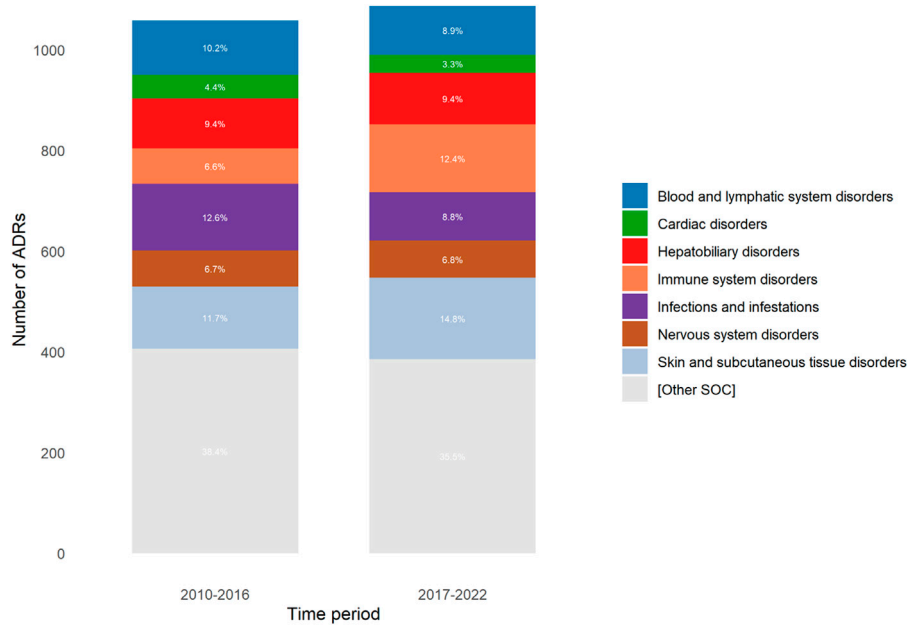

FIGURE 3
Distribution of adverse drug reactions (ADRs) according to SOC (System Organ Classification) for each period.

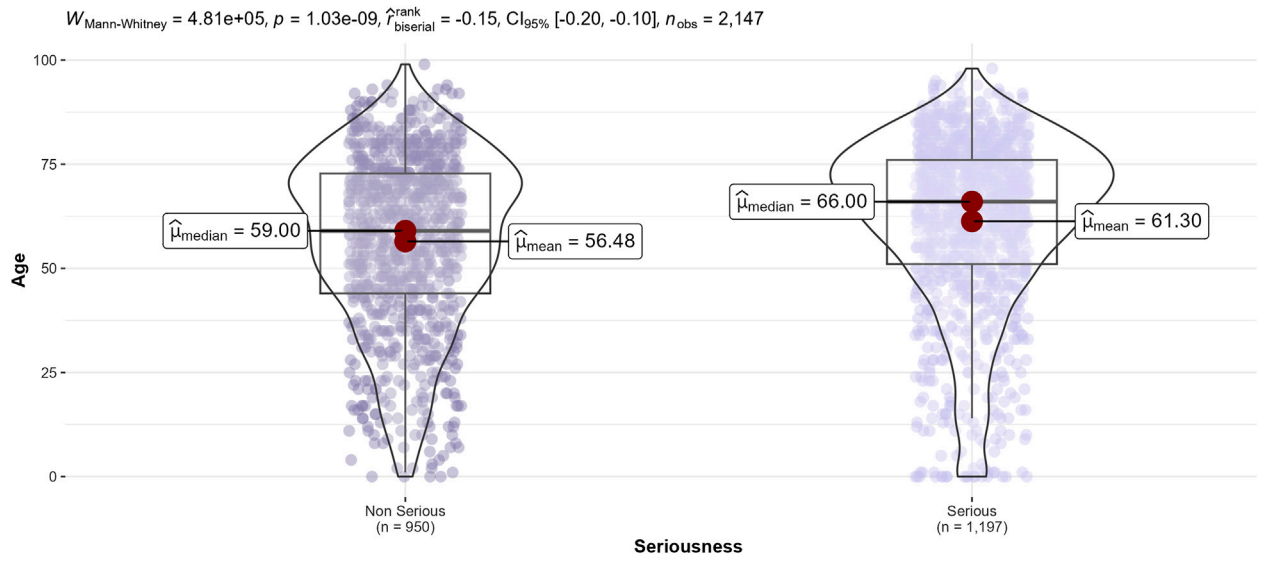

FIGURE 4
Distribution of patients' age of adverse drug reactions according to seriousness.

Spanish Medicines Agency as explained in a previous published article (López-Valverde et al., 2021); therefore, we stress the importance of reporting and recording ADRs that occur in the hospital setting, thus contributing to the generation of drug safety alerts at national or international level (Filippi-Arriaga et al., 2023). Furthermore, despite the major limitations of the spontaneous ADR reporting systems, HPVP role is valuable in monitoring internal patterns and carrying actions for improving patient safety, which can be addressed through internal hospital policies (Abu Esba et al., 2021). Examples of actions carried out in our centre are the warning of hypophosphatemia in the electronic application when prescribing intravenous iron in hospitalised patients and the mandatory reporting of drug allergies in the electronic prescription application to avoid prescription errors. To provide feedback to ADRs reporters, annual sessions are held to review trends and summarize the ADR analysis, and in a very short time, healthcare professionals will be able to access to RutiRAM database to monitor and

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TABLE 6 Comparison of characteristics of ADRs according to seriousness.

	Serious ADRs N = 1,198	Non-serious ADRs N = 950	Total N = 2,148	P
Sex, men (n, %)	619 (51.7%)	526 (55.4%)	1,145 (53.3%)	0.088
Age (years), median (range)	66 (0–98)	59 (0–99)	63 (0–99)	0.004
Hospital-acquired ADR	440 (36.7%)	580 (61.1%)	1,020 (47.5%)	<0.001
Drug-drug interaction	308 (25.7%)	85 (8.9%)	393 (18.3%)	<0.001
Drugs 'under additional monitoring'	102 (8.5%)	92 (9.7%)	194 (9%)	0.002
Positive rechallenge	53 (4.3%)	81 (8.5%)	134 (6.2%)	<0.001
Medication error	59 (4.9%)	35 (3.7%)	94 (4.4%)	<0.001

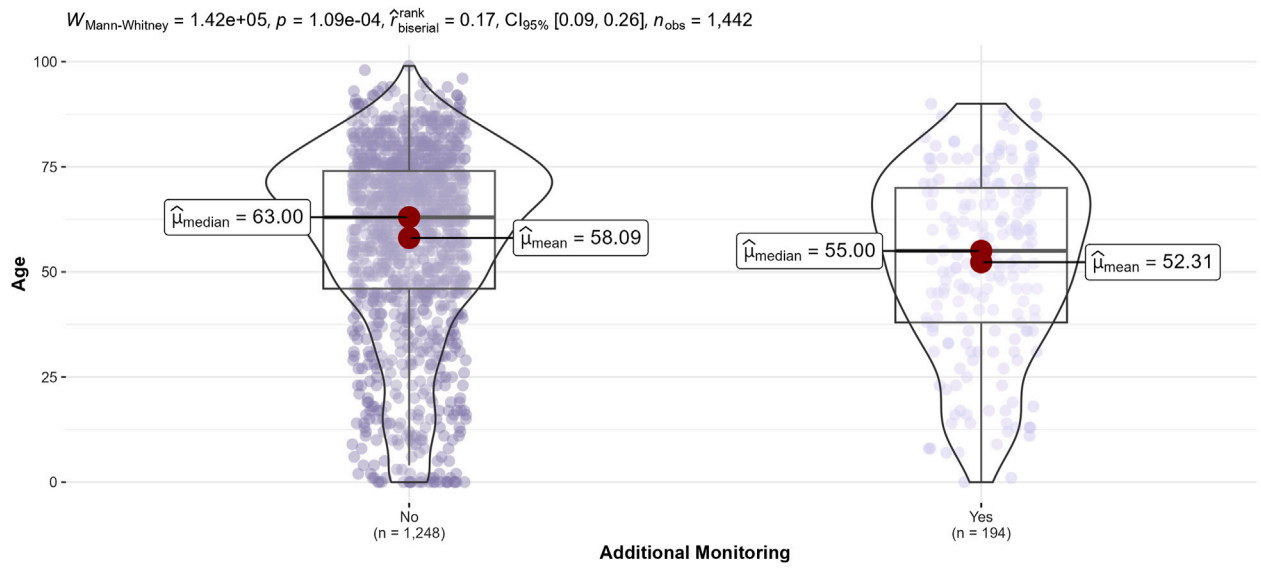

FIGURE 5
Distribution of patients' age of adverse drug reactions according to drugs 'under additional monitoring' involved.

analyse ADRs occurring in their area of hospitalisation. In addition, in a new pharmacovigilance project recently implemented in our centre, RutiRAM data are also used to calculate the risk of inpatients to present an ADR during their stay. Other ongoing actions carried out in the hospital that can improve the drug and patient safety include educational interventions such as training and informing health professionals about ADRs, having experienced nurses for managing critical drugs in hospitalized patients, encouraging consultation with clinical pharmacologists for causality assessment of suspected ADR, monitoring plasma levels of drugs with narrow therapeutic margins, and using electronic prescription tools to prevent errors and drug-drug interactions.

The comparison of the number of ADRs between two periods was similar. When comparing the ATC group of involved drugs, the percentage of L group drugs increased in the second period, probably due to the increase of its use for the treatment of cancer or autoimmune diseases (Kesik-Brodacka, 2018). When comparing the SOC of reported ADRs, those corresponding to 'Immune system disorders' and 'Skin and subcutaneous tissue disorders' have increased, probably due to the incorporation of specialists in dermatology and allergology in the pharmacovigilance committee integrated in the HPVP, one of its main objectives is to increase ADR reporting. On the other hand, the ADRs corresponding to 'Infections and infestations' have decreased in the second period due to organizational circumstances that delayed the notification of 17 cases that occurred in that period and, consequently, were not included.

The exploratory data analysis found that medication errors were more frequent in hospital-acquired ADRs, which could be explained by the fact that most cases have been identified through the medication error committee; drug-drug interactions were more frequent in serious ADRs, which include infections related to immunosuppressants and bleeding related to antithrombotic agents (Marengoni et al., 2014; Létinier et al., 2021). Serious ADRs were related to elderly patients (Monteiro et al., 2021), while drugs 'under additional monitoring' were more commonly involved with younger patients. These age differences can be explained by the fact that older patients have comorbidities that can complicate ADRs and lead to serious outomes, while some of the

drugs 'under additional monitoring' are for neoplastic diseases, which often affect adult patients.

4.1 Limitations and strengths

The study has several limitations. The primary limitation is associated with the inherent underreporting of ADRs in spontaneous reporting. This implies that these reported cases represent only a small fraction of the actual occurrences, estimated as 10% or less (Hazell and Shakir, 2006). It is necessary to recall that the incidence of ADRs cannot be obtained through spontaneous reporting because data on the number of patients exposed to a drug (denominator) and data on the number of patients with an ADR (numerator) are not known (Pal et al., 2013; Hazell and Shakir, 2006). Another limitation is the retrospective design of the study, which could affect the collection of some variables such as patients' comorbidities or number of concomitant drugs, although it would not change the overall results. In addition, this study was conducted in a single centre where there is a specific HPVP with its own characteristics, which introduces a reporting bias that complicates the extrapolation of results and robust comparisons with pharmacovigilance programs in other hospitals. Some of the ADRs reported in the RutiRAM database are closely linked to the fact that clinical pharmacologists specialized in pharmacovigilance are members of clinical hospital committees such as the mortality committee, the committee for the prevention of medication errors and the committee for the prevention of infections in patients on immunosuppressive biologic drugs.

The study also has strengths. This is the first study conducted in Europe based on a HPVP with data on suspected ADRs for more than 10 years. This study includes ADRs across all areas related to the hospital where patients are admitted, receive treatments or surgery, home hospitalization and outpatient clinics, unlike most of the available studies, which only evaluate specific clinical areas or services within the hospital. Information collected from cases is very detailed, and its quality is high because the data were carefully collected and validated by clinical pharmacologists with expertise in pharmacovigilance (Begaud et al., 1994). We have assessed many variables not included in previous pharmacovigilance studies, such as drugs 'under additional monitoring', medication error, positive rechallenge, and 'pharmacovigilance interest'. Some of the included drugs are used exclusively in hospitals. Furthermore, the study duration is sufficient to derive meaningful conclusions. An exploratory data analysis has also been conducted to identify associations between the study variables revealing new and interesting results.

5 Conclusions

This is the first study to provide an overview of ADRs reported in an HPVP over more than a decade. More than half of the ADRs were serious, which were related to older patients and drug-drug interactions. Almost two-thirds of the ADRs collected in the RutiRAM database are of sufficient quality to be classified as 'pharmacovigilance interest', and thus can contribute to signal detection and the issuing of drug alerts by pharmacovigilance systems. Analysing ADRs occurring in the hospital setting help to contribute to the improvement of patient safety with the implementation of specific actions to avoid medication errors or prevent ADRs, some of which can be generalized to other centres.

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 the Hospital Universitari Germans Trias i Pujol. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because it was a retrospective observational study using pseudo-anonymised data.

Author contributions

EM: Writing–review and editing, Writing–original draft. YS: Writing–review and editing. SM: Writing–review and editing. CP-M: Writing–review and editing. EP: Writing–review and editing. OH: Writing–review and editing. GR: Writing–review and editing. MF: 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.

Acknowledgments

We would like to thank healthcare professionals of the Hospital Universitari Germans Trias i Pujol for their contribution to the reporting adverse drug reactions.

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

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