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Pharmacoepidemiology and pharmacovigilance post-marketing drug safety studies

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Pharmacoepidemiology and pharmacovigilance post-marketing drug safety studies

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Editorial: Pharmacoepidemiology and pharmacovigilance post-marketing drug safety studies

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pharmacovigilance, drug, patient safety, real world data (RWD), adverse events

Editorial on the Research Topic
Pharmacoepidemiology and pharmacovigilance post-marketing drug safety studies

Introduction

Pharmacoepidemiology defined as "the study of the usage and effects of drugs in a large group of people" enables the cost-effective inclusion of significantly larger number of patients compared to pre-marketing studies, leading to a more accurate measurement of both the adverse and beneficial effects of drugs. Pharmacoepidemiological studies provide better quantification of the incidence of known adverse and beneficial effects in patients not enrolled in clinical trials, and those with multiple diseases and taking concurrent medication. These studies also assess the relative effectiveness and safety of drugs used for the same condition. Additionally, they provide information not obtainable from pre-marketing studies, such as insight into rare and delayed effects, pattern of drug utilization, effects of overdose, economic implications of drug use, and reassurance regarding drug safety (Strom, 2019; Crescioli et al., 2022). Whereas, pharmacovigilance defined as "the science and practices relating to the identification, assessment, understanding, and prevention of adverse drug events or any other potential drug-related problems" (WHO, 2002). It plays an important role in post-marketing drug safety studies. It encompasses detecting, assessing and reporting adverse drug reactions (ADRs), signal detection, elucidation of pharmacological and toxicological properties of drugs, identifying high risk patients, drug interactions, ADRs risk management, post-marketing surveillance, and taking regulatory actions when safety concerns arise (Raj et al., 2019; Trifirò and Crisafulli, 2022).

The full implementation of pharmacovigilance practices is one of the prerequisites for the rational use of drugs. Pharmacoepidemiology provides vital methodological support in achieving and maintaining this pharmacovigilance contribution in the periods before, during and after the use of drugs (Akici and Oktay, 2007; Gulmez et al., 2020). Pharmacoepidemiology and pharmacovigilance work in synergy (Bérard, 2021; Lavertu et al., 2021; Crescioli et al., 2022). These studies are crucial for augmenting pre-marketing evidence, providing insights into the risk-benefit profile of drugs as well as its use in larger patient populations. They hold significant potential to contribute to post-marketing drug safety assessments. Utilizing real-world data sources, including spontaneous reporting system databases like the World Health Organization (WHO) global pharmacovigilance database (VigiBase), the FDA Adverse Event Reporting System (FAERS), the EudraVigilance database of European Medication Agency, as well as claims databases, electronic healthcare records, and drug/disease registers, pharmacovigilance and pharmacoepidemiologic studies continuously monitor approved and marketed drugs. This ongoing monitoring process is crucial for the timely detection of new ADRs (Bérard, 2021; Crisafulli et al., 2023).

This Research Topic included 16 articles with various study approaches. These included disproportionality analysis of antiarrhythmic drugs (AADs) associated with cardiac arrhythmias by Wang et al. Additionally, Wei et al. investigated differences in adverse events among methylphenidate, atomoxetine and amphetamine, adverse events associated with molnupiravir by Liang et al. and post-marketing safety surveillance of sacituzumab govitecan were examined by utilizing FDA FAERS database in a study conducted by Liu et al. Moreover, Liu et al. also examined the pharmacovigilance and clinical characteristics of heparin-induced thrombocytopenia caused by low-molecular-weight heparin. Giner-Soriano et al. explored the information on the effectiveness and safety of oral anti-coagulants for the prevention of stroke in non-valvular atrial fibrillation was gathered from the electronic health records of Primary Healthcare. Data mining of the WHO global pharmacovigilance database (VigiBase) was conducted Sharif et al. to examine sex -specific safety response to dual Interleukin 4 (IL-4) and Interleukin 13 (IL-13) blockade by dupilumab. Prevost et al. analyzed the real-world cases of neurocognitive impairment with endocrine therapies and cycline-dependent-kinase-4/6 inhibitors (iCDK4/6s) in breast cancer were analyzed by utilizing WHO VigiBase. An opinion based article by Luthra and Toklu within this Research Topic underscored the importance of reporting safety concerns and adverse events associated with nutraceuticals. The authors advocated for the incorporation of pharmacovigilance into health programs curricula, public awareness initiatives and future post-marketing drug safety studies, specifically emphasizing the need for nutrivigilance to enhance the overall pharmacovigilance system.

A study conducted in Korea by Kim et al. compared the antidepressant ADR signal profiles between data from the national health insurance claim and the Korea Adverse Event Reporting System highlighted the importance of integrating data from various sources, providing significant regulatory insights and broadening the scope of pharmacovigilance. Zou et al. examines the FDA's FAERS database in relation to mepolizumab side effects including 18,040 reports of adverse events linked to mepolizumab. This study indicated that these details will be very helpful in putting the medication to use practically in clinical settings.

A study conducted by Xia et al. observed the possible correlation between pericarditis and biological disease-modifying antirheumatic medications (bDMARDs) as well as the clinical features of ankylosing spondylitis (AS). This study reported 1,874 reports of pericarditis caused by bDMARDs (11.3% of which were fatal). This study encouraged additional studies to understand the underlying mechanisms and uncover patient-related susceptibility factors, therefore promoting earlier diagnosis and safer prescribing of bDMARDs. While, Sun et al. examined the AE signals using four anti- Calcitonin gene-related peptide antibodies (CGRP) monoclonal antibodies (mAbs) including erenumab, galcanezumab, fremanezumab and eptinezumab in the FDA FAERS database to investigate the post-marketing safety profile of these drugs. The number of reports obtained from FDA FAERS database for erenumab, galcanezumab, fremanezumab and eptinezumab were 38,515, 19,485, 5,332, and 2,460, respectively. This study has detected new adverse events (AEs) such as menstruation disorders, Raynaud's phenomenon, weight gain, throat tightness and oral paraesthesia that were not mentioned in the drug leaflets but appeared simultaneously with multiple drugs. These findings contribute to our understanding of anti-CGRP mAb safety in clinical settings and providing valuable information regarding the clinical selection of drugs.

Furthermore, Lu et al. study included in this Research Topic uses the FDA FAERS database to examine human serum albumin (HSA) adverse event signals for the safe therapeutic usage of this medication. This study used the Medicines and Healthcare Products Regulatory Agency (MHRA), the Bayesian confidence propagation neural network (BCPNN), and the reporting odds ratio (ROR) to clean and analyze adverse event reports for 76 quarters (Q) spanning Q1 2004 to Q4 2022. A total of 535 reports of adverse events were found using a combination of three techniques. These reports comprised 1,885 cases of adverse reactions; the most frequent ones involved respiratory, thoracic, mediastinal, general disorders and administration site problems. One notable new signal was the happening of transfusion-related acute lung injury. This study found that HSA increases the risk of transfusion-related acute lung injury. Moreover, adverse reactions such as hypertension, pulmonary oedema, paraesthesia, loss of consciousness and vomiting were more commonly observed in females. This study suggested more research to corroborate these findings. This study recommended further research to confirm these findings.

A retrospective study of drug-induced infusion reactions (IRs) conducted by Yin et al. in a hospital pharmacovigilance center during a 5-year period identified 505 cases of inpatient drug-induced IRs. About 105 cases (20.8%) were classified as severe IRs. According to this study, antibiotics and antineoplastic drugs were the main culprit drugs as per the local real-world data from hospital pharmacovigilance center. This study recommended a complete understanding regarding the clinical characteristics of IRs to enable active pharmacovigilance and the adoption of suitable preventive interventions for susceptible populations with risk factors. A recent study of Zhang et al. included 40,474 reports of oxaliplatin as the primary or secondary suspect drug revealed that

few ADEs related to immune system disorders caused by oxaliplatin remain unrecognized, especially type II hypersensitivity, which displayed strong intensity signals as a pharmacovigilance signal. This study advocates for more observational real-world studies to better understand the prevalence of different AEs.

In conclusion, articles included in this Research Topic highlight the importance pharmacoepidemiology and pharmacovigilance studies in enhancing our understanding of drug utilization and safety issues in patients suffering from different diseases. Pharmacovigilance based studies are crucial in crisis situation such as the recent COVID-19 pandemic. It also advocates that real world data sources are instrumental in timely detection of ADRs and continued surveillance of marketed drugs throughout the duration of their use to ensure that their benefit to risk ratio are and remain in acceptable limits.

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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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Proarrhythmia associated with antiarrhythmic drugs: a comprehensive disproportionality analysis of the FDA adverse event reporting system

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Objective: This study aimed to identify the different associations between antiarrhythmic drugs (AADs) and arrhythmias, and to determine whether pharmacokinetic drug interactions involving AADs increase the risk of AAD-related arrhythmias compared to using AADs alone.

Materials and methods: The disproportionality analysis of AAD-associated cardiac arrhythmias, including AAD monotherapies and concomitant use of pharmacokinetic interacting agents involving AADs, was conducted by using reporting odds ratio (ROR) and information component (IC) as detection of potential safety signals based on FAERS data from January 2016 to June 2022. We compared the clinical features of patients reported with AAD–associated arrhythmias between fatal and non-fatal groups, and further investigated the onset time (TTO) following different AAD regimens.

Results: A total of 11754 AAD–associated cardiac arrhythmias reports were identified, which was more likely to occur in the elderly (52.17%). Significant signals were detected between cardiac arrhythmia and all AAD monotherapies, with ROR ranging from 4.86 with mexiletine to 11.07 with flecainide. Regarding four specific arrhythmias in High Level Term (HLT) level, the AAD monotherapies with the highest ROR were flecainide in cardiac conduction disorders (ROR025 = 21.18), propafenone in rate and rhythm disorders (ROR025 = 10.36), dofetilide in supraventricular arrhythmias (ROR025 = 17.61), and ibutilide in ventricular arrhythmias (ROR025 = 4.91). Dofetilide/ibutilide, ibutilide, mexiletine/ibutilide and dronedarone presented no signal in the above four specific arrhythmias respectively. Compared with amiodarone monotherapy, sofosbuvir plus amiodarone detected the most significantly increased ROR in arrhythmias.

Conclusion: The investigation showed the spectrum and risk of AAD–associated cardiac arrhythmias varied among different AAD therapies. The early identification and management of AAD-associated arrhythmias are of great importance in clinical practice.

KEYWORDS

antiarrhythmic drugs, arrhythmia, adverse event reporting system, AAD, ventricular arrhythmia

Introduction

Antiarrhythmic drugs (AADs) are prescribed to treat symptomatic or life-threatening arrhythmias, such as supraventricular arrhythmias and ventricular arrhythmias (Al-Khatib et al., 2018; January et al., 2019; Viskin et al., 2019; Andrade et al., 2022). Although most AADs used for treating arrhythmia have been available for decades, there is still a significant knowledge gaps in their comparative safety.

The proarrhythmic effect of AADs is a significant concern in using them (Reimold and Reynolds, 2018), which had not been systematically studied and only limited numbers of arrhythmias involving AADs were captured in clinical trials and incidental reports (Hindricks et al., 2021; Wharton et al., 2022). Despite the type of proarrhythmic events reported in previous clinical trials and meta-analyses differed among AAD treatments (Freemantle et al., 2011; Friberg, 2018; Valembois et al., 2019; Hindricks et al., 2021; Wharton et al., 2022; Singh et al., 2023), it is almost impossible to reach definitive conclusions from these studies on whether one AAD is more likely than another to result in a higher incidence of arrhythmias. The American Heart Association released a scientific statement for clinical evaluation of drug-induced arrhythmias (Tisdale et al., 2020), which have not systematically focused on the incidence of many general and specific AAD-induced arrhythmias. Moreover, drug-drug interaction (DDI) has been reported to affect the safety of AAD use, resulting in new or recurrent arrhythmias and other adverse events (Haddad and Anderson, 2002; Rajpurohit et al., 2014; Back and Burger, 2015; Mar et al., 2022). The concomitant use of amiodarone with sofosbuvir had been reported to cause serious cases of bradycardia, which may be due to sofosbuvir-based treatments displacing amiodarone from plasma binding proteins and potentiating the bradycardic effects of amiodarone (Back and Burger, 2015; Mar et al., 2022). Additionally, case reports suggested concomitant administration of flecainide with CYP2D6 inhibitors like venlafaxine and citalopram caused serious arrhythmias (Garcia, 2008; Rajpurohit et al., 2014). It is still unclear whether subsequent alterations in plasma AAD concentrations due to drug-drug interaction (DDI), compared with AAD monotherapies, can increase reporting of arrhythmias. In addition, the overviewed relationship between AADs and arrhythmias, factors related to death, potential signal spectra, as well as clinical information of AAD–related arrhythmias are still unknown.

Therefore, post-marketing surveillance is important to mine and reflect profiles of arrhythmias caused by different AAD regimens. In this study, we leveraged the Food and Drug Administration Adverse Event Reporting System (FAERS) to comprehensively characterize and investigate arrhythmias associated with AAD monotherapy and combination.

Methods

Data source

To investigate the association between cardiac arrhythmias and AADs, we used the FAERS database containing spontaneous adverse event reports between 1 January 2016, and 30 July 2022 to perform a disproportionality analysis. The AADs in the study included quinidine, disopyramide, mexiletine, flecainide, propafenone, sotalol, dofetilide, amiodarone, dronedarone, ibutilide, ivabradine, and adenosine. To our knowledge, pharmacokinetic drug interactions involving AADs increased the plasma concentration of AADs (Mar et al., 2022). Thus, the following concomitant use of pharmacokinetic interacting agents involving AADs were also considered in our studies: fluoxetine plus flecainide, duloxetine plus flecainide, paroxetine plus flecainide, amiodarone plus flecainide, citalopram plus propafenone, venlafaxine plus propafenone, sofosbuvir plus amiodarone, verapamil plus dronedarone, diltiazem plus dronedarone, verapamil plus ivabradine, and amiodarone plus ivabradine. Meanwhile, we searched for all adverse event reports related to concomitant use of AAD with pharmacokinetic interacting agents mentioned above. Open Vigil FDA, a pharmacovigilance tool, was adapted to extract FAERS data (Bohm et al., 2021).

Procedures

Based on Medical Dictionary for Drug Regulatory Activities (MedDRA version 23.0), the high-level group term (HLGT) we researched was "Cardiac arrhythmias (10007521)." The full list of preferred terms (PTs) within considered cardiac arrhythmias was provided in Supplementary Table S1. The above PT level adverse events (AEs) belonged to the following four High Level Terms (HLTs): "Supraventricular arrhythmias (10042600)," "Rate and rhythm disorders NEC (10037908)," "Cardiac conduction disorders (10000032)," and "Ventricular arrhythmias and cardiac arrest (10047283)." Moreover, we collected clinical and demographic features of AE cases when data was available, including drug information (indication, concurrent medications, receipt date, treatment start and end dates), patient characteristics (gender, age, country of origin), and final patient outcomes (symptoms, seriousness). Clinical characteristics of patients with AAD-associated arrhythmias were compared between fatal and non-fatal groups. The fatal group referred to patients whose final outcome was death. The monotherapy of AAD-associated cardiac arrhythmias was defined as AAD as a primary suspected (PS) drug, without another AAD and pharmacokinetic interacting agent listed as concomitant, interacting or second suspected drugs.

Statistical analysis

Descriptive statistics were utilized to present the clinical characteristics of the cardiac arrhythmias associated with AADs. The chi-square test was used to compare the categorical variables between the fatal and non-fatal group. We used the *t*-test and non-parametric tests (Kruskal–Wallis tests) to compare the onset time of AAD-related cardiac arrhythmias. Disproportionality analysis was conducted by using reporting odds ratio (ROR) and information component (IC) as detection of potential safety signals for AEs in the FAERS (Noren et al., 2013; Zhai et al., 2019). If there were at least three reports and one algorithm are positive, it was defined as a significant signal. All the data analysis was performed by SPSS 24.0

TABLE 1 Characteristics of patients with AAD-associated cardiac arrhythmias sourced from the FAERS database (January 2016 to June 2022).

Characteristics		Total reports, *n* (%)	Fatal cases, *n* (%)	Non-fatal cases, *n* (%)	*p-value*
Total		11754	2,673	9,081	
Patient age (year)	—				*NS*
	Median (IQR)	70 (59–78)	69 (57–78)	70 (60–78)	
	<18	301 (2.56%)	82 (3.07%)	219 (2.41%)	
	18–64	3,046 (25.91%)	792 (29.63%)	2,254 (24.82%)	
	65–74	2,777 (23.63%)	586 (21.92%)	2,191 (24.13%)	
	≥75	3,355 (28.54%)	801 (29.97%)	2,554 (28.12%)	
	Unknown	2,275 (19.36%)	412 (15.41%)	1863 (20.52%)	
Gender	—				*NS*
	Female	5,240 (44.58%)	1,148 (42.95%)	4,092 (45.06%)	
	Male	5,565 (47.35%)	1,317 (49.27%)	4,248 (46.78%)	
	Unknown	949 (8.07%)	208 (7.78%)	741 (8.16%)	
Reporting year	—				$p < 0.001$
	2016	1,325 (11.27%)	153 (5.72%)	1,172 (12.91%)	
	2017	1,469 (12.50%)	204 (7.63%)	1,265 (13.93%)	
	2018	2,175 (18.50%)	294 (11.00%)	1881 (20.71%)	
	2019	2015 (17.14%)	284 (10.62%)	1731 (19.06%)	
	2020	2094 (17.82%)	267 (9.99%)	1827 (20.12%)	
	2021	1709 (14.54%)	588 (22.00%)	1,121 (12.34%)	
	2022	967 (8.23%)	883 (33.03%)	84 (0.93%)	
Area	—				*NS*
	Africa	53 (0.45%)	16 (0.60%)	37 (1.38%)	
	Asian	662 (5.63%)	185 (6.92%)	477 (17.85%)	
	Europe	5,252 (44.68%)	1,075 (40.22%)	4,177 (156.27%)	
	North America	5,264 (44.78%)	1,224 (45.79%)	4,040 (151.14%)	
	Oceania	125 (1.06%)	24 (0.90%)	101 (3.78%)	
	South America	213 (1.81%)	40 (1.50%)	173 (6.47%)	
	Unknown	185 (1.57%)	109 (4.08%)	76 (2.84%)	
Reporters	—				*NS*
	Physician	3,849 (32.75%)	997 (37.30%)	2,852 (31.41%)	
	Pharmacist	1,095 (9.32%)	252 (9.43%)	843 (9.28%)	
	Other health–professional	3,779 (32.15%)	838 (31.35%)	2,941 (32.39%)	
	Consumer or Non–health professional	2,818 (23.97%)	555 (20.76%)	2,263 (24.92%)	
	Unknown	213 (1.81%)	31 (1.16%)	182 (2.00%)	
AAD as suspected drug	—				*NS*
	Monotherapy	11344 (96.51%)	2,587 (96.78%)	8,757 (96.43%)	*NS*
	Quinidine	27 (0.23%)	7 (0.26%)	20 (0.22%)	
	Disopyramide	54 (0.46%)	14 (0.52%)	40 (0.44%)	

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of patients with AAD-associated cardiac arrhythmias sourced from the FAERS database (January 2016 to June 2022).

Characteristics		Total reports, *n* (%)	Fatal cases, *n* (%)	Non-fatal cases, *n* (%)	*p-value*
	Mexiletine	65 (0.55%)	19 (0.71%)	46 (0.51%)	
	Flecainide	1,675 (14.25%)	346 (12.94%)	1,329 (14.63%)	
	Propafenone	644 (5.48%)	86 (3.22%)	558 (6.14%)	
	Sotalol	1,179 (10.03%)	225 (8.42%)	954 (10.51%)	
	Dofetilide	778 (6.62%)	96 (3.59%)	682 (7.51%)	
	Amiodarone	5,657 (48.13%)	1,502 (56.19%)	4,155 (45.75%)	
	Dronedarone	379 (3.22%)	46 (1.72%)	333 (3.67%)	
	Ibutilide	6 (0.05%)	1 (0.04%)	5 (0.06%)	
	Ivabradine	757 (6.44%)	212 (7.93%)	545 (6.00%)	
	Adenosine	123 (1.05%)	33 (1.23%)	90 (0.99%)	
	Combination therapy	410 (3.49%)	86 (3.22%)	324 (3.57%)	*NS*
	Fluoxetine + Flecainide	29 (0.25%)	10 (0.37%)	19 (0.21%)	
	Duloxetine + Flecainide	39 (0.33%)	6 (0.22%)	33 (0.36%)	
	Paroxetine + Flecainide	20 (0.17%)	2 (0.07%)	18 (0.20%)	
	Amiodarone + Flecainide	95 (0.81%)	35 (1.31%)	60 (0.66%)	
	Citalopram + Propafenone	17 (0.14%)	3 (0.11%)	14 (0.15%)	
	Venlafaxine + Propafenone	20 (0.17%)	2 (0.07%)	18 (0.20%)	
	Sofosbuvir + Amiodarone	66 (0.56%)	6 (0.22%)	60 (0.66%)	
	Verapamil + Dronedarone	3 (0.03%)	0 (0.00%)	3 (0.03%)	
	Diltiazem + Dronedarone	27 (0.23%)	4 (0.15%)	23 (0.25%)	
	Verapamil + Ivabradine	18 (0.15%)	2 (0.07%)	16 (0.18%)	
	Amiodarone + Ivabradine	76 (0.65%)	16 (0.60%)	60 (0.66%)	

Abbreviations: FAERS, Food and Drug Administration's Adverse Event Reporting System; IQR, interquartile range; N, number of records; AAD, antiarrhythmic drug; *p* values was calculated by the chi-square test.

(SPSS Inc., Chicago, IL, United States), and p values <0.05 were considered significant.

Results

Descriptive analysis

The FAERS database recorded 70,100 AAD-associated adverse events (AEs) and 177,896 reports related to cardiac arrhythmias between January 2016 and June 2022. We identified 11754 cases of AAD-related arrhythmias and described the clinical features of reports in Table 1. The AAD-related cardiac arrhythmia AE records were mainly from the North America (5264, 44.78%) and Europe (5252, 44.68%). Regarding cardiac arrhythmia AEs, the proportion of males is greater than that of females (47.35% vs. 44.58%). Amiodarone monotherapy generated the highest number of cases related with arrhythmias (5657, 48.13%), followed by flecainide monotherapy (1675, 14.25%), and sotalol (1179, 10.03%).

As shown in Table 1, no significant difference was found in patient gender, age, area, reporter and AAD regimen for fatal vs. non-fatal reports.

Signal values related to different AAD regimens

The signal values and the association between AADs and arrhythmias were shown in Table 2. All studied AAD monotherapies were significantly correlated with the reporting frequency of cardiac arrhythmia (HLGT), with ROR ranging from 4.86 with mexiletine to 11.07 with flecainide (Table 2). Regarding four specific arrhythmias in HLT level, the AAD monotherapies with the highest ROR were flecainide in cardiac conduction disorders (ROR025 = 23.22), propafenone in rate and rhythm disorders (ROR025 = 11.32), dofetilide in supraventricular arrhythmias (ROR025 = 18.85), and ibutilide in ventricular arrhythmias (ROR025 = 11.47). Dofetilide/ibutilide, ibutilide, mexiletine/ibutilide and dronedarone presented no signal in the

TABLE 2 Associations of different AAD regimens with cardiac arrhythmias in HLGT and HLT level.

Strategy	Drug	Arrhythmias		Cardiac conduction disorders		Rate and rhythm disorders NEC		Supraventricular arrhythmias		Ventricular arrhythmias and cardiac arrest	
		N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Total	Antiarrhythmic Drugs	11754	8.53 (8.41–8.66)	1,101	12.02 (11.5–12.57)	4,241	7.49 (7.32–7.66)	5,126	12.81 (12.54–13.09)	3,474	8.18 (7.98–8.39)
Monotherapy	Quinidine	27	5.03 (3.78–6.69)	12	15.08 (9.96–22.82)	7	2.95 (1.72–5.05)	7	3.86 (2.26–6.60)	10	5.17 (3.29–8.12)
	Disopyramide	54	5.55 (4.54–6.8)	3	3.14 (1.39–7.06)	19	4.51 (3.25–6.26)	16	5.15 (3.60–7.36)	26	7.87 (5.93–10.44)
	Mexiletine	65	4.86 (4.05–5.84)	5	4.05 (2.16–7.59)	17	3.00 (2.13–4.24)	6	1.52 (0.86–2.71)	48	10.80 (8.75–13.32)
	Flecainide	1,675	11.07 (10.65–11.51)	243	23.22 (21.18–25.46)	664	10.63 (10.04–11.26)	752	16.99 (16.09–17.93)	396	8.44 (7.85–9.08)
	Propafenone	644	10.89 (10.24–11.6)	71	16.32 (13.78–19.31)	278	11.32 (10.36–12.36)	305	17.43 (16.01–18.98)	159	8.59 (7.66–9.63)
	Sotalol	1,179	7.60 (7.27–7.94)	82	7.68 (6.57–8.98)	394	6.15 (5.72–6.62)	556	12.25 (11.52–13.04)	296	6.16 (5.67–6.69)
	Dofetilide	778	9.01 (8.52–9.52)	8	1.37 (0.84–2.26)	188	5.26 (4.74–5.84)	479	18.85 (17.61–20.18)	198	7.36 (6.65–8.15)
	Amiodarone	5,657	8.16 (7.99–8.33)	503	10.86 (10.19–11.58)	1996	7.00 (6.78–7.23)	2,297	11.40 (11.05–11.76)	1899	8.88 (8.59–9.19)
	Dronedarone	379	7.69 (7.11–8.31)	21	5.76 (4.24–7.83)	123	6.00 (5.27–6.83)	254	17.34 (15.80–19.02)	19	1.25 (0.91–1.73)
	Ibutilide	6	9.08 (3.89–21.19)	1	—	0	—	1	—	6	11.47 (4.91–26.78)
	Ivabradine	757	6.99 (6.62–7.39)	72	9.49 (8.04–11.21)	350	7.82 (7.24–8.45)	234	7.37 (6.71–8.10)	222	6.60 (6.00–7.27)
	Adenosine	123	6.55 (5.72–7.5)	24	14.29 (10.70–19.10)	34	4.29 (3.36–5.48)	51	8.84 (7.23–10.82)	52	8.54 (6.99–10.42)
	Fluoxetine + Flecainide vs. Flecainide	29	1.15 (0.85–1.56)	8	2.05 (1.22–3.46)	13	1.29 (0.85–1.96)	13	1.15 (0.76–1.74)	14	2.26 (1.50–3.38)
	Duloxetine + Flecainide vs. Flecainide	39	0.87 (0.68–1.12)	9	1.36 (0.84–2.21)	18	1.02 (0.72–1.44)	16	0.80 (0.55–1.16)	20	1.85 (1.32–2.60)
	Paroxetine + Flecainide vs. Flecainide	20	0.71 (0.50–0.99)	1	—	15	1.31 (0.89–1.93)	0	—	6	0.90 (0.50–1.62)
	Amiodarone + Flecainide vs. Flecainide	95	1.29 (1.08–1.54)	8	0.76 (0.46–1.27)	36	1.23 (0.96–1.59)	32	0.97 (0.74–1.27)	40	2.27 (1.77–2.90)
	Citalopram + Propafenone vs. Propafenone	17	0.79 (0.54–1.16)	2	—	5	0.56 (0.29–1.07)	7	0.70 (0.40–1.22)	5	0.94 (0.49–1.81)
	Venlafaxine + Propafenone vs. Propafenone	20	1.23 (0.85–1.78)	0	—	18	2.47 (1.68–3.65)	1	—	2	—
	Sofosbuvir + Amiodarone vs. Amiodarone	66	4.10 (3.03–5.55)	16	8.69 (5.90–12.81)	35	5.87 (4.36–7.90)	31	4.58 (3.37–6.21)	18	3.20 (2.22–4.62)
	Verapamil + Dronedarone vs. Dronedarone	3	0.95 (0.35–2.00)	0	—	1	—	2	—	0	—

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TABLE 2 (*Continued*) Associations of different AAD regimens with cardiac arrhythmias in HLGT and HLT level.

Strategy	Drug	Arrhythmias		Cardiac conduction disorders		Rate and rhythm disorders NEC		Supraventricular arrhythmias		Ventricular arrhythmias and cardiac arrest	
	Diltiazem + Dronedarone vs. Dronedarone	27	1.96 (0.70–1.29)	1	—	4	0.46 (0.23–0.95)	23	1.21 (0.87–1.67)	1	—
	Verapamil + Ivabradine vs. Ivabradine	18	1.96 (1.32–2.89)	2	—	7	1.62 (0.92–2.84)	11	3.52 (2.19–5.64)	1	—
	Amiodarone + Ivabradine vs. Ivabradine	76	2.01 (1.65–2.45)	9	2.34 (1.41–3.88)	19	1.09 (0.78–1.54)	32	2.69 (2.03–3.56)	36	3.17 (2.42–4.16)

Abbreviations: HLGT, high-level group term; HLT, high level term; N: number of records; ROR025, the lower end of the 95% confidence interval of ROR; ROR975, the upper end of the 95% confidence interval of IC; IC025, the lower end of the 95% confidence interval of IC; *p* values was calculated by the chi-square test.

above four specific arrhythmias respectively. Compared with amiodarone monotherapy, sofosbuvir plus amiodarone detected the most significantly increased ROR in arrhythmias. Four in eleven different class-specific AAD combination therapy (amiodarone plus flecainide, sofosbuvir plus amiodarone, verapamil plus ivabradine, and amiodarone plus ivabradine) were detected with pharmacovigilance signals of cardiac arrhythmias (HLGT) compared with AAD monotherapy.

The signal spectrum of cardiac arrhythmias differs in AAD strategies

The arrhythmia signal spectra of different AAD therapies were shown in Table 3. Amiodarone presented a broadest spectrum of cardiac arrhythmias AEs, with 42 PTs detected as positive signals, ranging from cardiac flutter (IC 025 = 0.72) to torsade de pointes (TdP) (IC 025 = 4.93). There were 38 PTs as signals associated with flecainide, with signal values ranging from IC 025 = 1.08 (long QT syndrome) to IC 025 = 4.88 (atrioventricular block first degree). However, the drug with the least PTs was ibutilide, with only one signal detected, followed by quinidine, with five signals detected. Ventricular tachycardia, ventricular fibrillation and atrial fibrillation were three overlapping PTs, all of which were found significantly associated with disopyramide, flecainide, propafenone, sotalol, dofetilide, amiodarone, ivabradine, and adenosine. Torsade de pointes were detected as the strongest signal in amiodarone (IC 025 = 4.93).

Time to onset of AAD–Associated cardiac arrhythmia adverse effects

A total of 3742 AAD–associated cardiac arrhythmias reported the time to onset (TTO), as shown in Table 4. (There were no or few known data on quinidine and ibutilide, which was not shown in Table 4). According to all AADs, the median onset time is 45 days, and the interquartile range is 3–331 days. Among AAD monotherapies, we found significant differences in the reported TTO of arrhythmias ($p < 0.001$). The median TTO was 46 days for amiodarone (IQR 5-330), 47 days for flecainide (IQR 4-349), 112 days for propafenone (IQR 3-433), 165 days for dronedarone (IQR 14-565), 64 days for sotalol (IQR 3-351), 13 days for disopyramide (IQR 0-84), 0 days for ibutilide (IQR 0-0), 14 days for ivabradine (IQR 0-132), 65 days for adenosine (IQR 0-366), 43 days for dofetilide (IQR 2-332), and 11 days for mexiletine (IQR 1-139), respectively. Moreover, there was no significant difference in the TTO between AAD monoregimen and combinationtherapy (flecainide vs. fluoxetine/duloxetine/paroxetine/amiodarone plus flecainide, $p = 0.117$; propafenone vs. citalopram/venlafaxine plus propafenone, $p = 0.525$; amiodarone vs. sofosbuvir plus amiodarone, $p = 0.061$; dronedarone vs. verapamil/diltiazem plus dronedarone, $p = 0.411$; dronedarone vs. verapamil/diltiazem plus dronedarone, $p = 0.525$; ivabradine vs. verapamil/amiodarone plus ivabradine, $p = 0.444$).

Discussion

This study comprehensively evaluated the adverse events of AAD-induced cardiac arrhythmias based on the FAERS database. By employing the FAERS database, we analyzed the clinical characteristics, spectrum, TTO, and outcomes of AAD-induced arrhythmia AEs.

To assess the proarrhythmic effects of AADs, our research detected significant signals between cardiac arrhythmia and all AAD monotherapies, with ROR ranging from 4.86 with mexiletine to 11.07 with flecainide. In the disproportionate analysis of arrhythmias at HLT level, ibutilide monotherapy presented no signal in three specific arrhythmias except for ventricular arrhythmias and cardiac arrest, while mexiletine, dofetilide and dronedarone monotherapy demonstrated negative signal in supraventricular arrhythmias, cardiac conduction disorders, and ventricular arrhythmias and cardiac arrest, respectively. Notably, the risk of ventricular arrhythmia/TdP of dronedarone varied in different literatures, some of which showed a lower risk of dronedarone (Lafuente-Lafuente et al., 2012; Friberg, 2018; Tisdale et al., 2020), while others showed the opposite (Kao et al., 2012; Wu et al., 2022). Previous study reported 138 cases of ventricular arrhythmia associated with dronedarone between July 2009 and June 2011 (Kao et al., 2012), while our research identified only 19 reports during January 2016–June 2022.

TABLE 3 Arrhythmia signal profiles of different AAD strategies.

PT	Atrioventricular block complete	—	—	—	3.31	3.33	1.41	—	3.15	0.77	—	1.64	2.07
	Atrioventricular block first degree	—	—	—	4.88	3.71	1.47	—	2.75	—	—	−0.08	—
	Brugada syndrome	0.71	—	—	4.45	0.43	—	—	1.17	—	—	—	—
	Bundle branch block right	—	—	—	3.90	2.39	0.53	—	2.23	—	—	1.46	—
	Defect conduction intraventricular	—	—	—	4.23	1.78	—	—	0.89	—	—	—	—
	Atrioventricular block	3.12	—	—	2.68	2.21	2.12	−1.10	3.17	2.37	—	2.01	3.33
	Atrioventricular block second degree	—	—	—	2.10	—	1.89	—	2.11	2.70	—	2.20	—
	Bundle branch block	—	—	—	2.54	—	—	—	2.91	—	—	—	—
	Bundle branch block left	—	—	—	3.32	2.87	−1.04	—	2.95	1.08	—	3.43	0.37
	Conduction disorder	—	—	—	3.69	2.40	—	—	1.82	—	—	1.50	—
	Long QT syndrome	—	—	1.68	1.08	—	2.76	—	3.67	—	—	—	—
	Sinoatrial block	—	—	—	3.29	—	—	—	2.71	—	—	—	—
	Arrhythmia	0.44	1.63	1.31	3.58	3.58	2.92	3.21	2.68	2.75	—	1.58	−1.43
	Bradyarrhythmia	—	—	—	4.08	2.85	—	—	3.02	2.20	—	—	—
	BRASH syndrome	—	—	—	—	—	3.05	—	4.26	—	—	—	—
	Cardiac flutter	—	—	—	2.81	2.60	1.84	2.24	0.72	1.67	—	—	—
	Tachyarrhythmia	—	—	—	4.62	0.72	—	0.49	4.59	—	—	1.20	—
	Bradycardia	0.31	1.22	—	3.81	3.83	3.00	−0.29	3.63	1.71	—	3.67	1.43
	Cardiac fibrillation	—	—	—	1.39	2.19	0.49	0.16	1.65	0.38	—	0.71	—
	Extrasystoles	—	—	—	1.77	2.47	0.76	2.71	1.99	0.70	—	1.17	—
	Tachycardia	—	—	−0.61	1.99	1.34	0.69	1.19	1.21	0.98	—	1.97	0.57
	Arrhythmia supraventricular	—	—	—	1.98	1.62	0.10	1.01	2.27	—	—	1.81	—
	Atrial fibrillation	—	1.56	−1.91	4.04	3.84	3.65	4.40	3.50	4.27	—	1.48	1.34
	Nodal arrhythmia	—	—	—	1.44	3.12	—	—	3.48	—	—	—	—
	Sinus arrest	—	—	—	1.74	1.89	1.72	—	1.56	—	—	2.44	0.60
	Sinus bradycardia	—	—	—	3.28	4.09	2.61	0.21	3.66	−0.76	—	3.85	—
	Sinus tachycardia	—	—	—	−0.01	—	−1.26	—	−0.67	—	—	3.03	−0.22
	Atrial flutter	—	—	—	4.53	3.7	3.76	3.69	3.94	3.12	—	1.12	—

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TABLE 3 (*Continued*) Arrhythmia signal profiles of different AAD strategies.

	Atrial tachycardia	—	—	—	2.81	—	2.09	1.95	4.41	—	—	4.08	—
	Nodal rhythm	—	—	—	0.00	1.07	—	—	2.50	—	—	—	—
	Sinus arrhythmia	—	—	—	—	—	—	1.49	1.65	0.49	—	—	—
	Sinus node dysfunction	—	—	—	3.50	—	1.50	0.98	4.05	0.15	—	2.73	—
	Supraventricular extrasystoles	—	—	—	2.14	−1.81	1.08	2.77	3.28	—	—	3.21	—
	Supraventricular tachycardia	—	—	—	3.06	2.61	1.16	1.34	1.81	—	—	0.65	4.50
	Cardiac arrest	—	1.74	−1.55	2.66	2.36	1.37	2.00	2.24	−1.68	—	1.29	1.26
	Sudden death	—	—	—	—	—	0.65	—	1.58	—	—	2.45	—
	Ventricular arrhythmia	—	0.52	2.81	2.73	—	2.71	0.07	3.73	—	—	3.16	—
	Ventricular extrasystoles	—	—	2.60	2.14	—	1.08	2.77	3.28	0.04	—	3.21	0.73
	Ventricular tachycardia	1.05	1.29	3.90	4.35	4.12	3.49	3.92	4.57	−1.17	—	3.43	3.39
	Cardio-respiratory arrest	—	0.62	—	1.98	2.45	1.63	−1.92	2.10	—	—	1.64	−1.19
	Pulseless electrical activity	—	—	—	3.59	0.26	—	—	1.92	—	—	1.19	—
	Torsade de pointes	—	—	1.80	3.31	—	4.84	4.51	4.93	—	1.89	4.35	—
	Ventricular fibrillation	—	2.18	1.33	3.93	2.00	1.85	3.07	4.34	−0.75	—	3.26	3.67
	IC025 ≤ 0	Quinidine	Disopyramide	Mexiletine	Flecainide	Propafenone	Sotalol	Dofetilide	Amiodarone	Dronedarone	Ibutilide	Ivabradine	Adenosine
	4> IC025 > 0												
	IC025 ≥ 4												

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TABLE 4 Onset time of AADs–associated arrhythmias.

	Median (IQR)	0–30	31–60	61–90	91–120	121–180	181–360	Greater than 360	Unknown
Quinidine (*n* = 27)	--	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	27 (100.00%)
Disopyramide (*n* = 54)	13 (0–84)	10 (18.52%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	2 (3.70%)	40 (74.07%)
Mexiletine (*n* = 65)	11 (1–139)	12 (18.46%)	0 (0.00%)	1 (1.54%)	1 (1.54%)	1 (1.54%)	1 (1.54%)	3 (4.62%)	46 (70.77%)
Flecainide (*n* = 1,675)	47 (4–349)	216 (12.90%)	37 (2.21%)	23 (1.37%)	10 (0.60%)	21 (1.25%)	50 (2.99%)	118 (7.04%)	1,200 (71.64%)
Propafenone (*n* = 644)	112 (3–433)	63 (9.78%)	7 (1.09%)	5 (0.78%)	10 (1.55%)	9 (1.40%)	20 (3.11%)	47 (7.30%)	483 (75.00%)
Sotalol (*n* = 1,179)	64 (3–351)	181 (15.35%)	22 (1.87%)	29 (2.46%)	22 (1.87%)	16 (1.36%)	41 (3.48%)	103 (8.74%)	765 (64.89%)
Dofetilide (*n* = 778)	43 (2–332)	128 (16.45%)	18 (2.31%)	11 (1.41%)	12 (1.54%)	15 (1.93%)	23 (2.96%)	66 (8.48%)	505 (64.91%)
Amiodarone (*n* = 5,657)	46 (5–330)	864 (15.27%)	141 (2.49%)	97 (1.71%)	38 (0.67%)	101 (1.79%)	219 (3.87%)	446 (7.88%)	3,751 (66.31%)
Dronedarone (*n* = 379)	165 (14–565)	29 (7.65%)	9 (2.37%)	3 (0.79%)	3 (0.79%)	8 (2.11%)	11 (2.90%)	36 (9.50%)	280 (73.89%)
Ibutilide (*n* = 6)	0 (0–0)	2 (33.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (66.67%)
Ivabradine (*n* = 757)	14 (0–132)	135 (17.83%)	17 (2.25%)	13 (1.72%)	9 (1.19%)	13 (1.72%)	12 (1.59%)	39 (5.15%)	519 (68.56%)
Adenosine (*n* = 123)	65 (0–366)	11 (8.94%)	1 (0.81%)	4 (3.25%)	1 (0.81%)	2 (1.63%)	1 (0.81%)	6 (4.88%)	97 (78.86%)
Fluoxetine/Duloxetine/Paroxetine/ Amiodarone + Flecainide (*n* = 183)	18 (2–245)	26 (14.21%)	1 (0.55%)	1 (0.55%)	0 (0.00%)	2 (1.09%)	5 (2.73%)	7 (3.83%)	140 (76.50%)
Citalopram/Venlafaxine + Propafenone (*n* = 37)	19 (12–474)	5 (13.51%)	1 (2.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (8.11%)	28 (75.68%)
Sofosbuvir + Amiodarone (*n* = 66)	18 (0–81)	12 (18.18%)	2 (3.03%)	4 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.58%)	43 (65.15%)
Verapamil/Diltiazem + Dronedarone (*n* = 30)	325 (1–668)	3 (10.00%)	1 (3.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.67%)	5 (16.67%)	19 (63.33%)
Verapamil/Amiodarone + Ivabradine (*n* = 94)	0 (0–146)	18 (19.15%)	1 (1.06%)	1 (1.06%)	1 (1.06%)	2 (2.13%)	1 (1.06%)	5 (5.32%)	65 (69.15%)

Abbreviations: N, number of records; IQR, interquartile range; AAD, antiarrhythmic drug.

Additionally, the FAERS database recorded 61 cases of TdP related to dronedarone from the first quarter of 2009 to the fourth quarter of 2015 but only 2 reports between January 2016 and June 2022, resulting in the positive signal of TdP in dronedarone after incorporating data before 2016 (Kao et al., 2012; Wu et al., 2022). The higher reports of ventricular arrhythmia/TdP before 2016 and the lower cases after 2016 may be related to the early non-standard use of dronedarone, as it clearly worsens outcomes in patients with decompensated heart failure (Kober et al., 2008) and permanent atrial fibrillation (Rosenstein and Woods, 2012). The negative signal of dronedarone in ventricular arrhythmia/TdP shown in our study is updated and more consistent with clinical research and meta-analysis (Hohnloser et al., 2009; Freemantle et al., 2011; Lafuente-Lafuente et al., 2012; Friberg, 2018; Reimold and Reynolds, 2018; Valembois et al., 2019; Tisdale et al., 2020; Wharton et al., 2022), and will provide more accurate reference for the selection of AAD in clinical practice.

As compared to studied AAD monotherapy, seven pharmacokinetic drug interactions involving AADs were associated with a higher risk of reports of cardiac arrhythmias at HLGT or HLT level, which provided evidence for and endorsed the warnings included in the prescribing information of these drugs (Gareri et al., 2008; Back and Burger, 2015; McDonald et al., 2015; Tisdale, 2016; Mar et al., 2022). Four in eleven different specific AAD combination therapies (paroxetine plus flecainide vs. flecainide, diltiazem/verapamil plus dronedarone vs. dronedarone, citalopram plus propafenone vs. propafenone) were detected with no signal of cardiac arrhythmias at HLGT and HLT level compared with monotherapy, which was not affected by an increase in ADD concentrations demonstrated in previous studies (Garcia, 2008; Tisdale, 2016; Mar et al., 2022). Owing to the lack of studies on arrhythmias associated with AAD combination therapy, the rationale for no increased signal for the above four combination need to be further elucidated and explored.

Atrial fibrillation (AF) induced by disopyramide, adenosine and ivabradine was over-reported, but the signal intensity was weak; quinidine, mexiletine and ibutilide did not present a significant signal value. Ivabradine presented weak association with over-reporting frequency of AF in our study, consistent with the increased AF incidence with ivabradine found in previous clinical trials (Fox et al., 2008; Swedberg et al., 2010; Tendera et al., 2011; Fox et al., 2014; Bohm et al., 2015; Fox et al., 2015; Koruth et al., 2017). Prior studies showed that patients in the ivabradine group were more likely to develop new-onset AF (Fox et al., 2015; Koruth et al., 2017), and were associated with increased risk of AF in a previous meta-analysis (Martin et al., 2014). Moreover, the evidence concerning effect of ivabradine on AF in preclinical and clinical studies was conflicting, which provided modest evidence for ivabradine to reduce the incidence of AF in animal models (Li et al., 2015; Wang et al., 2019), but provided strong evidence for increased incidence of AF in human models by ivabradine (Fox et al., 2008; Swedberg et al., 2010; Tendera et al., 2011; Fox et al., 2014; Bohm et al., 2015); however, there is a concept that ivabradine in combination with beta-blockers could successfully control heart rate in AF, which is currently being investigated in a placebo-controlled clinical trials (RCT) (Fontenla et al., 2020). Although at risk of inducing atrial fibrillation, according to the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment, a history of paroxysmal AF is not a contraindication to ivabradine (Writing et al., 2021). Further studies are needed to establish the role of ivabradine in AF.

The time interval between the initial of AAD therapy to the onset of arrhythmia varies greatly. There was significant difference in the distribution of TTO among AAD mono-regimens ($p < 0.001$). According to all AADs, the median onset time is 45 days, with a interquartile range of 3–331 days, suggesting the significance of cardiac monitoring during the higher-risk time window of 45 days and individualized cardiac monitoring after AAD administration. Moreover, there was no significant difference in the TTO between AAD mono regimen and combination therapy.

Our study has certain limitations inherent to pharmacovigilance databases. Firstly, the true incidence of AE is unclear owing to the voluntary nature of FAERS reporting, including missing information, misspelled drug names, under-reporting and over-reporting, all of which are common in databases. Secondly, a slight increase of ROR only provided safety signals, not real risks of AE in clinical practice, which may be relevant and need further confirmation. Thirdly, due to the lack of denominator, we can neither calculate the incidence rate nor quantify the adverse reaction signals for AAD-related arrhythmias.

Conclusion

We reviewed arrhythmia AEs related with AADs from the FAERS database, as well as assessing whether pharmacokinetic drug interactions involving AADs increased the risk of arrhythmias compared to using AADs alone. Our research is practical for clinicians to understand the safety profile of AADs for arrhythmia and optimize their use among individual patients.

Data availability statement

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

Ethics statement

Ethical 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 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

The manuscript was designed and written by FW and XW. The data acquisition, statistical analysis and revising were performed by FW, HS, and BZ. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1170039/full#supplementary-material

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Safety profiles of methylphenidate, amphetamine, and atomoxetine: analysis of spontaneous reports submitted to the food and drug administration adverse event reporting system

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Background: Methylphenidate, atomoxetine, and Amphetamine are the three most commonly used medications approved by the United States Food and Drug Administration (FDA) for the treatment of attention deficit/hyperactivity disorder (ADHD). However, a comprehensive analysis of their safety profiles across various age groups and genders in real-world contexts has yet to be conducted. In this study, a pharmacovigilance analysis was performed using the FDA Adverse Event Reporting System (FAERS) database to examine differences in adverse events between methylphenidate, atomoxetine, and Amphetamine.

Methods: From January 2014 to September 2022, FAERS reports listing "Methylphenidate," "Dexmethylphenidate," "Atomoxetine," "Amphetamine," "Lisdexamfetamine," "Dextroamphetamine," and "Methamphetamine" as primary suspects were analyzed after removing duplicate reports. We used the standardized Medical Dictionary for Regulatory Activities (MedDRA) query generalized search for adverse events at the preferred term level based on case reports. After filtering duplicate reports, disproportionality analysis was used to detect safety signals according to the proportional reporting ratio (PRR). In order to delve into potential safety concerns, we undertook a two-step analysis of the data. Initially, the data was segmented based on age cohorts: 0–5 years, 6–12 years, 13–18 years, and individuals aged ≥19 years. Following this, after partitioning the data into males and females within the 0–18 years age group, and similarly for those aged ≥19 years, further analysis was conducted.

Results: The pharmacovigilance analysis uncovered substantial safety signals in the standardized MedDRA queries. Methylphenidate was associated with dyskinesia (PRR = 21.15), myocardial infarction (PRR = 12.32), and hypertension (PRR = 8.95) in children aged 0–5, 6–12, and 13–18 years, respectively, as well as neonatal exposures via breast milk (PRR = 14.10) in adults aged ≥19 years. Atomoxetine was linked to hostility/aggression (PRR = 15.77), taste and smell disorders (PRR = 6.75), and hostility/aggression (PRR = 6.74) in children aged 0–5,

6–12, and 13–18 years, respectively, as well as hostility/aggression (PRR = 14.00) in adults aged ≥19 years. Amphetamine was associated with psychosis and psychotic disorders (PRR = 16.78), hostility/aggression (PRR = 4.39), and Other ischaemic heart disease (PRR = 10.77) in children aged 0–5 years, 6–12 years, and 13–18 years, respectively, and hostility/aggression in adults aged ≥19 years (PRR = 9.16). Significant and noteworthy adverse event signals were also identified at the preferred term level. Specifically, methylphenidate was associated with myocardial infarction, acute myocardial infarction, coronary artery dissection, electrocardiogram QT prolonged, growth retardation, self-destructive behavior, suicidal ideation, and completed suicide. Atomoxetine was linked to electrocardiogram QT prolonged, growth retardation, and tic. Amphetamine was recorded for coronary artery dissection, suicidal ideation, and completed suicide. It was observed that male patients, including both children and adults, showed a more significant and frequent occurrence of adverse events compared to females, particularly in terms of cardiac disorders. The intensity and quantity of adverse event signals were distinctly different between the two genders, with males having a higher number of signals. All detected safety signals were confirmed using signals obtained from the disproportionality analysis.

Conclusion: This pharmacovigilance analysis demonstrated significant variations in the safety profiles of methylphenidate, atomoxetine, and Amphetamine across different age groups and between different genders. Following an in-depth analysis of the FAERS database, we discerned prominent safety signals. Notably, the strength of the signals associated with coronary artery dissection induced by methylphenidate and amphetamine, as well as those related to suicide, demand particular attention. Consequently, it remains imperative to persist in monitoring these medications, assessing the associated risks, and carrying out comparative studies particularly geared towards ADHD drugs.

KEYWORDS

methylphenidate, atomoxetine, amphetamine, FDA adverse events reporting system, dextroamphetamine, dexmethylphenidate, methamphetamine, lisdexamfetamine

1 Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that manifests during childhood. It is characterized by symptoms such as hyperactivity, impulsivity, and inattention. These symptoms influence a child's cognitive function, academic performance, behavior, emotional wellbeing, and social skills (Wolraich et al., 2019). ADHD develops in approximately 9%–15% of school-aged children, rendering it one of the most common disorders in childhood (Merikangas et al., 2010; Wolraich et al., 2014; Rowland et al., 2015; Zablotsky et al., 2019). Research suggests that almost 90% of children with ADHD eventually require pharmacological treatment (Stein, 2008; Danielson et al., 2018). Furthermore, approximately 60% of patients continue to exhibit symptoms into adulthood, leading to significant psychological, occupational, and social impairments throughout their lives (Kooij et al., 2010). Psychostimulants, including amphetamines and methylphenidate, are first-line pharmacotherapies for individuals with ADHD. Atomoxetine is the first non-stimulant medication approved by the United States Food and Drug Administration (FDA) for the treatment of ADHD. It is a selective norepinephrine reuptake inhibitor that can be employed to treat ADHD in children, adolescents, and adults, offering an alternative to methylphenidate (Kendall et al., 2008; Wolraich et al., 2011). In addition, both methylphenidate and atomoxetine have been approved by the FDA for the treatment of narcolepsy, while methamphetamine has been approved for the short-term treatment of exogenous obesity. ADHD is a chronic condition necessitating long-term medication. Therefore, the tolerability and safety of therapeutic interventions for ADHD are of paramount concern to regulators, healthcare providers, and caregivers alike (Cortese et al., 2013). Despite the demonstrated efficacy and good tolerability of ADHD medications, potential adverse reactions, particularly those involving cardiovascular and psychiatric aspects, remain a substantive issue (Clavenna and Bonati, 2017). Studies have already shown that ADHD medications may work differently for males and females. However, there has not been a comprehensive study on the gender-based differences in the negative side effects of these medications yet (Kok et al., 2020). The use of methylphenidate and other medications for ADHD continues to increase rapidly in numerous countries, underscoring the importance of issuing appropriate warnings regarding potential adverse effects.

This study performs a pharmacovigilance analysis using the FAERS database. Initially, Patients are initially categorized into various age groups for analysis. The subsequent analysis then separates these patients into two specific groups: males and females aged 0–18 years, and males and females aged ≥19 years. The primary objective is to examine the discrepancies in adverse events among patients of different age groups and genders who use methylphenidate, atomoxetine, and amphetamine in real-world

TABLE 1 PRR algorithm used for signal detection.

	Adverse events of interest	All other adverse events of interest	Total
Drug of interest	a	b	a + b
All other drugs of interest	c	d	c + d
Total	a + c	b + d	a + b + c + d

PRR = [a/(a + b)]/[c/(c + d)], $\chi 2 = [(ad\text{-}bc)^2](a + b + c + d)/[(a + c)\ (b + d)\ (a + b)\ (c + d)]$. Abbreviations: PRR, proportional reporting ratio.

situations. The study emphasizes the crucial need for continuous monitoring, risk assessment, and further comparative research.

2 Materials and methods

2.1 Data sources

This is a retrospective study utilizing the FAERS database, which gathers voluntary reports of adverse reactions and medication errors from healthcare professionals, patients, and pharmaceutical manufacturers worldwide (Dagenais et al., 2018). This publicly accessible database enables the analysis of extensive data to identify safety signals. The ability of FAERS to detect early safety concerns has been previously documented, especially for newly approved medications (Fukazawa et al., 2018) and rare adverse events (AEs) (Harpaz et al., 2013). Data for this study were retrieved from the public release of the FAERS database, which adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). OpenVigil FDA (Böhm et al., 2021), a pharmacovigilance tool, was employed to extract data from the FAERS database. The classification and standardization of AEs in the FAERS data are based on the Medical Dictionary for Regulatory Activities (MedDRA) (Brown et al., 1999). In the FAERS database, each report is coded using preferred terms (PTs) from MedDRA terminology; a given PT can be assigned to one or more High-level Terms, High-level Group Terms, and System Organ Class levels within MedDRA. Furthermore, different PTs can be amalgamated to define a specific clinical syndrome using an algorithmic approach termed standardized MedDRA queries. Definitions provided by MedDRA were utilized in this study.

2.2 Data processing and AE signal detection

From January 2014 to September 2022, FAERS reports listing "Methylphenidate," "Dexmethylphenidate," "Atomoxetine," "Amphetamine," "Dextroamphetamine," "Lisdexamfetamine," and "Methamphetamine" as primary suspects were analyzed after removing duplicate reports (i.e., with the same identifier number). Two researchers used standardized MedDRA query and PT to categorize related AEs, and extracted patient and drug information from the reports. The data extracted included the gender, age, drug name, indication, event, outcome, date received, and so on. Disproportionality analyses were conducted using OpenVigil 2.1. In the "Data Presentation and Statistics Box" of OpenVigil 2.1, the proportional reporting ratio (PRR) was calculated to assess the adverse effects of methylphenidate, atomoxetine, and amphetamine. Table 1 illustrates the methodology employed for the calculation of the Proportional Reporting Ratio (PRR). A higher PRR suggests a stronger association; for example, a PRR of 2 indicates that the AE occurs twice as frequently in drug users compared with the background population. According to the criteria established by Evans et al. (2001), a positive signal of disproportionality was defined as a PRR ≥ 2, a chi-squared value ≥4, and at least three cases. The data was first segmented based on age cohorts: 0–5 years, 6–12 years, 13–18 years, and individuals aged ≥19 years. It was then further partitioned into males and females within the 0–18 years and ≥19 years age groups for a more detailed analysis.

3 Results

3.1 Descriptive analysis

As of September 2022, the FAERS database had received a total of 3,797,604 AE reports. A breakdown by gender reveals that males contributed 1,516,511 (39.93%) of these AE reports while females accounted for a higher proportion with 2,184,508 (57.52%) reports. The distribution of AE reports across various age groups, along with the percentage representation of both genders within each age group, is depicted in Figure 1. We further retrieved a total of 37,046 AE reports, including 15,073 reports for methylphenidate and dexmethylphenidate, 5,920 reports for atomoxetine, and 16,053 reports for amphetamine, dextroamphetamine, methamphetamine, and lisdexamfetamine. Table 2 describes the characteristics of AE reports submitted for these drugs. Consistent with the epidemiology of ADHD, the majority of reported patients were male (Xu et al., 2018). However, among amphetamine users, females accounted for 53.77%, surpassing male patients. Among methylphenidate and atomoxetine users, those aged ≤18 years accounted for 54.46% and 51.28% of cases, respectively. In contrast, in the population using amphetamines, only 18.42% of patients were 18 years old or younger.

3.2 Signal of standardized MedDRA queries

In this study, standardized MedDRA query searches were conducted for methylphenidate, atomoxetine, and amphetamine across different age groups. Moreover, signal detection was performed to comprehensively identify specific clinical cases with AEs related to these three drugs. Among methylphenidate users, the strongest signals for patients aged 0–5 years were linked to dyskinesia (PRR = 21.15), followed by dystonia (PRR = 19.13) and suicide/self-injury (PRR = 11.20). For those aged 6–12 years, the strongest signals were obtained for myocardial infarction (PRR =

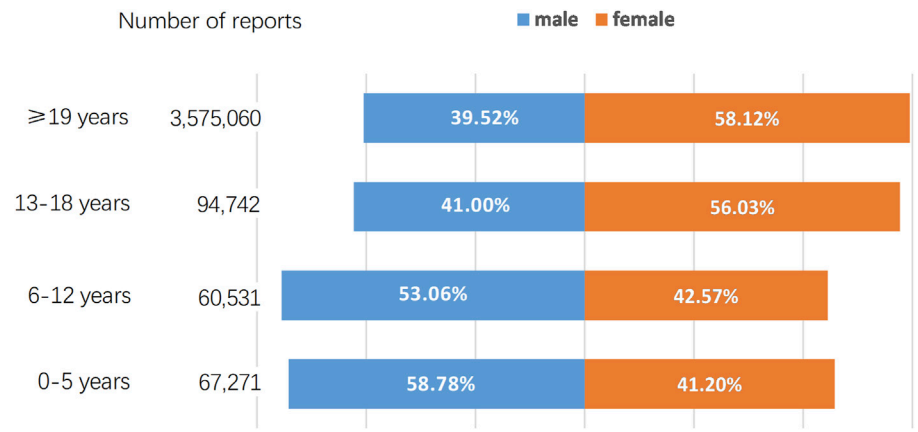

FIGURE 1
Proportional gender distribution of AE reports across various age groups.

12.31), followed by other ischemic heart diseases (PRR = 9.84) and dystonia (PRR = 5.48). For patients aged 13–18 years, the strongest signals were recorded for hypertension (PRR = 8.95), followed by hostility/aggression (PRR = 5.90) and gallstone-related disorders (PRR = 5.10). For those aged ≥19 years, the strongest signals were detected for neonatal exposures via breast milk (PRR = 14.1), followed by neuroleptic malignant syndrome (PRR = 7.07) and dystonia (PRR = 6.50). Among Atomoxetine users, the strongest signals for patients aged 0–5 years were obtained for hostility/aggression (PRR = 15.77), followed by suicide/self-injury (PRR = 14.45) and psychosis and psychotic disorders (PRR = 10.12). For those aged 6–12 years, the strongest signals were linked to suicide/self-injury (PRR = 5.73), followed by non-specific cardiac arrhythmia terms (PRR = 4.38) and hostility/aggression (PRR = 4.16). For patients aged 13–18 years, the strongest signal was detected for hostility/aggression (PRR = 6.74). For those aged ≥19 years, the strongest signals were recorded for hostility/aggression (PRR = 14.00), followed by fertility disorders (PRR = 12.73) and ocular motility disorders (PRR = 6.76). Among amphetamine users, the strongest signals for patients aged 0–5 years were linked to psychosis and psychotic disorders (PRR = 16.78), followed by dyskinesia (PRR = 16.00) and suicide/self-injury (PRR = 13.17). For those aged 6–12 years, the strongest signals were obtained for hostility/aggression (PRR = 4.39), followed by taste and smell disorders (PRR = 4.03) and psychosis and psychotic disorders (PRR = 3.19). For patients aged 13–18 years, the strongest signals were recorded for other ischaemic heart disease (PRR = 10.77), followed by cardiomyopathy (PRR = 4.87) and embolic and hostility/aggression (PRR = 4.32). For those aged ≥19 years, the strongest signals were detected for hostility/aggression (PRR = 9.16), followed by renovascular disorders (PRR = 6.35) and cardiomyopathy (PRR = 5.50). Detailed results are provided in Figure 2.

Furthermore, we stratified patients using these drugs based on gender. Among male methylphenidate users aged 0–18 years, the strongest signals were linked to other ischaemic heart disease (PRR = 3.17). For female patients within the same age range, the strongest signals were associated with dyskinesia (PRR = 3.99). Among male patients aged ≥19 years, the strongest signals were linked to dystonia (PRR = 9.78). In contrast, for females in the same age group, the strongest signals were detected for neonatal exposures via breast milk (PRR = 15.55). Among Atomoxetine users, the strongest signals for male patients aged 0–18 years were linked to taste and smell disorders (PRR = 9.76). For female patients within this age group, the strongest signals were associated with hostility/aggression (PRR = 7.18). For male patients aged ≥19 years, the strongest signals were linked to fertility disorders (PRR = 23.20). For females of the same age group, the strongest signals were recorded for ocular motility disorders (PRR = 11.66). Among amphetamine users, the strongest signals for male patients aged 0–18 years were associated with psychosis and hostility/aggression (PRR = 3.78). For females within this age group, the strongest signals were linked to other ischaemic heart disease (PRR = 10.08). For male patients aged ≥19 years, the strongest signals were detected for central nervous system vascular disorders not specified as haemorrhagic or ischaemic (PRR = 7.84). For females in the same age group, the strongest signals were recorded for renovascular disorders (PRR = 6.80). Detailed results are provided in Figure 3.

3.3 Signal of PTs

In adherence to the latest guidelines (Wolraich et al., 2019), and considering our practical clinical experiences as well as concerns and anxieties of ADHD patients and their families encountered in our pharmaceutical outpatient department, We further detected PT signals and, in combination with FAERS data and literature review analysis, Firstly, we grouped by age and identified 72 PTs (involved in five System Organ Classes) for further exploration. We then stratified by gender and again identified 79 PTs (involved in five System Organ Classes) for further exploration. These System Organ Classes included cardiac disorders, vascular and lymphatic disorders, various examinations, musculoskeletal and connective tissue diseases, and psychiatric disorders. Figure 4 illustrates the adverse reaction signals of the three drugs by different age groups, while Figure 5 demonstrates the adverse reaction signals by different genders among both child and adult patients.

TABLE 2 Clinical characteristics of patients from the FAERS database.

Characteristic	Number of reports, n (%)					
	Methylphenidate		Atomoxetine		Amphetamine	
Gender						
Male	9,333	(61.92)	3,372	(56.96)	6,969	(43.41)
Female	5,458	(36.21)	2,375	(40.12)	8,631	(53.77)
Unknown	282	(1.87)	173	(2.92)	453	(2.82)
Age (years)						
0–5	851	(5.65)	156	(2.64)	232	(1.45)
6–12	4,938	(32.76)	1,781	(30.08)	1,464	(9.11)
13–18	2,420	(16.06)	1,099	(18.56)	1,261	(7.86)
≥19	6,864	(45.54)	2,884	(48.72)	13,096	(81.58)
Year						
2022 (q1–q3)	1,763	(11.7)	472	(7.97)	2,817	(17.55)
2021	1,989	(13.2)	413	(6.98)	2,722	(16.96)
2020	1,208	(8.01)	199	(3.36)	1,894	(11.80)
2019	1,608	(10.67)	268	(4.53)	1,777	(11.07)
2018	2,214	(14.69)	242	(4.09)	2,095	(13.05)
2017	2,000	(13.27)	243	(4.1)	1,633	(10.17)
2016	1,539	(10.21)	394	(6.66)	1,276	(7.95)
2015	1,729	(11.47)	3,360	(56.76)	1,184	(7.38)
2014	1,023	(6.79)	329	(5.56)	655	(4.08)
Indication						
Attention deficit/hyperactivity disorder	4,498	(29.84)	1,953	(32.99)	4,018	(25.03)
Disturbance in attention	111	(0.74)	26	(0.44)	41	(0.26)
Narcolepsy	166	(1.10)	-		120	(0.75)
Autism spectrum disorder	121	(0.80)	16	(0.27)	12	(0.07)
Binge eating	-		-		89	(5.54)

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TABLE 2 (*Continued*) Clinical characteristics of patients from the FAERS database.

Characteristic	Number of reports, n (%)					
	Methylphenidate		Atomoxetine		Amphetamine	
Outcome						
Hospitalization	3,477	(23.07)	544	(9.19)	1,136	(7.08)
Death	965	(6.40)	112	(1.89)	1,433	(8.93)
Life-Threatening	700	(46.44)	184	(3.11)	361	(2.25)
Congenital Anomaly	263	(1.74)	20	(0.34)	10	(0.06)
Disability	301	(2.00)	62	(1.05)	619	(3.86)

Abbreviations: FAERS, United States food and drug administration adverse event reporting system; q1, quarter 1; q3, quarter 3.

4 Discussion

In this study, we performed a pharmacovigilance analysis using the FDA Adverse Event Reporting System (FAERS) database to examine the differences in adverse events between methylphenidate and, atomoxetine and amphetamine. The results of our analysis unveiled the well-established adverse reactions listed on the drug labels, as well as the emergence of previously unreported and rare adverse reaction signals. Additionally, the medical community is growing increasingly aware of the influence of gender on therapeutic outcomes, with females increasingly seen as a risk factor for clinically relevant ADR (Franconi and Campesi, 2014; Anderson et al., 2018). Therefore, we also further investigated the differences in adverse reaction signals between male and female patients. This underscores the importance of ongoing pharmacovigilance in detecting and monitoring potential safety concerns associated with these medications.

According to our study, we note considerable differences in the manifestation of adverse reaction signals of these drugs across different ages and genders. Individual variations in physiological responses tend to increase with age as it influences structural and functional changes in organs. These alterations can impact how drugs are absorbed and cleared within the body, leading to changes in pharmacokinetics and drug sensitivity (Mangoni and Jackson, 2004). Additionally, since each ADHD medication exhibits some degree of gender-based efficacy (Kok et al., 2020), physiological differences between males and females could potentially lead to variations in adverse reactions. Furthermore, a study by Holm et al. (2017) points out that spontaneous reports of adverse reactions are influenced by age and gender, all of which could contribute to the observed differences in adverse reaction signals among different ages and genders.

4.1 Cardiac disorders, vascular disorders, and investigations

In the present study, we identified several adverse reaction signals related to the heart rate and blood pressure for both methylphenidate and atomoxetine across all age groups, as illustrated in Figure 4. Clinicians, patients, parents, and the general public have expressed significant concern regarding the cardiovascular safety of medications for ADHD (Kratochvil, 2012). Initial apprehensions regarding the cardiovascular safety of methylphenidate emerged in 1958 (Maxwell et al., 1958). By 1976, researchers discovered that treatment with methylphenidate substantially elevated the blood pressure and heart rate (Ballard et al., 1976). In 2012, it was revealed that children with ADHD exhibit autonomic dysfunction (Buchhorn et al., 2012). Treatment with methylphenidate and atomoxetine may further exacerbate the cardiovascular risk. Lamberti et al. (2015) observed that the average heart rate in children receiving methylphenidate increased from 80.5 ± 15.5 bpm to 87.7 ± 18.8 bpm; however, there were no significant changes detected in electrocardiogram parameters. To investigate the discrepancies in adverse reactions across different age groups, we analyzed the differences in adverse reaction signals among various age groups for the three medications. As studies have demonstrated physiological differences between males and

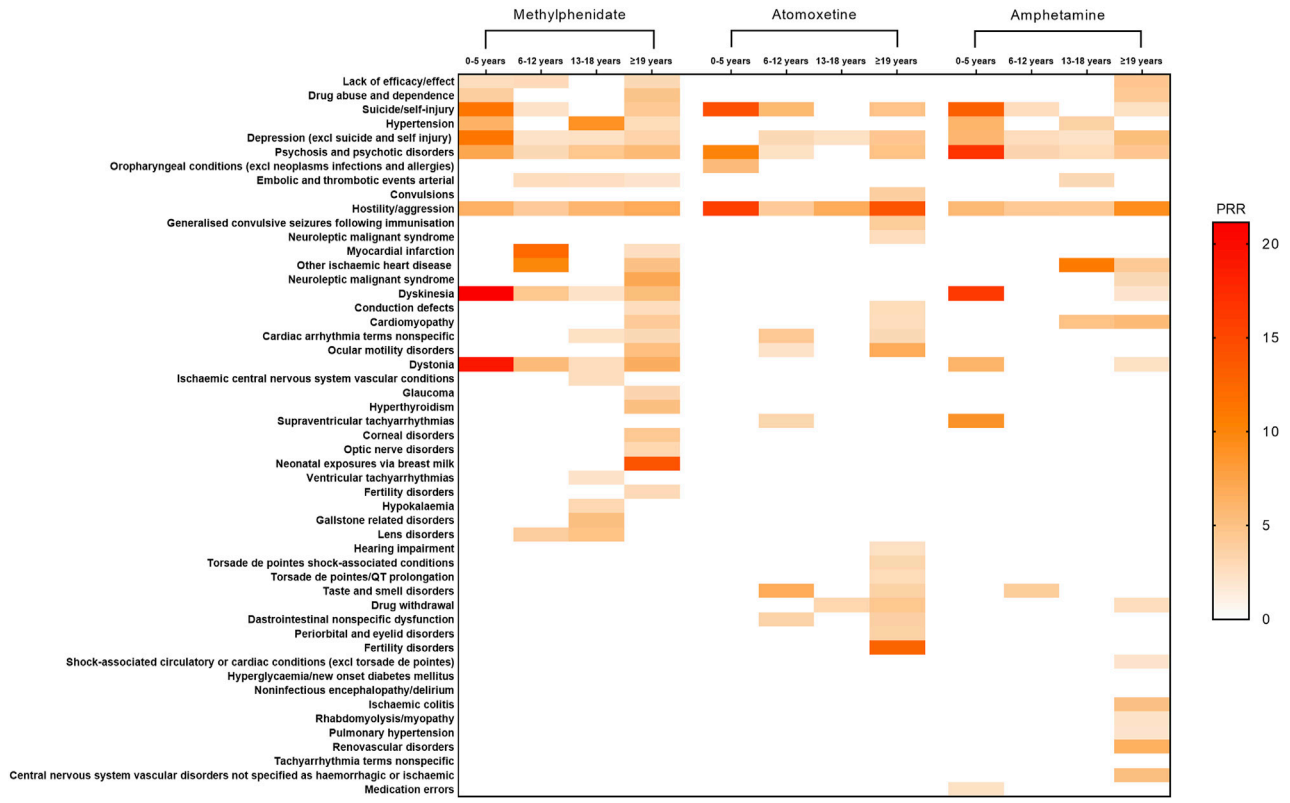

FIGURE 2
Positive signal distribution for methylphenidate, atomoxetine, and amphetamine using standardized MedDRA queries. Abbreviations: excl, excluding; MedDRA, Medical Dictionary for Regulatory Activiti; PRR, Proportional Reporting Ratio.

females, with distinct gender differences in the clinical manifestation of cardiovascular diseases (Stolarz and Rusch, 2015). Hence, we further examined the differences in adverse reaction signals between males and females. The present analysis identified hypertension signals in patients of all age groups treated with methylphenidate and atomoxetine. Firstly, we detected adverse reaction signals affecting the heart rate in patients treated with methylphenidate, amphetamine and atomoxetine (except in those aged 0–5 years). Subsequently, through stratified analysis by gender, we found no significant differences between males and females. In general, methylphenidate and amphetamine manifested more pronounced adverse effect signals compared to atomoxetine. Consequently, we recommend that patients undergoing treatment with methylphenidate, amphetamine, or atomoxetine have their heart rate and blood pressure routinely monitored throughout the course of therapy. Despite the established efficacy, favorable safety profile, and extensive utilization history, lingering apprehensions remain regarding the likelihood of infrequent, yet severe, cardiovascular AEs linked to pharmacological interventions for ADHD. Of note, in patients aged ≥19 years, we identified signals of electrocardiogram QT prolongation as an adverse reaction associated with both methylphenidate (PRR = 2.04) and atomoxetine (PRR = 4.07). Through stratified analysis by gender, we found that signals of electrocardiogram QT prolongation were present in female patients aged ≥19 years who were administered methylphenidate (PRR = 2.74). For atomoxetine, these signals were detected in male patients, specifically in those aged 0–18 years (PRR = 2.37) and those aged ≥19 years (PRR = 6.03). Drug-induced fatalities predominantly stem from torsades des pointes, a potentially lethal polymorphic ventricular tachycardia frequently correlated with prolonged QT intervals. Given that the QT interval diminishes as the heart rate increases, it is customarily adjusted for heart rate (QTc). Drug-induced QT/QTc prolongation and torsades des pointes represent relatively uncommon adverse reactions to medications for ADHD commonly employed in clinical settings (Roden, 2004). A meta-analysis conducted by Martinez-Raga et al. (2013) posited that, when administered at therapeutic dosages, medications for ADHD are not linked to a heightened risk of cardiac incidents or other grave cardiovascular complications (inclusive of QTc prolongation) in pediatric, adolescent, or adult populations. Nevertheless, utmost prudence is warranted when contemplating the prescription of methylphenidate or atomoxetine for patients with ADHD of any age who present with personal or familial histories of cardiovascular disorders or other predisposing factors to the occurrence of cardiovascular events. Increased vigilance is necessitated when concurrently prescribing medications associated with the risk of cardiac AEs (Martinez-Raga et al., 2013).

Furthermore, it is important to highlight that, in patients aged ≥19 years using methylphenidate, we identified statistically significant adverse reaction signals for coronary artery dissection (PRR = 101.65), acute myocardial infarction (PRR = 5.47),

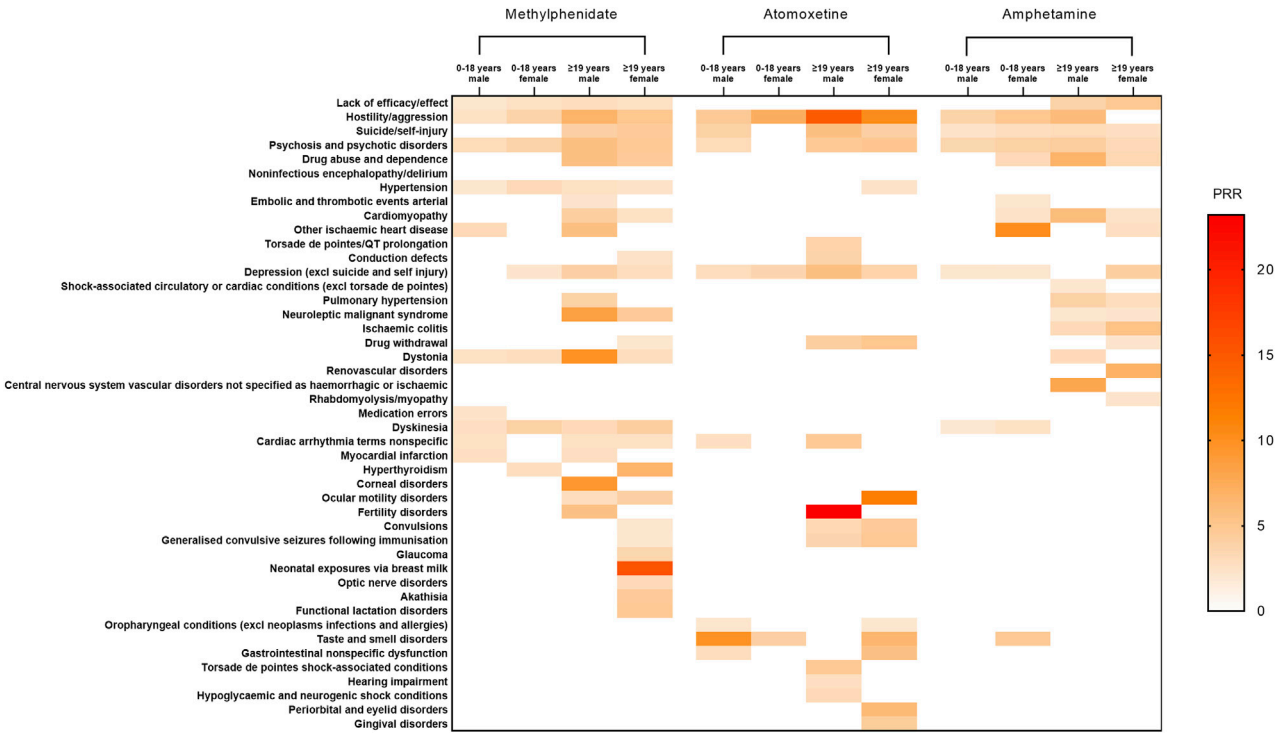

FIGURE 3
Positive signal distribution for methylphenidate, atomoxetine, and amphetamine using standardized MedDRA queries. Abbreviations: excl, excluding; MedDRA, Medical Dictionary for Regulatory Activiti; PRR, Proportional Reporting Ratio.

myocardial infarction (PRR = 2.02), and electrocardiogram ST elevation (PRR = 15.58). In those aged 6–12 years, an adverse analysis signal for myocardial infarction was detected (PRR = 12.02). Among the users of amphetamines aged ≥19 years, we likewise identified an adverse reaction signal for coronary artery dissection (PRR = 143.65). Notably, through stratified analysis by gender, we found that signals of coronary artery dissection as an adverse reaction were exclusively present in male patients using methylphenidate, specifically in those aged 0–18 years (PRR = 430.52) and those aged ≥19 years (PRR = 133.75). Meanwhile, in patients aged ≥19 years using amphetamines, we detected signals of coronary artery dissection in both male and female patients, specifically in males aged ≥19 years (PRR = 48.58) and females of the same age group (PRR = 105.69). Coronary artery dissection is a major cause of acute myocardial infarction (Kim, 2020), and spontaneous coronary artery dissection is a rare, yet potentially severe, condition (Liang et al., 2018). A meta-analysis focusing on five studies with >43,000 children and adolescents did not find significant differences in adverse cardiac events between methylphenidate and atomoxetine. Similarly, a meta-analysis of three studies involving 775 adults did not reveal significant differences in adverse cardiac events between methylphenidate and placebo (Stammschulte et al., 2022). Nonetheless, AE reports from Canada and Germany (Wonnacott and Berringer, 2016; Stammschulte et al., 2022), including cases of acute myocardial infarction and coronary artery dissection, have raised concerns regarding the safety of these medications (Anders and Sharfstein, 2006). Furthermore, through a PubMed search, we discovered several case reports of amphetamine users experiencing coronary artery dissection, all suspected to be caused by the use of amphetamines. The present findings further emphasize the need for enhanced vigilance concerning the occurrence of severe cardiovascular AEs in patients using methylphenidate or amphetamine. Although the underlying mechanism remains to be clarified, the risk of myocardial infarction may be attributable to the cardiopressor dopaminergic/noradrenergic effects of psychostimulant drugs like amphetamine and methylphenidate, leading to increased heart rate and blood pressure (Volkow et al., 2003; Purper-Ouakil et al., 2011).

4.2 Musculoskeletal and connective tissue disorders

In patients aged 13–18 years, we identified adverse reaction signals associated with growth retardation for both methylphenidate (PRR = 12.04) and atomoxetine (PRR = 9.86). Further stratified by gender, we found that in atomoxetine users, growth retardation was only detected in male patients aged 0–18 years (PRR = 2.81). For those using methylphenidate, we found signals of growth retardation in both male and female patients aged 0–18 years, with PRR values of 4.44 and 4.10 respectively. The signal strength was approximately the same, but there were 85 reported cases in males, significantly more than the 15 cases reported in females. The potential impact of medications for ADHD on growth and development has long

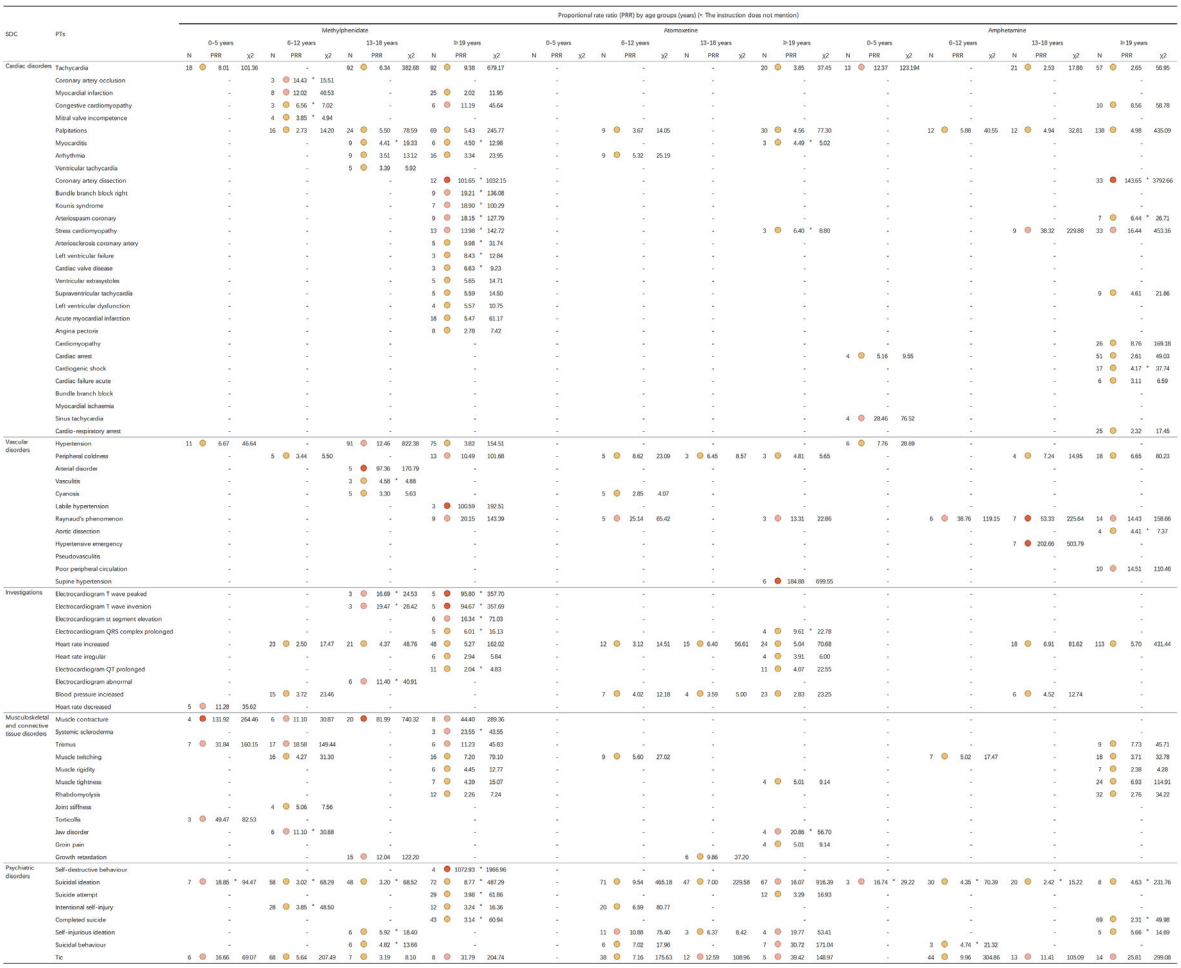

FIGURE 4
Signal strength for methylphenidate, atomoxetine, and amphetamine based on the PT level in FAERS. Abbreviations: FAERS, United States Food and Drug Administration Adverse Event Reporting System; PT, preferred term; SOC, System Organ Class.

been a matter of concern. Conclusions from existing research remain contentious. The study conducted by Swanson et al. (2007) suggested that the central nervous system stimulant methylphenidate may impede growth and development. Their investigation examining the influence of the non-stimulant atomoxetine on growth and development in the treatment of ADHD, spanning a period >5 years, revealed that the effects of atomoxetine on the height and weight of children were transient, with a gradual rebound and recovery as treatment progressed. Longitudinal studies suggested that, during the initial 3 years of methylphenidate usage, height growth was impaired by 1 cm annually, representing a clinically significant reduction (Poulton, 2005). Some evidence indicates that these effects may wane over time, leaving the ultimate adult height unaffected by prior exposure to methylphenidate (Kramer et al., 2000; Faraone et al., 2008; Biederman et al., 2010; Peyre et al., 2013). Moreover, other researchers have reported that alterations in height or weight could be innate manifestations of ADHD rather than consequences of medication (Spencer et al., 1992; Swanson et al., 2007; Hanć and Cieślik, 2008). The possible influence of medications for ADHD on the growth and development of children and adolescents may stem from several factors. Several neurobiological mechanisms could potentially lead to the expected growth defects associated with methylphenidate. These may include the drug's impact on liver and/or central nervous system growth factors, as well as its direct effect on cartilage. Dysregulation of molecular receptors involved in growth systems could explain the short-term effects of the drug. On the other hand, receptor adaptation over time may be the basis for tolerance to growth suppression and catch-up or compensatory growth after discontinuation of the stimulant (Cortese et al., 2013). As for atomoxetine, a meta-analysis of seven double-blind/placebo-controlled studies and six open-label studies found that the actual average weight and height at 24 months were 2.5 kg and 2.7 cm lower, respectively, than expected based on baseline weight and height percentiles (Kratochvil et al., 2006). However, the mechanism behind this occurrence still requires further investigation. Consequently, we advise that patients (especially adolescents) receiving methylphenidate and atomoxetine should continuously monitor

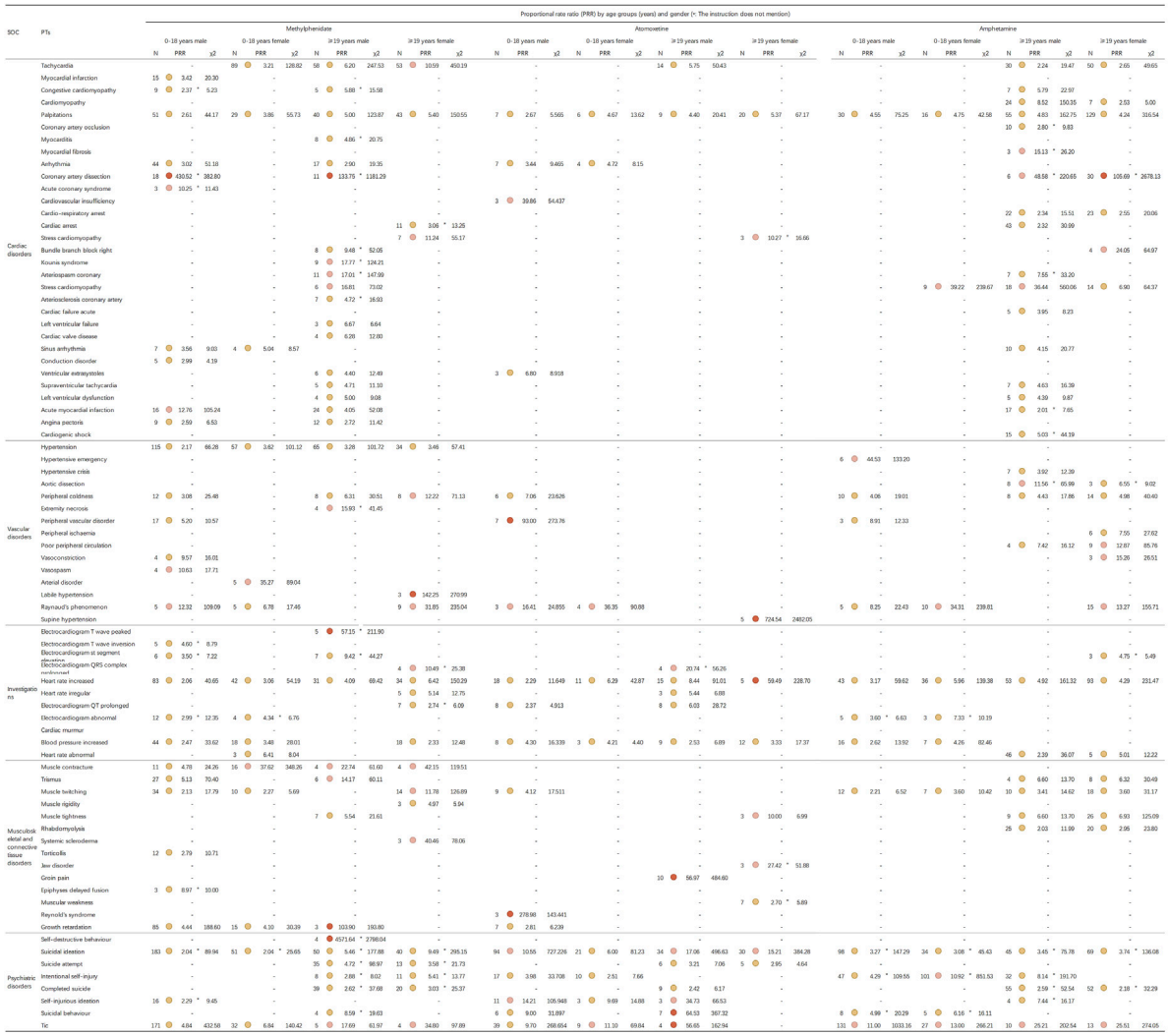

FIGURE 5
Signal strength for methylphenidate, atomoxetine, and amphetamine based on the PT level in FAERS. Abbreviations: FAERS, United States Food and Drug Administration Adverse Event Reporting System; PT, preferred term; SOC, System Organ Class.

their height and weight before and during treatment to evaluate their growth and development status.

4.3 Psychiatric disorders

The FDA has issued a black box warning for atomoxetine due to the potential elevation of suicidal ideation risk in children, urging clinicians to meticulously assess the risk-benefit ratio when prescribing this drug. An Italian investigation involved 2,239 patients with ADHD aged <18 years who were treated with either methylphenidate (1,268 cases, 56.7%) or atomoxetine (971 cases, 43.3%). The results revealed that all seven reported instances of suicidal ideation, self-harm, or related symptoms during treatment were observed in patients receiving atomoxetine, indicating an associated risk (Capuano et al., 2014). This finding aligns with our results, as we identified relevant signals in patients aged 6–12, 13–18, and ≥19 years using atomoxetine. In contrast, it is proposed that the stimulant medication methylphenidate or amphetamine exerts positive effects in mitigating the risk of suicide. A comprehensive review analyzing the influence of medication for ADHD on suicide-related behavior concluded that, unlike the non-stimulant atomoxetine, treatment with a stimulant significantly decreased suicidal intent in patients with ADHD of all ages (overall odds ratio = 0.72); notably, longer-term treatment with medication was correlated with a reduction in risk (Chang et al., 2020). Researchers suggested that stimulant therapy might lower the risk of suicidal behavior in patients with ADHD by ameliorating core symptoms, enhancing executive function, and diminishing the incidence of comorbidities (e.g., depression and substance abuse) over extended treatment periods (Öhlund et al., 2020). Nonetheless, we also detected signals of adverse reactions associated with suicide in patients using methylphenidate. The most prominent signals were self-destructive behavior in the ≥19 years age group (PRR = 1072.93), followed by completed suicide (PRR = 60.94), intentional self-harm (PRR = 16.36), and suicidal ideation detected across all age groups (0–5 years: PRR = 18.85; 6–12 years PRR = 3.02;

13–18 years: PRR = 3.2; ≥19 years: PRR = 8.77). In users of amphetamine, we also identified adverse reaction signals related to suicide across all age groups. Further stratification by gender revealed that the signal strength was generally stronger in male patients than in female patients. Instances of suicidal ideation resulting from the use of methylphenidate in the treatment of ADHD have been previously reported in the literature (Fettahoglu et al., 2009). Some reports have posited that suicidal ideation may arise from impulsivity as an inherent aspect of ADHD or potentially be a consequence of depressive moods induced by the use of methylphenidate. A case report from India documented two cases of suicidal ideation in male children initiating treatment with methylphenidate for ADHD (Arun and Sahni, 2014). The investigators contended that suicidal ideation occurred as a side effect of methylphenidate. Moreover, a Dutch cohort study indicated an increased risk of attempted suicide in adults aged <40 years following the commencement of treatment with methylphenidate (Tobaiqy et al., 2011; Stricker et al., 2022). The mechanism underlying the methylphenidate-induced risk of suicide remains unclear. For users of amphetamine, the mortality rate of individuals with stimulant use disorders, such as methamphetamine, is five times that of the general population, with suicide being one of the main causes of death. The reasons for suicide could be due to the direct impact of amphetamine, the adverse effects of psychosomatic comorbidities, or social factors. The rates of suicide and accidental deaths in males are significantly higher than those in females (Lee et al., 2021). Considering the present research findings, clinicians should closely monitor patients for the potential development of adverse reactions related to suicidal ideation when prescribing methylphenidate or amphetamine. Ensuring that the parents and teachers of patients receive education on potential adverse reactions associated with methylphenidate or amphetamine is of equal importance.

Unexpectedly, we detected signals related to Psychosis and psychotic disorders, as well as Suicide/self-injury as Adverse Drug Events (ADEs) in the age group of 0–5 years. The pathophysiology, vulnerability, and physical development of children diverge substantially from adults in various ways. Age differences often alter a child's reaction to psychotropic drugs (Safer, 2011), with children, especially pre-schoolers, being particularly susceptible to stimulant-related ADEs. However, identifying adverse reactions in pediatrics is challenging, as many of the available tools are ill-suited for pediatric use (Bracken et al., 2018). Reporting adverse reactions in children poses a greater challenge than in adults, as it typically involves parents as critical intermediaries, and children may not be as capable of describing their symptoms as adults are (Blake et al., 2014). Despite Methylphenidate being recommended as the first-line treatment for pre-school children (Wolraich et al., 2019), a thorough risk-benefit assessment for off-label use of ADHD medications is pivotal (Leporini et al., 2022).

It has been demonstrated that methylphenidate elevates the concentration of dopamine within the nigrostriatal pathway, thereby intensifying the symptoms of tic disorder (Bailey, 2003). As a result, clinicians have displayed reluctance to prescribe stimulants for the treatment of children presenting with both ADHD and tics, due to the potential aggravation of tic symptoms. Our investigation substantiates these concerns, as we uncovered noteworthy adverse reaction signals for tics among patients utilizing methylphenidate (0–5 years: PRR = 16.66; 6–12 years: PRR = 5.64; 13–18 years: PRR = 3.19; ≥19 years: PRR = 31.79). Among amphetamine users, we also found adverse signals about tic (6–12 years: PRR = 9.96; 13–18 years: PRR = 11.41; ≥19 years: PRR = 25.81). Upon further stratification by gender, we found that the strength of adverse reaction signals was roughly the same for both males and females. Osland et al. (2018) stated that, in certain instances, the stimulant medication methylphenidate or amphetamine could exacerbate tics; therefore, they suggested the use of atomoxetine as a potential alternative therapy. Nevertheless, it is crucial to acknowledge that we also identified adverse reaction signals for tics in patients who received atomoxetine (6–12 years: PRR = 7.16; 13–18 years: PRR = 12.59; ≥19 years: PRR = 39.42). Consequently, atomoxetine, methylphenidate, and amphetamine may provoke or worsen tic manifestations in a limited number of patients, particularly among boys and those with a prior history of tics (Yang et al., 2017). Hence, it is imperative for physicians to remain cognizant of and vigilant towards this potential complication.

4.4 Limitations

This study has certain limitations stemming from the FAERS database and the study design. Firstly, the FDA does not require proof of a causal relationship between the adverse event and the drug at the time of the report submission, which prevents us from establishing a causal relationship between the occurrence of adverse reactions and drug use, or determining whether the adverse reactions are attributable to the drugs, ADHD comorbidities, or other factors. Secondly, the FDA cannot collect all reports on adverse events or medication errors for a drug product. The ability to report adverse events or medication errors is influenced by several factors, such as when the product was marketed and the level of public awareness of adverse events and medication errors. FAERS data cannot be used to calculate the incidence of adverse events or medication errors in the monitored population, and are primarily used for hypothesis generation rather than confirmation. Detailed information from clinical follow-ups and other studies would be required to verify the potential associations identified in our analysis. Finally, due to the accessibility of medications in different regions of the world, this study focused only on the most commonly used medications in ADHD treatment rather than all medications.

5 Conclusion

In conclusion, our pharmacovigilance analysis has revealed significant variations in the safety profiles of methylphenidate, atomoxetine, and amphetamine across different age groups and genders. We discovered prominent safety signals, with those associated with coronary artery dissection induced by methylphenidate and amphetamine, as well as those linked to suicide, demanding particular attention. These findings underscore the importance of personalized prescribing and careful monitoring of patients taking these medications. However, the limitations of this study, including potential inaccuracies and underreporting in the FAERS database and the inability to establish causality, highlight the need for further research. We recommend in-depth, prospective studies to

confirm these findings and explore the mechanisms underlying these adverse reactions. Meanwhile, clinicians should be aware of these potential risks and consider them in their decision-making process, especially for patients who are at higher risk. Patient education about these potential adverse reactions and regular monitoring should be a standard part of the treatment plan.

Data availability statement

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

Author contributions

All authors were involved in the study. Study design: WW, LC, and LH; Extraction data: WW, LC, LH, and JL; Analysis and interpretation of data: WW, LC, LH, HZ, YZ, YB, and JL. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Effectiveness and safety of oral anticoagulants for non-valvular atrial fibrillation: a population-based cohort study in primary healthcare in Catalonia

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Objectives: Our objective was to analyse effectiveness and safety of oral anticoagulants (OAC) for stroke prevention in non-valvular atrial fibrillation.

Material and methods: Population-based cohort study including adults initiating oral anticoagulants, either direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA), during 2011–2020.

Data source: SIDIAP, capturing information from the electronic health records of Primary Health Care in Catalonia, Spain.

Study outcomes: stroke, cerebral and gastrointestinal (GI) haemorrhage, assessed by patients' subgroups according to different clinical characteristics.

Results: We included 90,773 patients. Male sex, older than 75, previous event, peripheral artery disease, deep vein thrombosis, or receiving antiplatelets, antidiabetics or proton pump inhibitors (PPI) was associated with higher stroke risk. For DOAC-treated, treatment switch increased stroke risk, while being adherent had a protective effect. Men, antidiabetic treatment or a previous event increased the risk of cerebral bleeding. Receiving direct oral anticoagulants had a protective effect in comparison to vitamin K antagonists. For DOAC-treated, treatment switch increased, and adherence decreased the bleeding risk. Men, people with chronic kidney disease or a previous event posed an increased risk of gastrointestinal bleeding, whereas receiving PPI had a protective effect. For DOAC-treated, switch was associated with a higher bleeding risk.

Abbreviations: AF, atrial fibrillation; ATC, Anatomical, Therapeutic, Chemical classification system; CI, confidence interval; CKD, chronic kidney disease; CMBD, minimum dataset of diagnoses at hospital discharge; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; ECAP, electronic health records in Primary Care in Catalonia; GI, gastrointestinal; ICD-10, International Classification of Diseases 10th version; IR, incidence rate; IRR, incidence rate ratio; MPR, medication possession ratio; NVAF, non-valvular atrial fibrillation; PAD, peripheral artery disease; PE, pulmonary embolism; PHC, Primary Health Care; PPI, proton pump inhibitors; SIDIAP, Information System for the Development of Research in Primary Care; VKA, vitamin K antagonists.

Conclusion: Being men, a previous event and DOAC-switch posed a higher risk for all study outcomes. direct oral anticoagulants had a protective effect against cerebral bleeding in comparison to vitamin K antagonists. Adherence to direct oral anticoagulants resulted in lower risk of stroke and cerebral bleeding. We found no differences in the risk of stroke and gastrointestinal bleeding when we compared direct oral anticoagulants vs. vitamin K antagonists.

KEYWORDS

oral anticoagulants, atrial fibrillation, adherence, effectiveness, safety, electronic health records, primary healthcare, stroke

Introduction

Atrial fibrillation (AF) is the most common form of chronic arrhythmia. It is associated with several cardiovascular conditions, and it increases the risk of stroke. Although men are more commonly affected by AF, women have a higher risk of experiencing stroke (Lip et al., 2012; Hindricks et al., 2021). Oral anticoagulants (OAC), either vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) are usually prescribed to prevent stroke in patients with non-valvular atrial fibrillation (NVAF).

In their pivotal randomized clinical trials, all DOAC demonstrated to be at least non-inferior to warfarin in stroke prevention (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). In recent years, multiple observational studies have analysed effectiveness and safety of DOAC in comparison to warfarin and coumarins (Anguita Sánchez et al., 2020; Durand et al., 2020; Lee et al., 2020; Crocetti et al., 2021; Lip et al., 2021; Grymonprez et al., 2023), between different DOAC (Rutherford et al., 2020; Jaksa et al., 2022; Talmor-Barkan et al., 2022), or in certain population subgroups of interest (Bang et al., 2020; Costa et al., 2020; Rodríguez-Bernal et al., 2021). Some studies have also assessed these outcomes based on the dose of DOAC or the adherence to treatment (Deshpande et al., 2018; Staerk et al., 2018; Kohsaka et al., 2020), considering that adequate levels of adherence have shown to decrease the occurrence of thromboembolic events (Amin and Marrs, 2015; Yao et al., 2016a).

We have recently analysed the baseline clinical characteristics and the sex and gender differences of patients initiating OAC for stroke prevention in NVAF from 2011–2020 in a Primary Health Care (PHC) cohort in Catalonia, Spain (Giner-Soriano et al., 2023). In the present manuscript, we have analysed the effectiveness and safety of OAC in the above-mentioned cohort, only including patients who collected their medication in the pharmacy, and assessed by different subgroups based on sex, age, renal impairment or with other frequent comorbidities and comedications; and by dose adequacy, treatment adherence or drug switch in the case of those people treated with DOAC.

Material and methods

Study design

Population-based cohort study including adults with NVAF who initiated OAC treatment. Cohort entry criteria are explained in Figure 1.

Population included

We included all ≥18 years-old individuals with an active diagnosis of NVAF registered in the PHC electronic records who initiated treatment with OAC from January 2011 to December 2020.

Population excluded

We excluded from the analysis those individuals who had been diagnosed with AF before 1980, people with valvular AF, those who had experienced pulmonary embolism (PE) or deep vein thrombosis (DVT) during the previous 12 months to the OAC prescription, those receiving OAC for surgical prophylaxis of hip or knee replacement during the previous 6 months, and those with an OAC prescribed during the study period but with no subsequent dispensing during the next 120 days.

Data source

The data source is the Information System for the Development of Research in Primary Care (SIDIAP) (Recalde et al., 2022; SIDIAP, 2022), which captures clinical information of approximately 5.8 million people from Catalonia, Spain (around 80% of the Catalan population). This information is pseudonymized, originated from different data sources:

1) ECAP (Electronic Health Records in PHC in Catalonia); including socio-demographic characteristics, residents in nursing homes/long-term care facilities, comorbidities registered as International Classification of Diseases (ICD)-10 codes (WHO, 2019), specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data, and drug prescriptions issued in PHC, registered as Anatomical, Therapeutic, Chemical classification system (ATC) codes (WHO Collaborating Centre for Drug Statistics Methodology, 2022).
2) Pharmacy invoice data corresponding to the PHC drug prescriptions, also by ATC.
3) Database of diagnoses at hospital discharge (CMBD-HA) (Català de la Salut, 2022).

ICD-10 codes for diagnoses and ATC codes for drugs studied are included in the Supplementary file, Supplementary Tables S1 and S2, respectively.

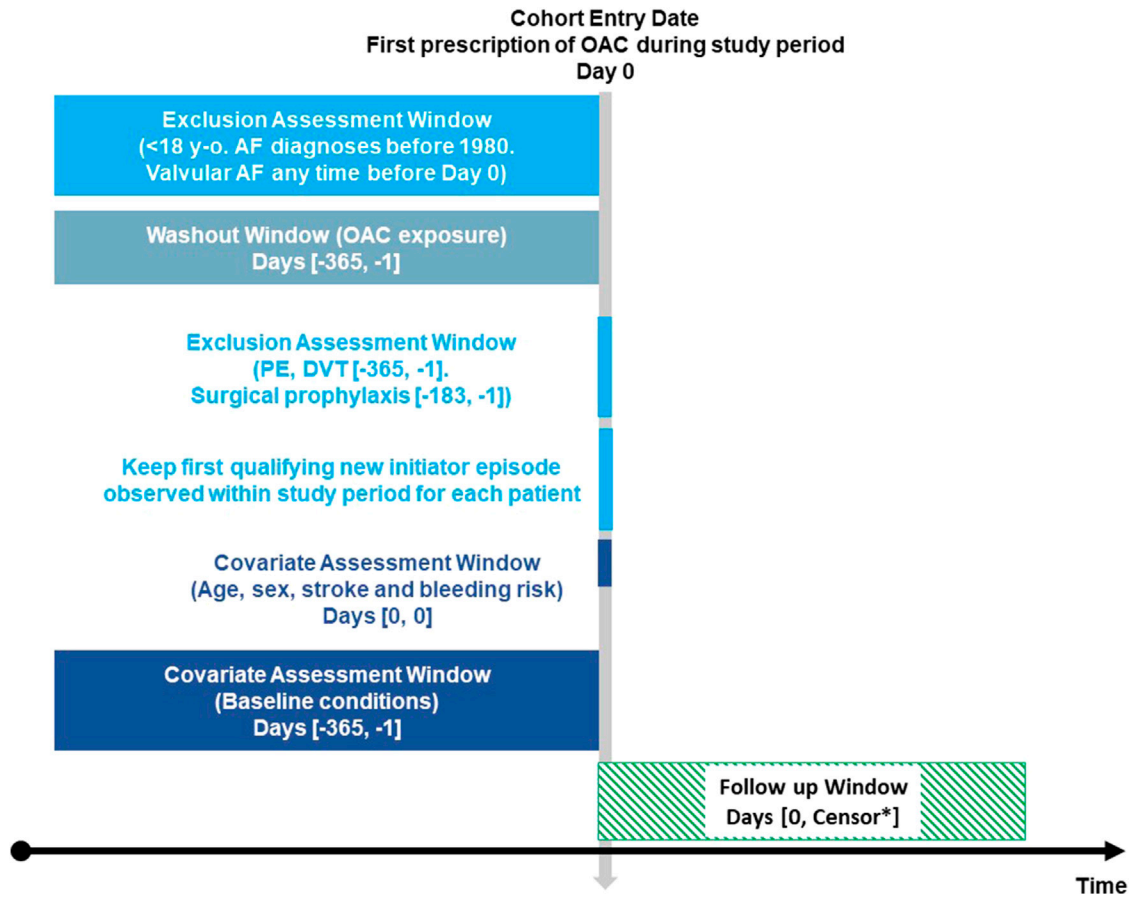

FIGURE 1
Exposure-based cohort entry Figure 1 depicts the time of variables' assessment at cohort entry. *Earliest of: outcome of interest (stroke, cerebral or gastrointestinal bleeding), death, disenrollment, end of study period. OAC: oral anticoagulants. AF: atrial fibrillation. PE: pulmonary embolism. DVT: deep vein thrombosis. Adapted from Schneeweiss et al., 2019; Schneeweiss et al., 2019).

Drug exposure

We included all NVAF patients who initiated an OAC treatment during the study period (2011–2020) and excluded the non-initiators, who did not have any dispensing during the subsequent 120 days. The duration of pharmacy invoice records was estimated based on the number of packages dispensed, assuming each package provided coverage for 30 days, as only the month of dispensing was available.

For DOAC-treated, we assessed: dose of DOAC; defining the dose adequacy according to the Summary of Product Characteristics, SPC (Supplementary Table S3), discontinuation; defined as no dispensing during more than 2 months after initiation, persistence; defined as no discontinuation of OAC treatment, adherence to treatment; measured by Medication Possession Ratio (MPR) (Hess et al., 2006) and considering adherents those with MPR ≥80%, and treatment switch; when the first OAC was discontinued and a different one was initiated during the study period.

Study outcomes

We estimated incidence rates (IR) of ischaemic stroke, cerebral haemorrhage, and gastrointestinal (GI) haemorrhage for all OAC initiators throughout the follow-up period. Patients were censored at the time when any of the following events occurred: outcome of interest (stroke, cerebral or GI bleeding), death, disenrollment from the database, or end of study period (Figure 1).

Statistical analysis

In order to model the longitudinal drug exposure, we used a computational technique, the smooth algorithm. This algorithm utilizes non-parametric statistical techniques to identify the most probable treatment based on all drug dispensations documented for each patient throughout the study period (Ouchi et al., 2022).

For the effectiveness and safety analyses, we calculated IR of all outcomes of interest as the cumulative number of events per 1,000 person-year for OAC initiators. We estimated incidence rate ratios (IRR) and 95% confidence intervals (CI), crude and adjusted, by fitting a negative binomial regression for stroke, cerebral and GI bleeding. The log (time) was used as an offset in the models, and the sandwich method was employed to estimate robust standard errors. The covariables were age (≥75 years), sex, CHA_2DS_2VASc, previous event for each outcome of interest,

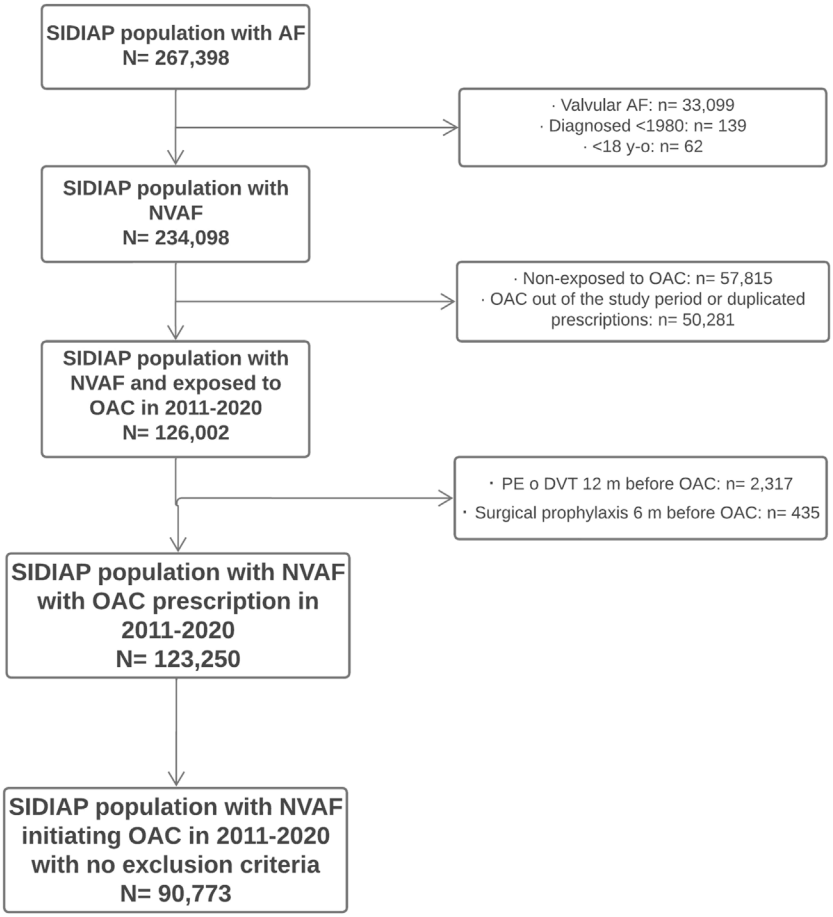

FIGURE 2
Flow diagram of population included Flowchart of patients' inclusion in the study. SIDIAP: Information System for the Development of Research in Primary Care. AF: atrial fibrillation. NVAF: non-valvular atrial fibrillation. OAC: oral anticoagulants. PE: pulmonary embolism. DVT: deep vein thrombosis.

comorbidities–including chronic kidney disease (CKD) defined by diagnosis and/or glomerular filtration rate –, and comedications.

We conducted subgroup analyses for those patients exposed to DOAC by dose adequacy according to the criteria in the SPC, adherence (MPR ≥80%), and treatment switch during follow-up.

All statistical analyses were conducted with R software (version 4.1 or superior) with a significance level of 5%.

Results

During the period spanning 2011 to 2020, 123,250 people with NVAF were prescribed a new OAC. Their baseline socio-demographic and clinical characteristics and the persistence and adherence to treatment have been described elsewhere (Giner-Soriano et al., 2023). Of these people, 90,773 (73.6%) received a dispensing for the OAC prescription and were included in the analyses of effectiveness and safety (Figure 2). The median follow-up time was 36.7 months (interquartile range, IQR, 17.9–61.2) and the median time to first treatment switch for all OAC was 18.7 months (IQR, 5.8–43.0).

Effectiveness analysis

Table 1 shows the number of stroke events, IR and IRR, crude and adjusted for covariates. The overall IR of stroke was 35.9 events per 1,000 person-year (95% CI 35.1–36.7). With regards to the binomial regression of all patients treated with OAC, the factors associated with an increased risk of stroke were age older than 75 (IRR 1.33, 95% CI 1.23–1.44), male sex (IRR 1.12, 95% CI 1.05–1.20), having experienced a previous stroke–which posed the greatest risk of stroke (IRR 8.27, 95% CI 7.75–8.83) –, being diagnosed with peripheral artery disease, PAD, (IRR 1.35, 95% CI 1.22–1.49) or DVT (IRR 1.83, 95% CI 1.01–3.33), and receiving concomitant treatment with antiplatelets (IRR 1.13, 95% CI 1.05–1.22), antidiabetic drugs (IRR 1.32, 95% CI 1.23–1.42) or proton pump inhibitors, PPI, (IRR 1.13, 95% CI 1.06–1.21). There was no difference in stroke risk when comparing DOAC vs. VKA and for patients with or without CKD.

For DOAC- treated patients, we found that being adherent to the treatment had a protective effect against stroke (IRR 0.74, 95% CI 0.65–0.83), whereas those who switched the DOAC during the follow-up were at increased risk (IRR 2.08, 95% CI 1.84–2.38). Receiving the correct dose of DOAC was not associated with

TABLE 1 Stroke incidence in initiators of oral anticoagulants during the study period.

		N total	N events	Sum of person-years	IR (95% CI), 1000 person/year	IRR (95% CI)	*p*-value	Adjusted IRR (95% CI)	*p*-value
All patients (DOAC and VKA)									
OAC	DOAC	36458	2814	60184	46.8 (45.0–48.5)	1.27 (1.19–1.34)	<0.001	1.02 (0.96–1.08)	0.443
	VKA	54315	4306	138385	31.1 (30.2–32.1)				
Age	>75	51046	4613	103500	44.6 (43.3–45.9)	1.66 (1.56–1.76)	<0.001	**1.33 (1.23–1.44)**	<0.001
	≤75	39727	2507	95069	26.4 (25.4–27.4)				
Sex	Men	48348	3961	103806	38.2 (37.0–39.4)	1.11 (1.05–1.18)	<0.001	**1.12 (1.05–1.20)**	0.001
	Women	42425	3159	94763	33.3 (32.2–34.5)				
CKD	Yes	8625	804	14731	54.6 (50.9–58.5)	1.42 (1.30–1.55)	<0.001	1.08 (0.98–1.18)	0.116
	No	75747	5964	172211	34.6 (33.8–35.5)				
Previous event	Yes	13818	4061	26513	153.2 (148.5–158.0)	9.30 (8.80–9.83)	<0.001	**8.27 (7.75–8.83)**	<0.001
	No	76955	3059	172056	17.8 (17,2–18,4)				
PAD	Yes	6293	878	11671	75.2 (70,3–80,4)	2.11 (1.93–2.31)	<0.001	**1.35 (1.22–1.49)**	<0.001
	No	84480	6242	186898	33.4 (32.6–34.2)				
DVT	Yes	114	17	172	98.8 (57.6–158.3)	1.99 (1.10–3.60)	0.023	**1.83 (1.01–3.33)**	0.048
	No	90659	7103	198397	35.8 (35.0–36.6)				
Antiplatelets	Yes	15179	1723	31318	55.0 (52.5–57.7)	1.69 (1.58–1.81)	<0.001	**1.13 (1.05–1.22)**	<0.001
	No	75594	5397	167251	32.3 (31.4–33.1)				
Antidiabetic drugs	Yes	22453	2446	48263	50.7 (48.7–52.7)	1.64 (1.54–1.74)	<0.001	**1.32 (1.23–1.42)**	<0.001
	No	68320	4674	150306	31.1 (30.2–32.2)				
PPI	Yes	48819	4575	105649	43.3 (42.1–44.6)	1.64 (1.54–1.74)	<0.001	**1.13 (1.06–1.21)**	<0.001
	No	41954	2545	92921	27.4 (26.3–28.5)				
DOAC patients									
Dose initiated	Overdosed	4975	249	6962	35.8 (31.5–40.5)	0.68 (0.57–0.80)	<0.001	0.88 (0.72–1.07)	0.187
	Underdosed	7837	685	12761	53.7 (49.7–57.9)	1.13 (1.02–1.25)	0.019	1.05 (0.94–1.17)	0.420
	Recommended dose	23646	1880	40462	46.5 (44.4–48.6)				
MPR	≥80%	31114	2432	56883	42.8 (41.1–44.5)	0.69 (0.62–0.78)	<0.001	**0.74 (0.65–0.83)**	<0.001

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TABLE 1 (*Continued*) Stroke incidence in initiators of oral anticoagulants during the study period.

		N total	N events	Sum of person-years	IR (95% CI), 1000 person/year	IRR (95% CI)	*p*-value	Adjusted IRR (95% CI)	*p*-value
	<80%	5344	382	3301	115.7 (104.4–127.9)				
DOAC switch	Yes	3523	459	5836	78.7 (71.6–86.2)	1.80 (1.59–2.03)	<0.001	**2.08 (1.84–2.38)**	<0.001
	No	32935	2355	54348	43.3 (41.6–45.1)				

IR, Incidence rate per 1000 person/year. IRR, incidence rate ratio. VKA, vitamin K antagonists. OAC, oral anticoagulant treatment. CKD, chronic kidney disease, estimated by glomerular filtration rate <45 mL/min. PAD, peripheral artery disease. DVT, deep vein thrombosis. PPI, proton pump inhibitors. DOAC, direct oral anticoagulants. MPR, medication possession ratio. The bold value means statistically significant.

different IR for stroke when compared under- or overdosing (Table 1; Figure 3).

Safety analysis

Cerebral haemorrhage

The overall IR of cerebral haemorrhage was 3.2 events per 1,000 person-year. In reference to the results of the regression analysis (Table 2), the risk of cerebral haemorrhage increased significantly with male sex (IRR 1.49, 95% CI 1.23–1.82), previous occurrence of the event (IRR 9.26, 95% CI 6.60–12.98) and treatment with antidiabetic drugs (IRR 1.23, 95% CI 1.01–1.50), while receiving DOAC had a protective effect compared to VKA (IRR 0.71, 95% CI 0.59–0.86).

Among patients treated with DOAC, adherence to treatment was protective against the event (IRR 0.43, 95% CI 0.29–0.65), while switching drug during follow-up resulted in an increased risk of cerebral bleeding (IRR 2.40, 95% CI 1.59–3.61), and receiving an adequate dose had no significant effect compared to under- or overdosing (Table 2; Figure 3).

Gastrointestinal bleeding

The overall IR of GI haemorrhage was 1.2 events per 1,000 person-year. As shown in Table 3, male sex (IRR 2.14, 95% CI 1.56–2.94), presence of CKD (IRR 1.75, 95% CI 1.17–2.62) and history of previous event (IRR 5.93, 95% CI 2.78–12.66) were associated with a higher risk of haemorrhage, while treatment with PPI (IRR 0.59, 95% CI 0.44–0.78) and a history of DVT (IRR 0, 95% CI 0–0) had a protective effect.

For patients treated with DOAC, switching drug during follow-up was associated with an increased risk of GI bleeding (IRR 2.43, 95% CI 1.28–4.63), while correct dose compared to under- or overdosing or MPR ≥80% vs. non-adherent did not result in significantly different bleeding risk (Table 3; Figure 3).

Discussion

In this cohort study including 90,773 people with NVAF who initiated OAC between 2011 and 2020 and with up to 10 years of follow-up, we have studied effectiveness and safety of OAC treatment, according to age categories, sex, and the presence of prevalent comorbidities and comedications. We have also investigated these outcomes for people receiving DOAC in terms of dose, adherence and treatment switch, which had not been analysed so far in our setting, although DOAC initiation already accounts for more than 50% of new treatments (Giner-Soriano et al., 2023). To obtain more accurate information on drug intake, we have conducted the analyses in the cohort of patients with OAC dispensed rather than relying solely on prescription data (Grégoire and Moisan, 2016).

The IR of stroke in our cohort was 35.9 events per 1,000 person-years, with a narrow 95% CI of 35.1–36.7. This estimate is in line with recent studies reporting IR ranging from 15.0–36.6 events per 1,000 person-years for NVAF patients treated with OAC, depending on the population characteristics and the OAC type and dose (Lee et al., 2020; Crocetti et al., 2021; Lip et al., 2021;

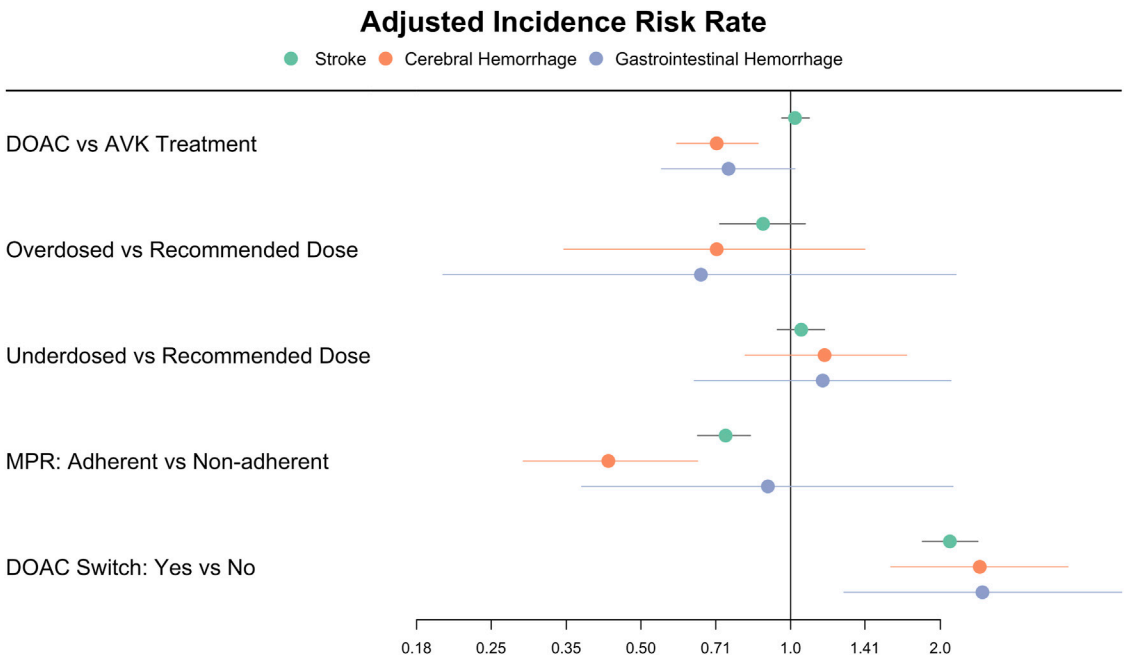

FIGURE 3
Forest plot of the incidence rate ratios of stroke, cerebral and gastrointestinal haemorrhages in patients treated with oral anticoagulants Figure 3 depicts the adjusted Incidence Rate Ratios of stroke, cerebral and gastrointestinal haemorrhages in the group of patients treated with DOAC in comparison with VKA, and in those receiving DOAC according to dose adequacy, adherence, and treatment switch. DOAC: direct oral anticoagulants. VKA: vitamin K antagonists. MPR: medication possession ratio.

Grymonprez et al., 2023). It should be noted that the IR of stroke may vary depending on the geographical area and the healthcare system in which the study is conducted. In addition, differences in IR across studies may reflect variations in patient characteristics, comorbidities, and healthcare practices, as well as differences in the accuracy and definition of stroke events. Therefore, caution should be exercised when comparing IR between studies in different populations or settings.

Even so, our study provides valuable information on stroke IR in NVAF patients treated with OAC in Catalonia and highlights the importance of optimising OAC therapy to prevent these serious complications. Our results on effectiveness showed no differences in stroke risk when all DOAC-treated were compared with VKA-treated, as also found by Anguita-Sánchez et al. (Anguita Sánchez et al., 2020) and Sjögren et al. (Sjögren et al., 2017) but different to other authors who found DOAC to be protective against stroke compared to VKA (Durand et al., 2020; Lee et al., 2020). Several authors have found protection against stroke with DOAC vs. VKA when analysed by active substance (Deitelzweig et al., 2017; Halvorsen et al., 2017; Hernandez et al., 2017; Bang et al., 2020; Kohsaka et al., 2020; Crocetti et al., 2021; Lip et al., 2021; Grymonprez et al., 2023).

As mentioned above, these results must be interpreted with caution, as they might be influenced by several factors not related with drugs, such as the healthcare system, and other variables must be considered, such as adherence, doses or INR values. We found that older than 75, male, or those who had experienced a prior stroke had a higher risk of stroke. Regarding these patients with a prior history of stroke, it is necessary to highlight the critical role of this factor in predicting future stroke risk. Other authors have described stroke rates based on similar categories and found heterogeneous results (Bengtson et al., 2017; Rodríguez-Bernal et al., 2021; Jaksa et al., 2022). For DOAC-treated, adherence showed a protective effect against stroke, in line with similar studies with DOAC (Yao et al., 2016a; Deshpande et al., 2018).

Regarding cerebral bleeding, DOAC were protective compared to VKA, in line with most studies showing DOAC as the safest option with respect to cerebral haemorrhage risk (Halvorsen et al., 2017; Forslund et al., 2018; Bang et al., 2020; Durand et al., 2020; Lee et al., 2020; Rodríguez-Bernal et al., 2021; Grymonprez et al., 2023). We found an increased risk of cerebral haemorrhage for males, people with a previous event or people receiving antidiabetic drugs, being these results also heterogeneous with respect to the studies mentioned above (Bengtson et al., 2017; Rodríguez-Bernal et al., 2021; Jaksa et al., 2022). As in the case of stroke, those who had previously experienced a cerebral haemorrhage had a significantly higher risk of experiencing a new event compared to those without this antecedent. Again, optimal adherence to DOAC showed a protective effect against this outcome. Other studies analysing the impact of adherence on DOAC safety did not demonstrate a protective effect against major bleeding (Deshpande et al., 2018) or intracranial haemorrhage (Yao et al., 2016a).

With regards to GI bleeding, we found no significant differences between DOAC and VKA, in line with other studies (Bengtson et al., 2017; Durand et al., 2020; Rodríguez-Bernal et al., 2021), although multiple studies showed a favourable profile for DOAC in general, especially for apixaban, compared to other OAC (Abraham et al., 2017; Deitelzweig et al., 2017; Hernandez et al., 2017; Staerk et al.,

TABLE 2 Cerebral haemorrhage incidence in initiators of oral anticoagulants during the study period.

		N total	N events	Sum of person-years	IR (95% CI), 1000 person/year	IRR (95% CI)	*p*-value	Adjusted IRR (95% CI)	*p*-value
All patients (DOAC and VKA)									
OAC	DOAC	36458	185	62584	3.0 (2.6–3.4)	0.74 (0.62–0.89)	0.001	**0.71 (0.59–0.86)**	<0.001
	VKA	54315	465	142771	3.3 (3.0–3.6)				
Age	>75	51046	414	107582	3.9 (3.5–4.2)	1.55 (1.31–1.84)	<0.001	1.24 (1.00–1.55)	0.052
	≤75	39727	236	97773	2.4 (2.1–2.7)				
Sex	Men	48348	372	107381	3.5 (3.1–3.8)	1.20 (1.02–1.42)	0.029	**1.49 (1.23–1.82)**	<0.001
	Women	42425	278	97974	2.8 (2.5–3.2)				
CKD	Yes	8625	73	15257	4.8 (3.8–6.0)	1.42 (1.10–1.84)	0.007	1.21 (0.93–1.58)	0.148
	No	75747	551	178129	3.1 (2.8–3.4)				
Previous event	Yes	1153	38	2447	15.5 (11.0–21.3)	6.66 (4.69–9.46)	<0.001	**9.26 (6.60–12.98)**	<0.001
	No	89620	612	202908	3.0 (2.8–3.3)				
PAD	Yes	6293	48	12219	3.93 (2.9–5.2)	1.18 (0.86–1.62)	0.299	0.92 (0.66–1.27)	0.601
	No	84480	602	193136	3.1 (2.9–3.4)				
DVT	Yes	114	1	190	5.3 (0.1–29.3)	1.67 (0.24–11.89)	0.607	2.02 (0.28–14.45)	0.482
	No	90659	649	205165	3.2 (2.9–3.4)				
Antiplatelets	Yes	15179	128	32757	3.9 (3.3–4.7)	1.29 (1.05–1.59)	0.016	1.14 (0.92–1.43)	0.229
	No	75594	522	172598	3.0 (2.8–3.3)				
Antidiabetic drugs	Yes	22453	214	50173	4.3 (3.7–4.9)	1.56 (1.31–1.86)	<0.001	**1.23 (1.01–1.50)**	0.042
	No	68320	436	155182	2.8 (2.6–3.1)				
PPI	Yes	48819	386	109765	3.5 (3.2–3.9)	1.30 (1.10–1.53)	0.002	1.11 (0.94–1.33)	0.225
	No	41954	264	95590	2.8 (2.4–3.1)				
DOAC patients									
Dose initiated	Overdosed	4975	14	7126	2.0 (1.1–3.3)	0.55 (0.32–0.96)	0.036	0.71 (0.35–1.41)	0.326
	Underdosed	7837	54	13269	4.1 (3.1–5.3)	1.36 (0.97–1.92)	0.076	1.17 (0.81–1.71)	0.404
	Recommended dose	23646	127	42163	3.0 (2.5–3.6)				
MPR	≥80%	31114	162	59144	2.7 (2.3–3.2)	0.50 (0.33–0.74)	<0.001	**0.43 (0.29–0.65)**	<0.001
	<80%	5344	33	3415	9.7 (6.7–13.6)				
DOAC switch	Yes	3523	34	6221	5.5 (3.8–7.6)	1.96 (1.32–2.91)	<0.001	**2.40 (1.59–3.61)**	<0.001
	No	32935	161	56338	2.9 (2.4–3.3)				

IR, Incidence rate per 1000 person/year. IRR, incidence rate ratio. VKA, vitamin K antagonists. OAC, oral anticoagulant treatment. CKD, chronic kidney disease, estimated by glomerular filtration rate <45 mL/min. PAD, peripheral artery disease. DVT, deep vein thrombosis. PPI, proton pump inhibitors. DOAC, direct oral anticoagulants. MPR, medication possession ratio. The bold value means statistically significant.

TABLE 3 Gastrointestinal haemorrhage incidence in initiators of oral anticoagulants during the study period.

		N total	N events	Sum of person-years	IR (95% CI), 1000 person/year	IRR (95% CI)	*p*-value	Adjusted IRR (95% CI)	*p*-value
All patients (DOAC and VKA)									
OAC	DOAC	36458	65	62644	1.0 (0.8–1.3)	0.70 (0.52–0.94)	0.018	0.75 (0.55–1.02)	0.071
	VKA	54315	180	142977	1.3 (1.1–1.5)				
Age	>75	51046	149	107709	1.4 (1.2–1.6)	1.34 (1.02–1.76)	0.036	1.12 (0.78–1.61)	0.543
	≤75	39727	96	97911	1.0 (0.8–1.2)				
Sex	Men	48348	163	107478	1.5 (1.3–1.8)	1.83 (1.38–2.43)	<0.001	**2.14 (1.56–2.94)**	<0.001
	Women	42425	82	98143	0.8 (0.7–1.0)				
CKD	Yes	8625	33	15256	2.2 (1.5–3.0)	1.84 (1.26–2.70)	0.002	**1.75 (1.17–2.62)**	0.007
	No	75747	202	178383	1.1 (1.0–1.3)				
Previous event	Yes	581	8	1143	7.0 (3.0–13.8)	6.38 (3.08–13.22)	<0.001	**5.93 (2.78–12.66)**	<0.001
	No	90192	237	204478	1.2 (1.0–1.3)				
PAD	Yes	6293	26	12235	2.1 (1.4–3.1)	1.87 (1.24–2.82)	0.003	1.39 (0.88–2.21)	0.158
	No	84480	219	193386	1.1 (1.0–1.3)				
DVT	Yes	114	0	192	0 (0–19.3)	0 (0–0)	<0.001	**0 (0–0)**	<0.001
	No	90659	245	205429	1.2 (1.1–1.4)				
Antiplatelets	Yes	15179	39	32822	1.2 (0.8–1.6)	1.01 (0.71–1.43)	0.961	0.89 (0.61–1.28)	0.522
	No	75594	206	172799	1.2 (1.0–1.4)				
Antidiabetic drugs	Yes	22453	77	50270	1.5 (1.2–1.9)	1.44 (1.08–1.92)	0.014	1.17 (0.83–1.65)	0.378
	No	68320	168	155351	1.1 (0.9–1.3)				
PPI	Yes	48819	108	110010	1.0 (0.8–1.2)	0.67 (0.51–0.87)	0.003	**0.59 (0.44–0.78)**	<0.001
	No	41954	137	95610	1.4 (1.2–1.7)				
DOAC patients									
Dose initiated	Overdosed	4975	4	7129	0.6 (0.2–1.4)	0.47 (0.17–1.31)	0.147	0.66 (0.20–2.15)	0.490
	Underdosed	7837	15	13304	1.1 (0.6–1.9)	1.01 (0.56–1.84)	0.961	1.16 (0.64–2.10)	0.627
	Recommended dose	23646	46	4221	1.1 (0.8–1.5)				
MPR	≥80%	31114	58	59230	1.0 (0.7–1.3)	0.85 (0.39–1.87)	0.690	0.90 (0.38–2.12)	0.811
	<80%	5344	7	3414	2.1 (0.8–4.2)				
DOAC switch	Yes	3523	14	6234	2.3 (1.2–3.8)	2.67 (1.43–4.98)	0.002	**2.43 (1.28–4.63)**	0.006
	No	32935	51	56410	0.9 (0.7–1.2)				

IR: Incidence rate per 1000 person/year. IRR: incidence rate ratio. VKA: vitamin K antagonists. OAC: oral anticoagulant treatment. CKD: chronic kidney disease, estimated by glomerular filtration rate <45 mL/min. PAD: peripheral artery disease. DVT: deep vein thrombosis. PPI: proton pump inhibitors. DOAC: direct oral anticoagulants. MPR: medication possession ratio.

2018; Vinogradova et al., 2018; Bang et al., 2020; Rutherford et al., 2020; van Ganse et al., 2020; Grymonprez et al., 2023). In our study, males and CKD patients or with a previous haemorrhage were at increased risk of this event, as in other studies (Keskar et al., 2017; Kumar et al., 2018), and receiving PPI had a protective effect against this outcome, as has been widely demonstrated (Ahn et al., 2022). DOAC adherence had no protective effect against GI bleeding compared to non-adherence. Yao et al. analysed effectiveness and safety according to treatment persistence and found that, for those with CHA_2DS_2-VASc ≥2, being persistent for at least 6 months had a protective effect in front of GI bleeding. They also analysed adherence, but not its effects on the outcomes (Yao et al., 2016a).

For DOAC-treated, switching increased the risk of all three outcomes of study. Unfortunately, we were not able to ascertain the reasons for the switch, which might be contributing to these higher risks of events. It is usual in similar studies to exclude or to censor patients who switch treatment during follow-up (Crocetti et al., 2021; Grymonprez et al., 2023).

We could not find a protective effect against any of the events when an adequate dose of DOAC was prescribed in comparison to an inadequate one. As we had previously described non-despicable numbers of under- and overdosed patients according to the SPC (Giner-Soriano et al., 2023), we aimed to analyse if those people treated with inadequate doses might have associated worst clinical outcomes. Thus, we had previously hypothesized that those individuals receiving a lower dose than recommended could have shown an increased risk of stroke, but we did not find significant differences when they were compared to those receiving an adequate dose of DOAC. For haemorrhages, we could have expected higher risk for overdosed patients and lower risk for underdosed, but once more, the differences were not statistically significant. Nevertheless, we only analysed the first dose prescribed but not further changes in posology. Other authors have analysed the effects of the initial dose on the effectiveness and safety, splitting by standard and reduced dose for each DOAC, but none of them have evaluated these effects by the dose adequacy (Li et al., 2017; Nielsen et al., 2017; Staerk et al., 2018; Vinogradova et al., 2018; Kohsaka et al., 2020).

Strengths and limitations

Strengths of our study include the long follow-up and the number of patients included from a database which has already demonstrated to be representative of the Catalan population (Recalde et al., 2022). We have analysed all four approved DOAC, in new and old users of OAC, have analysed the impact of treatment adherence or switch on the outcomes, and studied all the doses authorised in NVAF and their adequacy according to the SPC, which had not been evaluated in other studies (Li et al., 2017; Nielsen et al., 2017; Staerk et al., 2018; Vinogradova et al., 2018; Kohsaka et al., 2020).

The study also places some limitations due to the observational nature of the data, such as the potential unexamined confounding variables, missing values, or coding errors, which might have introduced bias into the study, but which are present in all database observational studies. The most important limitation is the under-registration of GI haemorrhages in CMBD database, as it captures diagnoses at hospital discharge, but in our setting most GI haemorrhages are attended and treated in short-stay hospital wards of the Emergency Departments which do not routinely register those diagnoses in the CMBD database, as they use their own database, to which we did not have access to. In fact, IR of cerebral haemorrhage have been widely documented to be lower than IR of GI haemorrhage, and this was not the case in our study (see Tables 2; 3) (Yao et al., 2016b; Halvorsen et al., 2017; Durand et al., 2020; Rodríguez-Bernal et al., 2021; Grymonprez et al., 2023). Another limitation is that we have not analysed the mortality due to the inability of capturing the cause of death in our database.

Our results should be considered hypothesis-generating due to their observational design but they give us insight into how OAC are used in clinical practice and may help to design interventions to improve dose adequacy or adherence to treatment.

Further analyses may include the study of VKA discontinuations and adherence and the impact of time in therapeutic range on the clinical outcomes or include proxies of the cause of death to study the mortality rates in the OAC-treated population.

Conclusion

Our study in a cohort of patients with NVAF treated with OAC revealed that those with a history of previous events (stroke, cerebral and GI haemorrhage) and male patients had a higher risk for all study outcomes. For DOAC-treated, switching DOAC during follow-up was associated with an increased risk of all outcomes.

We observed a protective effect of DOAC against cerebral haemorrhage when compared to VKA. Adherence to DOAC treatment resulted in lower risks of both stroke and cerebral haemorrhage.

When compared DOAC and VKA, we did not find any substantial differences in the risk of stroke and GI bleeding.

These findings highlight the importance of considering patients' baseline characteristics and comorbidities when prescribing OAC. Clinicians should exercise caution when prescribing OAC to patients with a history of stroke, cerebral or GI haemorrhage, older patients, men, and those with PAD or DVT, as they are at an increased risk of adverse events. Adherence to DOAC treatment and avoiding switching DOAC during follow-up could help to reduce the risk of stroke and cerebral haemorrhage.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Research Ethics Committee of IDIAPJGol (October 2019). 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 the need for consent was waived

by the Research Ethics Committee of IDIAPJGol as it is deemed unnecessary according to European legislation (Regulation [EU] 2016/679).

Author contributions

Conceptualization and research design MG-S, RV, AM, AV, and RM. Data acquisition and operativization MG-S and RV. Data curation, statistical analyses and visualization DO and CV-C. Interpretation of results all authors Writing–original draft MG-S Writing–review and editing all authors. All authors contributed to the article and approved the submitted version.

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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.2023.1237454/full#supplementary-material

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Heparin-induced thrombocytopenia associated with low-molecular-weight heparin: clinical feature analysis of cases and pharmacovigilance assessment of the FAERS database

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Background: Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are commonly used anticoagulants for the management of arterial and venous thromboses. However, it is crucial to be aware that LMWH can, in rare cases, lead to a dangerous complication known as heparin-induced thrombocytopenia (HIT). The objective of this study was to evaluate the pharmacovigilance and clinical features of HIT associated with LMWH, as well as identify treatment strategies and risk factors to facilitate prompt management.

Methods: We extracted adverse event report data from the FDA Adverse Event Reporting System (FAERS) database for pharmacovigilance assessment. Case reports on LMWH-induced thrombocytopenia dated up to 20 March 2023 were collected for retrospective analysis.

Results: Significantly elevated reporting rates of HIT were shown in adverse event (AE) data of LMWHs in the FAERS database, while tinzaparin had a higher proportional reporting ratio (PRR) and reporting odds ratio (ROR) than other LMWHs, indicating a greater likelihood of HIT. Case report analysis indicated that a total of 43 patients showed evidence of LMWH-induced thrombocytopenia with a median onset time of 8 days. Almost half of the events were caused by enoxaparin. LMWHs were mainly prescribed for the treatment of embolism and thromboprophylaxis of joint operation. Patients with a history of diabetes or surgery appeared to be more susceptible to HIT. Clinical symptoms were mostly presented as thrombus, skin lesion, and dyspnea. Almost 90% of the patients experienced a platelet reduction of more than 50% and had a Warkentin 4T score of more than 6, indicating a high likelihood of HIT. In all patients, LMWHs that were determined to be the cause were promptly withdrawn. Following the discontinuation of LMWHs, almost all patients were given alternative anticoagulants and eventually achieved recovery.

Conclusion: LMWH-induced thrombocytopenia is rare but serious, with increased risk in patients with diabetes or a surgical history. Prompt recognition and management are crucial for the safe use of LMWHs.

KEYWORDS

low-molecular-weight heparin, heparin-induced thrombocytopenia, characteristics, treatments, pharmacovigilance

Introduction

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been extensively studied and have demonstrated efficacy in the treatment of arterial and venous thromboses. They are commonly prescribed for conditions such as deep vein thrombosis, pulmonary embolism, acute coronary syndrome, and prophylaxis in high-risk surgical procedures (Burness and Perry, 2014; Ortel et al., 2020). Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication that can occur after exposure to UFH, less commonly with LMWHs, and rarely with fondaparinux (Linkins et al., 2012). HIT has been estimated to occur in approximately 1%–5% of patients receiving therapeutic doses of heparin. Additionally, it has been observed that up to 1 in 1,500 hospitalized patients may suffer from HIT (Greinacher, 2015; McGowan et al., 2016; Rice, 2017; Dhakal et al., 2018; Hogan and Berger, 2020; Nilius et al., 2023). HIT caused by UFH is approximately 10-fold higher than that caused by LMWHs. HIT is an immune-mediated reaction caused by the formation of antibodies against the complex of platelet factor 4 (PF4) and heparin. These antibodies can activate platelets to a hypercoagulable state, which resulted in thrombocytopenia and increased the risk of venous and arterial thromboses (Rollin et al., 2022). The most common complications associated with heparin are bleeding, allergic reaction, and osteoporosis (Schindewolf et al., 2012; Signorelli et al., 2019), while thrombocytopenia is a rare complication that often goes unnoticed, especially when it is associated with LMWHs. HIT remains a significant cause of morbidity and mortality in hospitalized patients exposed to heparin, particularly those undergoing cardiac and surgical procedures (Linkins, 2015).

In recent years, increasing efforts have been made to improve the diagnosis and management of HIT. Advances in laboratory testing, including enzyme-linked immunosorbent assays (ELISAs) and functional assays, have improved the specificity and sensitivity to HIT antibodies. In addition, novel non-heparin anticoagulants, such as direct oral anticoagulants (DOACs), have been developed as alternative therapies for HIT. However, despite these advances, HIT remains a challenging diagnosis that requires a high index of suspicion and prompt initiation of appropriate therapy to reduce the risk of thromboembolic complications. The importance of early recognition and appropriate management of HIT cannot be overstated, as delays in diagnosis and treatment can result in terrible consequences, including limb loss, organ damage, and even death (Pishko et al., 2019).

To date, there is a paucity of data regarding HIT associated with LMWHs. In our study, we extracted adverse event report data from the FAERS database for pharmacovigilance assessment and subsequently collected case reports on LMWH-induced thrombocytopenia for a real-world retrospective analysis. We summarized clinical features, risk factors, management, and outcomes of patients with HIT after anticoagulation with LMWHs, which will provide valuable information for the prompt recognition and management of HIT.

Methods

Pharmacovigilance study

Data extraction from the FAERS database

The FAERS database, which is the drug adverse event reporting system of the US FDA, collects adverse event report data for various drugs, providing strong evidence for drug safety and pharmacovigilance. In order to assess the safety of LMWHs and evaluate the risk of their adverse events (AEs) in clinical use, we retrieved and extracted AE data reported between Quarter 1(Q1) in 2004 and Q3 in 2022 for seven types of LMWHs (enoxaparin, nadroparin, dalteparin, tinzaparin, bemiparin, reviparin, and parnaparin) from the data publicly released by the FAERS database (FDA, 2023).

Data analysis of the FAERS database

After extraction, the data were initially utilized for baseline analysis, which included variables like gender, age, outcomes, and reporter country. The AEs extracted were then classified according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 26.0), which included categories such as vascular and lymphatic disorders, gastrointestinal disorders, infections and infestations, respiratory disorders, and metabolic and nutritional disorders, among others. We selected HIT among AEs related to vascular and lymphatic disorders and analyzed the association of these LMWHs with HIT by calculating the proportional reporting ratio (PRR) and reporting odds ratio (ROR). In this process, the keywords of PT were set as "heparin-induced thrombocytopenia," "heparin-induced thrombocytopenia test," and "heparin-induced thrombocytopenia test positive."

Disproportionality analysis

In pharmacovigilance assessment, disproportionality emerges when a specific AE is induced by a given drug. We used PRR and ROR to identify the statistical associations between LMWHs and HIT. PRR and ROR are calculated using the following formulas: PRR = [a/(a+b)]/[c/(c + d)]; ROR = (a/c)/(b/d). In the formula, "a" represents the number of reports of a specific AE caused by the given drug; "b" represents the total number of

all other AEs related to the given drug; "c" represents the number of reports of a specific AE caused by all other drugs; and "d" represents the total number of all other AEs related to all other drugs (Supplementary Table S1). For PRR, the screening criteria for an AE defined as a significant signal were PRR >2, $\chi^2 > 4$, and N >2. For ROR, the screening criteria for a significant signal were the lower limit of two-sided 95% confidence interval (CI) > 1 and N >2.

Descriptive study

Search strategy

Using PubMed/MEDLINE, Web of Knowledge, Embase, Ovid, Springer Link, Elsevier, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese VIP databases, our searches for relevant literature were performed using the following keywords: "enoxaparin," "bemiparin," "edoxaban," "nadroparin," "tinzaparin," "reviparin," "parnaparin," "low-molecular-weight heparin," "heparin-induced thrombocytopenia," "heparin related thrombocytopenia," "anticoagulant-related HIT," "anticoagulant-related HIT," "anticoagulant associated HIT," and "HIT." Case reports and case series of HIT associated with LMWHs were included as preliminary studies. Duplicate literature, reviews, mechanism research, observational studies, animal studies, and articles without full text were excluded. We conducted thorough searches of various electronic databases without any specified start date up to 20 March 2023 and with no language restrictions.

Data extraction

We used self-designed tables to extract various clinical features of the patients from cases. These features included gender, age, anticoagulant administration, medical history, combined medication, baseline platelets or PLT, clinical manifestations of HIT, coagulation function, liver and kidney function, the time from taking LMWHs to HIT diagnosed, peak PLT at HIT diagnosis, anti-PF4 antibody, Warkentin 4T score, platelet recovery time, treatments, and prognosis. Specifically, the Warkentin 4T score in HIT incorporates four criteria: extent of platelet reduction, timing of platelet reduction, presence of thrombosis, and other causes of platelet reduction. Each criterion is assigned a score ranging from 0 to 2 points, with a higher cumulative score indicating a greater likelihood of HIT.

Results

Pharmacovigilance assessment of the FAERS database

Baseline information of HIT related to LMWHs

We retrieved information about three out of seven LMWHs available in the FAERS database: enoxaparin, dalteparin, and tinzaparin. As the FAERS database only recorded adverse events of HIT related to these three LMWHs, our analysis focused on these drugs. The AE data of three types of LMWHs in the FAERS database help comprehensively understand the safety profiles of these drugs. The overall number of the reported AEs of enoxaparin, dalteparin, and tinzaparin was 242, 34, and 30, respectively. Most AEs of the three LMWHs occurred in people aged over 60, ranging between 50% and 70%. The proportion of AEs in male and female patients is similar. Among the AEs of enoxaparin and tinzaparin, male patients accounted for more than 50%, and in the AEs of dalteparin, female patients accounted for more than 50%. The LMWH with the highest proportion of deaths among the outcomes of AEs was tinzaparin, accounting for 36.67%, while the lowest was enoxaparin, accounting for 21.90%. Enoxaparin had the highest proportion of reported cases in the United States, accounting for 38.43% (Table 1).

PRR and ROR for LMWHs

Since HIT related to nadroparin, bemiparin, reviparin, and parnaparin was not reported in the FAERS database, we only obtained PRR and ROR values of HIT for the other three drugs. PRR and ROR are used to measure the likelihood of a specific AE occurring with a drug, with higher values indicating a stronger association between the drug and the given AE. The PRR values of HIT for enoxaparin, dalteparin, and tinzaparin were 98.22, 100.48, and 195.81, and the ROR values for these three LMWHs were 100.51, 103.10, and 206.06, respectively. Tinzaparin had higher PRR and ROR values, indicating a greater likelihood of HIT occurring with this drug compared to the other two LMWHs (Table 2).

Clinical feature analysis of cases

Patients' information

A total of 43 patients from 40 studies were included in this analysis after full-text screening, involving 39 case reports (Plassat et al., 2002; Betrosian et al., 2003; Franke et al., 2003; Ng and Lee, 2003; Zamir et al., 2003; Dager and White, 2004; Patel and Knight, 2005; Doboszyńska et al., 2007; Rota et al., 2008; Famularo et al., 2009; Mumoli and Cei, 2010; Fesler et al., 2011; Illes et al., 2011; Iturbe et al., 2011; Yazbek et al., 2012; Klinkert et al., 2013; Leporini et al., 2013; Nazliel et al., 2014; Sinan et al., 2014; Brouns and Jie, 2015; Giuliani et al., 2015; Hantson et al., 2015; Koufakis et al., 2015; Larsen et al., 2015; Martinez and Burnett, 2015; Sartori et al., 2015; Wiegele et al., 2015; Pérez et al., 2016; Gan, 2017; Rivera et al., 2017; Le et al., 2019; Barcellona et al., 2020; Polák et al., 2020; Singh et al., 2020; Lovatt and Crowther, 2021; Tucker and Padarti, 2021; Byrne et al., 2022; Lázaro-García et al., 2022; Malinauskiene et al., 2022) and one case series (Hartman et al., 2006) (Figure 1). Patients' information is summarized in Table 3. These patients all had type II HIT. The median age of 43 patients (12 men and 31 women) with HIT in our study was 67 years, with an age range of 11–87 years. The types of LMWH administered were enoxaparin in 21 patients, nadroparin in 14 patients, dalteparin in four patients, tinzaparin in two patients, and bemiparin in two patients. LMWHs were mainly prescribed for embolism (10/43), joint operation (9/43), fracture (5/43), surgery (5/43), and dialysis (4/43). The common medical history in the patients with HIT was diabetes (10/43), surgical history (9/43), obesity (6/43), hypertension (6/43), and tumor history (4/43). As for dosage, all patients were handled in

TABLE 1 Baseline table of three types of LMWHs.

	Enoxaparin		Dalteparin		Tinzaparin	
	No. of HIT-associated AEs	Percentage	No. of HIT-associated AEs	Percentage	No. of HIT-associated AEs	Percentage
All	242		34		30	
Age						
<18	2	0.83%	0	0.00%	0	0.00%
18–60	66	27.27%	7	20.59%	7	23.33%
>60	143	59.09%	23	67.65%	16	53.33%
Unknown	31	12.81%	4	11.76%	7	23.33%
Gender						
Female	97	40.08%	18	52.94%	13	43.33%
Male	124	51.24%	15	44.12%	16	53.33%
Unknown	21	8.68%	1	2.94%	1	3.33%
Outcome of events						
Death	53	21.90%	8	23.53%	11	36.67%
Hospitalization-initial or prolonged/disability/life-threatening	157	64.88%	20	58.82%	14	46.67%
Others	32	13.22%	6	17.65%	5	16.67%
Reporter country						
US	93	38.43%	7	20.59%	1	3.33%
Other countries	149	61.57%	27	79.41%	29	96.77%

TABLE 2 PRR and ROR values of heparin-induced thrombocytopenia.

	χ^2	PRR (95% CI[a])	ROR (95% CI[a])
Enoxaparin	21,060.04	98.22 (86.17, 111.94)	100.51 (87.94, 114.88)
Dalteparin	3,208.847	100.48 (71.95, 140.33)	103.10 (73.19, 145.24)
Tinzaparin	5,558.40	195.81 (137.86, 278.11)	206.06 (142.45, 298.06)

PRR, proportional reporting ratio; ROR, reporting odds ratio; CI, confidence interval.
[a]Two-sided CI for ROR.

strict accordance with clinical guidelines, and there was no excessive anticoagulation.

Clinical manifestations

The clinical characteristics of HIT presented by the 43 included patients are summarized in Table 4. The time between the administration of LMWHs and the onset of HIT varied from 1 day to 30 days, with a median of 8 days. The onset time of HIT and its related outcomes differed based on the type of LMWH administered. The majority of patients (24/43) with HIT presented a typical fashion within 5–10 days. Among these patients, 13 had been administered enoxaparin (a total of 21 patients) while 10 had been given nadroparin (a total of 14 patients). Thrombus (39/43) was the most common clinical symptom, followed by skin lesions (15/43), dyspnea (13/43), hemorrhage (9/43), limb necrosis (5/43), cerebral infarction (5/43), and heart failure (5/43). Some patients may experience severe or even life-threatening symptoms, while others may only have very mild symptoms. We observed three cases (two from enoxaparin and one from nadroparin) of HIT with thrombosis involving multiple organs, including cerebral, pulmonary, abdominal, and lower extremity vessels (Betrosian et al., 2003; Barcellona et al., 2020; Tucker and Padarti, 2021). In contrast, only one case exhibited the symptom of thrombocytopenia (Franke et al., 2003).

All patients experienced a significant acute decrease in platelet (PLT) count compared to their baseline, with 77.5% of patients having a PLT count of less than 100×10^9/L. In a subset of cases, the decrease in PLT count was even more severe, with four patients

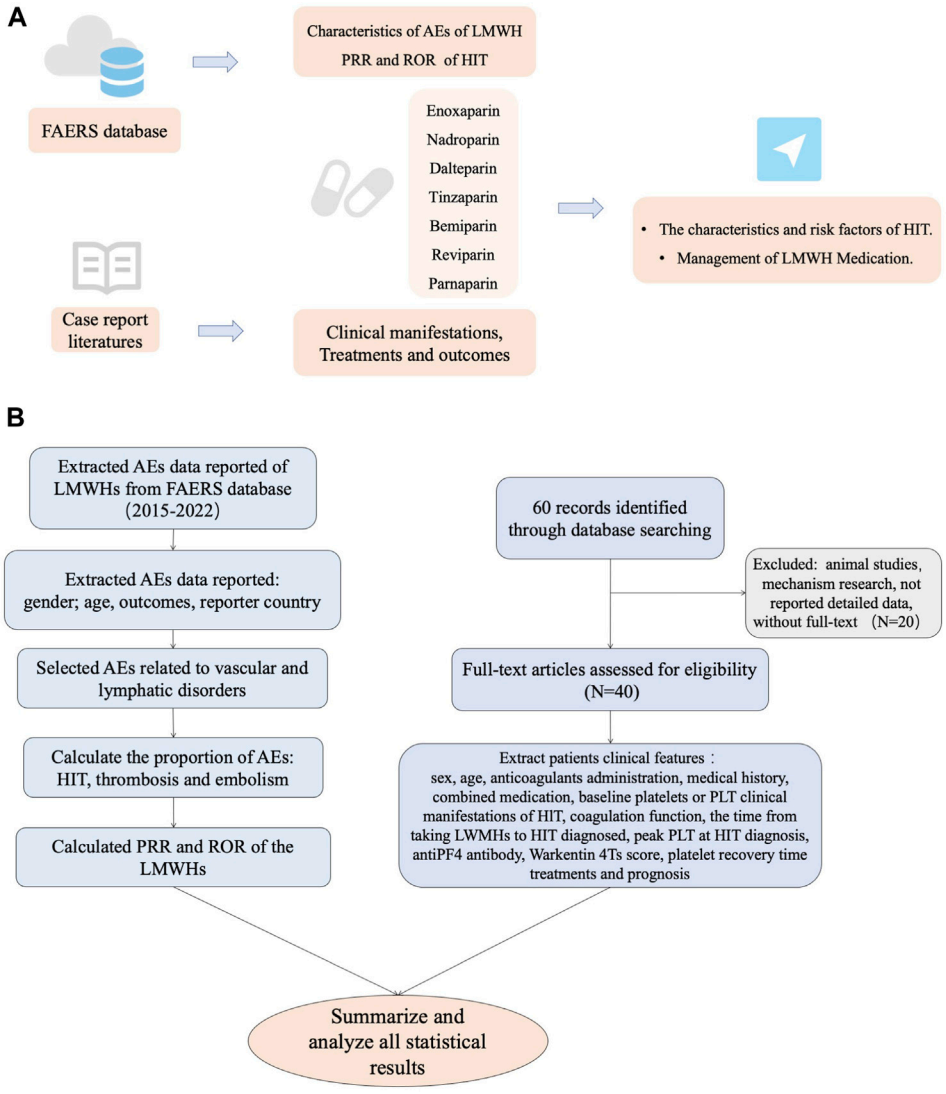

FIGURE 1
(A) Workflow of this research. **(B)** Technical route of this research.

having a PLT count below 20×10^9/L. Additionally, nearly 90% of patients had a PLT reduction ratio greater than 50%. The lowest PLT count and the proportion of PLT decrease varied among different drugs (Table 4). Among the cases analyzed, enoxaparin accounted for 15 out of 21 cases with PLT counts falling between 20 and 100, while nadroparin accounted for seven out of 14 cases. Regarding the proportion of PLT decrease, enoxaparin accounted for 19 out of 21 cases with a decrease of more than 50%, nadroparin accounted for eight out of 14 cases, and dalteparin accounted for three out of four cases. A total of 36 patients tested positive for anti-PF4 antibodies. Specifically, among these patients, 17 tested positive for enoxaparin (out of a total of 21), 12 tested positive for nadroparin (out of a total of 14), and four tested positive for dalteparin (out of a total of four). The Warkentin 4T scores of 18 patients (85.71%) were more than 6, meaning a high likelihood of HIT. Furthermore, additional laboratory examinations were conducted in some cases. Out of the total cases, 11 patients underwent D-dimer testing and five of them showed elevated D-dimer levels (Betrosian et al., 2003; Dager and White, 2004; Singh et al., 2020; Lovatt and Crowther, 2021; Tucker and Padarti, 2021). Elevated D-dimer levels can be indicative of the ongoing thrombotic activity. Additionally, five out of eight cases showed abnormal liver and kidney functions, which may be associated with HIT.

Treatments and outcomes

The treatments of HIT were recommended to immediately stop heparin therapy and initiate non-heparin-based anticoagulants. In our included cases, LMWHs, judged as the culprits, were immediately withdrawn in all patients (Table 5). Almost all patients (39/43) were administered other anticoagulants, which included fondaparinux (17/39), lepirudine (11/39), argatroban (7/39), warfarin (5/39), acenocoumarol (5/39), rivaroxaban (4/39), apixaban (2/39), dabigatran (1/39), and clopidogrel (1/39). Two patients with severe

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TABLE 3 Characteristics of the 43 included patients with HIT induced by LMWHs.

Parameter	Value	Percentage (%)
Gender		
Male	12	27.91
Female	31	72.09
Age (years)		
<18	1	2.33
18–60	15	34.88
>60	27	62.79
Low-molecular-weight anticoagulant		
Enoxaparin	21	48.84
Nadroparin	14	32.56
Dalteparin	4	9.30
Tinzaparin	2	4.65
Bemiparin	2	4.65
Primary disease		
Embolism	10	23.26
Joint operation	9	20.93
Fracture	5	11.63
Surgery	5	11.63
Dialysis	4	9.30
Tumor	3	6.98
Heart failure	3	6.98
Traffic accident	2	4.65
Infection	2	4.65
Pregnancy	1	2.33
Medical history		
Diabetes	10	23.26
Surgery	9	20.93
Obesity	6	13.95
Hypertension	6	13.95
Tumor	4	9.30
Chronic renal insufficiency	3	6.98
Myocardial disease	3	6.98
Cholecystectomy	1	2.33
Immune-related diseases	1	2.33
Thrombus history	1	2.33
No risk factors	9	20.93
Combined drugs		
Antihypertensive drugs	4	9.52
Antidiabetic drugs	2	4.76
Antibiotics	2	4.76
Chemotherapeutic drugs	1	2.38
Other types of anticoagulants	1	2.38
Without other drugs	36	85.71

(Continued in next column)

TABLE 3 (*Continued*) Characteristics of the 43 included patients with HIT induced by LMWHs.

systemic symptoms received PLT transfusion. In addition, one patient with SLE was administered glucocorticoid, and one patient with extensive sinus thrombosis was administered a thrombolytic agent. The PLT count recovered within 1 month in all patients, three-quarters (26/34) of whom recovered within 10 days. Finally, almost all patients (41/43) showed recovery; however, one patient died of extensive sinus thrombosis and cerebral hernia (Fesler et al., 2011), and one patient worsened (Betrosian et al., 2003).

Discussion

Concerns have been raised regarding the risk of HIT in patients exposed to UFH, while there are limited data on HIT associated with LMWHs in recent years. HIT induced by LMWHs is often overlooked. This study investigated the characteristics of the AEs caused by three types of LMWHs in the FAERS database, as well as the reporting rate for HIT events. Additionally, we conducted a literature review on the cases of HIT caused by LMWHs to further understand the features, treatments, and prognoses of these patients. The results from the literature review and the FAERS database analysis showed some similarities to a certain extent. Specifically, in terms of age, the proportion of AE reports involving LMWHs in the database was similar to that reported in the literature, with a higher proportion observed in older individuals (over 60 years of age). Regarding outcomes, the reporting rates of death events associated with the three types of LMWHs in the database ranged from 20% to 37%. Similarly, out of the 43 reported cases of HIT, one resulted in death, one worsened, and 41 patients recovered. These findings suggest that with appropriate clinical intervention, most cases of HIT can be successfully treated and resolved. Furthermore, the analysis of the database revealed that tinzaparin had the highest PRR and ROR values for HIT, indicating a potentially higher likelihood of causing HIT compared to other LMWHs. On the other hand, based on the case literature reports, enoxaparin was found to be associated with the highest number of HIT cases.

HIT is a rare and serious AE caused by heparin, which can be divided into type I and type II. Type I is an early-onset, mild thrombocytopenia that does not lead to thromboembolism, whereas type II is immune-mediated and clinically severe, causing both thrombocytopenia and thromboembolism with approximately 50% of patients developing arterial or venous thrombosis usually

TABLE 4 Clinical manifestations of HIT induced by LMWHs.

Parameter	Value	Percentage (%)
The time from taking LMWHs to HIT diagnosed (n = 43)		
<5 days	5	11.63
Enoxaparin	3	6.98
Nadroparin	1	2.33
Tinzaparin	1	2.33
5–10 days	24	55.81
Enoxaparin	13	30.23
Nadroparin	10	23.26
Bemiparin	1	2.33
>10 days	14	32.56
Enoxaparin	5	11.63
Dalteparin	4	9.30
Nadroparin	3	6.98
Bemiparin	1	2.33
Tinzaparin	1	2.33
Clinical manifestations of HIT (n = 43)		
Thrombus	39	90.70
Skin lesions	15	34.88
Dyspnea	13	30.23
Hemorrhage	9	20.93
Limb necrosis	5	11.63
Cerebral infarction	5	11.63
Heart failure	5	11.63
Acute renal failure	2	4.65
Shock	1	2.33
Fever	1	2.33
Peak PLT at HIT diagnosis		
PLT count (10^9/L) (n = 40)		
<10	1	2.50
Nadroparin	1	2.50
10–19	3	7.50
Enoxaparin	1	2.50
Dalteparin	1	2.50
Nadroparin	1	2.50
20–49	13	32.50
Enoxaparin	8	20.00
Nadroparin	2	5.00
Dalteparin	1	2.50
Bemiparin	1	2.50
Tinzaparin	1	2.50
50–100	14	35.00
Enoxaparin	7	17.50
Nadroparin	5	12.50
Dalteparin	1	2.50
Bemiparin	1	2.50
>100	9	22.50
Enoxaparin	5	12.50
Nadroparin	2	5.00
Dalteparin	1	2.50
Tinzaparin	1	2.50
Percentage of PLT decrease (n = 37)		
<30%	1	2.70
Tinzaparin	1	2.70
30%–50%	3	8.11
Enoxaparin	2	5.41
Nadroparin	1	2.70
>50%	33	89.19
Enoxaparin	19	51.35
Nadroparin	8	21.62
Dalteparin	3	8.11
Bemiparin	2	5.41
Tinzaparin	1	2.70
Anti-PF4 antibody(n = 36)		
Positive	36	100.00
Enoxaparin	17	47.22
Nadroparin	12	33.33
Dalteparin	4	11.11
Bemiparin	2	5.56
Tinzaparin	1	2.78
Warkentin 4T score (n = 21)		
0–3	0	0.00
4–5	3	14.29
Dalteparin	2	9.52
Enoxaparin	1	4.76
6–8	18	85.71
Nadroparin	9	42.86
Enoxaparin	6	28.57
Bemiparin	2	9.52
Tinzaparin	1	4.76
D-Dimer elevated (n = 11)	5	45.45
Abnormal liver and kidney functions (n = 8)	5	62.50

occurring 5–10 days after starting heparin therapy (Nazliel et al., 2014; Barcellona et al., 2020; Singh et al., 2020). LMWH has been widely used to prevent thromboembolism because of its safety and ease of administration. HIT caused by UFH is often overlooked in clinical practice due to its low incidence rate (2.6%). In contrast, the incidence rate of HIT caused by LMWH is approximately 0.2%, making it even more likely to be overlooked and not receive timely and effective intervention (Sahu et al., 2020). If patients are not treated in time, serious outcomes may occur, such as amputation, myocardial infarction, pulmonary embolism, cerebral infarction, and even death.

The immunopathological mechanism underlying the development of HIT is still unclear. PLT factor 4 (PF4) is a positively charged protein

TABLE 5 Treatments and outcomes of HIT induced by LMWHs.

Parameter	Value	Percentage (%)
Treatment		
Withdraw LMWHs (n = 43)	43	100.00
Surgical thrombectomy (n = 43)	6	13.95
Emergency treatment (n = 43)	1	2.33
Other relevant therapeutic drugs		
Other anticoagulants (n = 39)		
Fondaparinux	17	43.59
Lepirudin	11	28.21
Argatroban	7	17.95
Warfarin	5	12.82
Acenocoumarol	5	12.82
Rivaroxaban	4	10.26
Apixaban	2	5.13
Dabigatran	1	2.56
Clopidogrel	1	2.56
Platelet transfusion (n = 43)	2	4.65
Thrombolytic agent (n = 43)	1	2.33
Glucocorticoid (n = 43)	1	2.33
PLT recovery time (n = 34)		
<5 days	9	26.47
Nadroparin	4	11.76
Enoxaparin	3	8.82
Dalteparin	2	5.88
5–10 days	17	50.00
Enoxaparin	11	32.35
Nadroparin	4	11.76
Bemiparin	1	2.94
Tinzaparin	1	2.94
>10 days	8	23.53
Nadroparin	5	14.71
Enoxaparin	2	5.88
Bemiparin	1	2.94
Prognosis (n = 43)		
Recovery	41	95.35
Worse	1	2.33
Death	1	2.33

released from the α-granules of activated platelets and combines with the negatively charged heparin through the electrostatic interaction of the vascular epidermis to form a complex (Joglekar et al., 2015). Immunoglobulin G (IgG) antibodies against the PF4/heparin complex play a major role in the development of HIT II. Approximately 1%–8% of patients receiving LMWH produce these antibodies, only a small portion of which result in thrombosis (Warkentin et al., 2000; Arepally and Hursting, 2008). These antibodies bind to the complex and platelet Fcg receptor IIa, respectively, through their Fab and Fc sequences, activate platelets, generate procoagulant microparticles, and increase the production of thrombin. Immune complexes induce platelet aggregation, resulting in thrombocytopenia. At the same time, they also induce monocytes to express the procoagulant tissue factor, further promoting thrombus formation (Arepally and Mayer, 2001).

In this study, the primary causes of the use of LMWH were mainly the treatment of thrombosis and the thromboprophylaxis of joint operation, fractures, surgical procedures, and dialysis. In addition patients are often accompanied by a history of diabetes, surgery, obesity, hypertension, or tumors. These factors deserve special attention from clinical physicians. Greinacher et al. (2005) found that orthopedic surgery was the most critical factor causing thrombosis in 408 suspected HIT patients. Barcellona et al. (2020) reported a female patient who underwent left knee replacement with urosepsis and developed severe HIT, resulting in cerebral, pulmonary, hepatic, and lower extremity arterial and venous thromboses after receiving LMWH. Studies have shown that obese patients have more fat cells, which are more likely to activate inflammatory pathways, lead to cytokine imbalance, and increase the risk of HIT (Cave et al., 2008). There are also studies that believe that obese patients are prone to skin necrosis due to heparin residues in the subcutaneous fat tissue with poor blood circulation. This may also explain the higher risk of skin necrosis in female patients than in male patients, since female individuals have higher levels of body fat than male individuals (Gan, 2017). Obesity may also contribute to treatment failure due to pharmacokinetics. Larissa et al. reported a case of HIT in a morbidly obese female patient taking enoxaparin. She still experienced extensive thrombosis after 7 days of daily oral 10 mg fondaparinux replacement therapy, which may be due to obesity affecting the absorption of fondaparinux (Martinez and Burnett, 2015). Since HIT is an immune-mediated disease and PF4 is involved in the inflammatory process, Gram-negative bacterial infections can activate the immune system and increase the risk of HIT (Krauel et al., 2012). Skin necrosis is a rare symptom caused by LMWH and usually occurs at the injection site but can also occur elsewhere, primarily in female patients with a history of diabetes and thromboembolic disease (Lubenow et al., 2010). However, it has also been suggested that this skin injury may be caused by delayed type IV hypersensitivity rather than microvascular injury produced by HIT (Schindewolf et al., 2010). The specific mechanism still needs further research. For patients with the aforementioned primary causes and medical history, clinicians should closely monitor their clinical manifestations and laboratory tests after using LMWHs. The focus of laboratory tests is PLT count and HIT antibody.

Although the prognosis of HIT is relatively good, the mortality rate can be as high as 20%–30%, if timely diagnosis and intervention are not employed. It is extremely important to closely monitor the PLT count to prevent the occurrence of HIT (Lassen et al., 2010). It is suggested that for all patients receiving heparin treatment, the baseline PLT count should be monitored before the treatment begins and then every 2–3 days between the fourth and fifteenth day (Linkins et al., 2012). Since IgG antibodies in HIT have a unique transient property and can disappear in 50–80 days, it is recommended that patients exposed to LMWHs within 3 months continue to monitor their PLT counts (Lubenow et al., 2002). Rarely, IgG may persist in circulation for more than 80 days, as reported in an obese patient developing HIT 2 years after the initial exposure to

enoxaparin, but this is exceedingly rare (Wiegele et al., 2015). The current guidelines recommend that after the HIT onset, LMWH should be discontinued immediately and replaced with argatroban, bivalirudin, or fondaparinux (Cuker et al., 2018). Studies have shown that rivaroxaban is a safe and effective oral agent for the treatment of HIT and can be used as a replacement for heparin in the prevention of deep vein thrombosis in adults, which is more easily accepted by patients than parenteral administration and requires no laboratory monitoring (Joseph et al., 2014; Le et al., 2019).

This study is the first drug safety study that combines the FAERS database and case reports to study HIT induced by LMWHs. The advantage of this study is that it makes full use of the database and literature resources and comprehensively collects and analyzes a large amount of relevant data, so as to deepen the understanding of the occurrence and characteristics of HIT. This study can provide some guidance for improving clinical prognosis; however, there are certain limitations. First, although the sample size is relatively large, the data are not complete because the FAERS database and literature cases can only provide an analysis of the existing data and cases, ignoring unreported or unprocessed information, so the results may have selection bias. Second, this method cannot directly explain the mechanism underlying the development of HIT caused by LMWHs and requires specific mechanisms to be studied through cell and animal experiments. Third, the lack of multivariable analyses here to implicate the specific role of LMWH in the development of HIT while controlling for other clinical factors is a major limitation to the study. Lastly, prospective or randomized controlled trials are needed to elucidate the relevant characteristics of HIT induced by LMWH administration.

Conclusion

HIT is a rare but potentially fatal complication of LMWHs. Due to its low incidence and difficult diagnosis, it is often overlooked by clinicians, thus leading to serious outcomes without timely and effective intervention. However, adverse outcomes can be completely avoided by strengthening the understanding of the disease. Our research found that patients who are obese, diabetic, infected, or having a history of surgery, hypertension, or tumor are more likely to develop HIT during LMWH anticoagulation. The pathological mechanism underlying the development of HIT is complex, and the most obvious pathological features are thrombocytopenia and thrombosis. The current guidelines recommend close monitoring of PLT changes and timely HIT antibody testing, if HIT is suspected after LMWH administration. These are critical for treatment and prognosis. In the future, further prospective studies are needed to clarify the risk factors, pathological mechanisms, and related treatments of HIT.

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

LL and HZ contributed equally. LL: data collection, review, analysis, and interpretation of the results, primary role in writing the paper, and approval of the final version of the manuscript; HZ: data collection, review, analysis, and interpretation of the results, primary role in writing the paper, and approval of the final version of the manuscript; SC: critical review of the manuscript and approval of the final version of the manuscript; MY: planning the study, critical review of the manuscript, and approval of the final version of the manuscript; SW: planning the study, critical review of the manuscript, and approval of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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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

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Nutrivigilance: the road less traveled

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KEYWORDS

nutrivigilance, nutravigilance, nutraceuticals, nutrition support, adverse reactions, pharmacovigilance, adverse event report, phytovigilance

1 Introduction

1.1 Nutrivigilance/nutravigilance

The term "pharmacovigilance" defines the activities related to the collection, detection, assessment, monitoring, and prevention of adverse reactions (ADR) due to pharmaceuticals. An ADR is any response to a drug which is noxious and unintended, including lack of efficacy (Toklu and Mensah, 2016). The word "pharmacovigilance" is derived from pharmakon (drug in Greek) and vigilare (keep an eye on/monitor in Latin). Recently, the spectrum of this sort of "-vigilance" broadened to include safety of herbal products, cosmetics, and nutraceuticals (Chauhan et al., 2013; Schmitz et al., 2013; Toklu, 2016; Toklu et al., 2019). Furthermore, the prefixes nutra- and nutri-seem to interchangeably refer to the same idea, with prefix choice being primarily a regional spelling issue based on common language vowel structure. In a 2014 paper, Schmitz, et al. defined nutravigilance specifically as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects related to the use of a food, dietary supplement, or medical food" (Schmitz et al., 2013). Nutrivigilance is defined as "a set of activities and actions related to the detection, definition, and assessment of side effects that occur when consuming food and nutritional supplements" (Malve and Bhalerao, 2023). Indeed, many papers choose one spelling or the other, but with no differential in granular detail of the particular vigilance involved. Practically, both versions of the word point to the same idea; for the sake of consistency, we have used nutrivigilance in this paper.

Nutrivigilance is a term used to describe the monitoring of adverse effects related to the use of dietary supplements, functional foods, and other nutraceuticals. It involves the systematic collection, analysis, and evaluation of information on adverse effects associated with the use of these products. Nutrivigilance plays a critical role in ensuring safety and efficacy and is a vital component of any comprehensive public health strategy. In the absence of regulations regarding ostensibly nutritional products, however, consumers are forced to rely on a sponsoring company's evaluation and presentation of their product, or outside groups acting in watchdog roles, in order to make informed decisions about which products are safe and, perhaps more importantly, even useful (Malve and Bhalerao, 2023).

In recent years, with the explosion of more and more products that claim to enhance health in some manner, there has been a growing interest in nutrivigilance in both the United States (US) and Europe (Nasri et al., 2014; Lüde et al., 2016; Morgovan et al., 2019). This paper will examine the state of nutrivigilance in these two regions and discuss the need, challenges, and opportunities for improving nutrivigilance in the future. As regulation plays an important role within and between the US and Europe, the paper also examines complications that can occur in the field of nutraceuticals, which may add a layer of

complexity and often difficulty in adopting and amplifying tougher nutrivigilance stances and their impact.

The primary argument for this nutrivigilance is that any substance taken internally or applied cosmetically to a body's exterior, whether serving an explicitly medical purpose or not, should be evaluated both for efficacy and for safety before reaching the hands of a consumer. The problem is that US law does not have provisions requiring the approval of these products prior to commercialization.

1.2 Nutraceuticals

What classifies as a nutraceutical? Intended as a blend of the terms nutritional and pharmaceutical, "nutraceutical" gathers together substances that are valued not only for their nutritive contribution, such as calories, vitamins, or minerals, but certain extra health benefits–whether they are real or merely claimed (Nasri et al., 2014). Coined in 1989 by the Foundation for Innovation in Medicine, nutraceuticals are non-specific biological therapies that are intended to foster general wellbeing, control chronic symptoms, or prevent later uprisings of disease or adverse circumstances in the long term (Malve and Bhalerao, 2023). This focus on the prevention of eventual problems is of main importance to adherents of the nutraceutical field.

1.3 Classification of nutraceuticals

The categories that nutraceuticals are sorted into generally depend on the source of their provenance, which are essentially natural, pharmacological conditions, and/or chemical constitution of the product (Nasri et al., 2014; Malve and Bhalerao, 2023). To better understand the need for nutrivigilance, it is important to illustrate the general categories of nutraceuticals, which reveal the wide net that a system of evaluation needs to cast in order to be effective: dietary supplements, nutrients, herbal supplements, animal-based supplements, and functional foods.

While these categories provide useful umbrellas for common provenance, many supplements fit into more than one category. Flaxseed oil provides essential Omega-3 fatty acids (nutrients), but also falls into plant-based herbal supplements. Thus, the classification outline provides only a broad understanding of supplement types, while individual supplements may fall under multiple categories based on their provenance or chemical structure.

Dietary supplements are regulated by the Food and Drug Administration (FDA) as food products, but the rules are not the same as with drugs and other food items. These supplements contain specific nutrients that are derived from other food products and are typically contained in a liquid, capsule, powder or pill form. Examples include prebiotic and probiotics, certain useful enzymes, and fiber supplements.

Standard nutrients are the essential nourishing elements of sustaining healthy life, which users may take in support of their regular diets. These can include vitamins, omega fatty acids in fish or flaxseed oil, minerals such as zinc or potassium, collagen peptides and amino acids.

Herbal supplements are derived from plants and their oils, roots, seeds, berries, or flowers. Used for many centuries, herbals are thought to have unique healing properties. Examples here are green tea capsules, chamomile tea, echinacea, and ginkgo. Antioxidants such as resveratrol are also extracted from plants.

Animal-based supplements are any supplement derived specifically from animal products or tissue which might be useful to humans. Examples here include collagen peptides, shark cartilage, glucosamine and chondroitin, apitherapy products such as honey or royal jelly, and the digestive enzymes lipase and pepsin, often sourced from lambs and calves.

Functional foods refer specifically to whole foods on their own, or that have been fortified with specific vitamins or minerals, in addition to other components of a human diet which are thought to reduce certain risks in terms of chronic disease. These foods also are purported to hold unique health benefits beyond what the food would typically suggest in terms of its nutrients. Examples of functional foods include apple cider vinegar, protein powders, mushroom extract, or seaweed moss.

There are various ways to categorize these substances based on function or composition. We have chosen to present these substances as nutraceuticals as shown in Figure 1.

1.4 What is the current regulatory scheme in the US?

The FDA is responsible for enforcing the laws and regulations governing the production, marketing, and use of dietary supplements. In general, FDA is limited to post market enforcement. Currently, the FDA does not have the legal authority to approve dietary supplements for safety and effectiveness. Additionally, the FDA does not evaluate the claims made by companies about the dietary supplements that they manufacture prior to the introduction of these supplements into the marketplace. In fact, manufacturers can market many dietary supplements without first notifying the FDA (FDA, 2022a; FDA, 2022d; FDA, 2023).

Manufacturers of dietary supplements must ensure their products are safe before marketing them to consumers and also comply with labeling and quality assurance requirements. The FDA inspects facilities for compliance and monitors adverse event reports. When public health concerns arise about the safety of a dietary supplement, the FDA has the authority to take action to protect the public.

To facilitate the reporting of safety concerns to the FDA by the general public, the agency created an online reporting platform on the FDA website called the Safety Reporting Portal (SRP) (FDA, 2022d). Federal law only requires manufacturers of dietary supplements to report serious adverse events to the FDA (FDA, 2023). The FDA, therefore, likely does not receive reports of all adverse events that come with supplement use and operates on limited knowledge about the efficacy and safety of these purportedly beneficial supplements.

In recent years, however, the FDA has taken steps to improve nutrivigilance. For example, in 2022 the FDA issued a document on how to conduct "Post market Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," offering encouragement to manufacturers to have systems that monitor, and report adverse

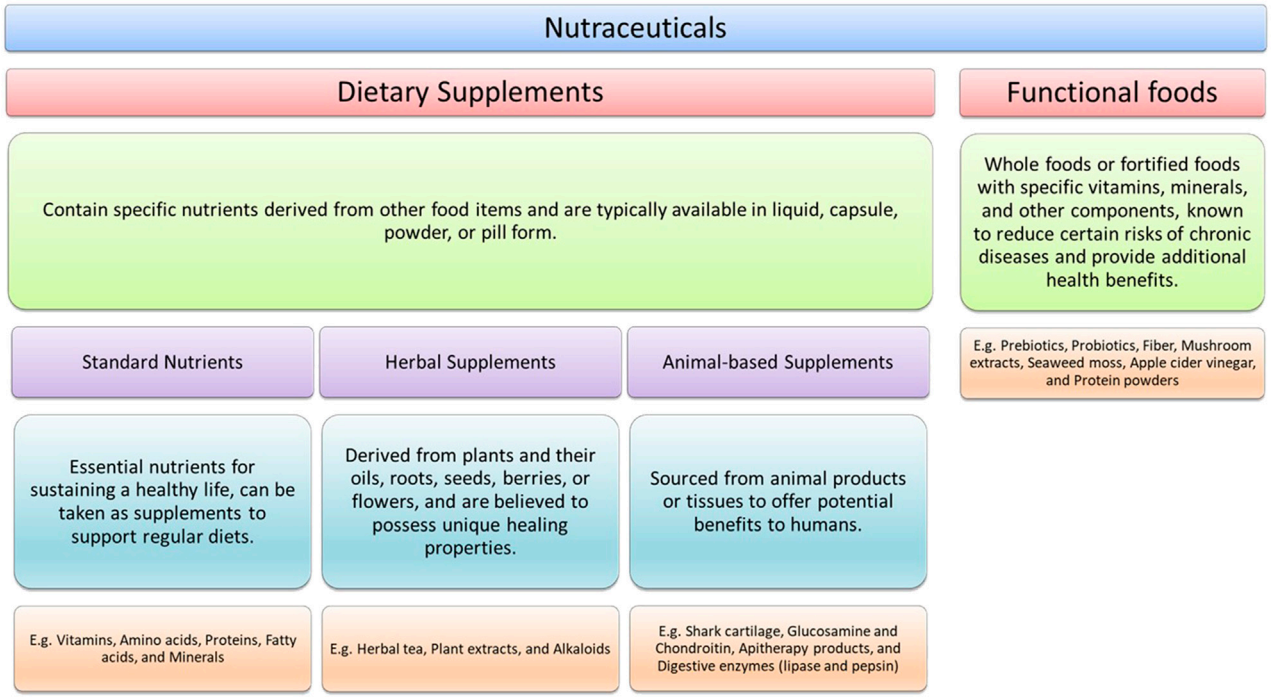

FIGURE 1
Classification of nutraceuticals.

events associated with their products (FDA, 2022b; FDA, 2022c). In addition to this, the FDA increased its enforcement actions against companies that make false or misleading claims about their product's safety; it remains the line of defense against companies indicating their products cure or treat disease.

Although, FDA investigates adverse event reports and complaints from consumers, healthcare professionals, other regulatory agencies, and industry, the information about the post-market safety of dietary supplements is still limited.

1.5 What are the current regulations in Europe?

Like the dietary supplements in the US, the food supplement market has enormously grown in Europe. To date, the European Union legislation does not include a provision to establish a dedicated nutrivigilance system for food supplements (Vo Van Regnault et al., 2021). In Europe, few countries have established their own national surveillance system: Italy (2002), France (2009), Denmark (2013), Portugal (2014), Czech Republic (2015), Slovenia (2016), and Croatia (2020).

Nutrivigilance encounters problems in Europe, where the free movement of goods across borders can allow dietary supplements that are acceptable in one country to enter the market of a country where they have not been evaluated. In other words, where some individual nations may have mechanisms of supplement evaluation and pre-market consumer notification, the overall European Union does not provide such legislation or regulation as a broad umbrella of protection. The collection of EU data and harmonization of nutrivigilance practice is needed from the public health perspective (Vo Van Regnault et al., 2021; de Boer et al., 2022; Wróbel et al., 2023).

2 Discussion

Since the reporting of safety concerns and adverse events by consumers is voluntary, manufacturers of dietary supplements stake holders should inform consumers on how to report their safety concerns and adverse events and encourage them to make such reports. On the other hand, this could lead to a voluntary response bias. However, an in-dept analysis could help assess the current situation or risk. A nutrivigilance system, capturing information spontaneously reported from the markets, or evaluation of the cumulative safety data from the manufacturer's database helps to confirm the safety of products. In a post-marketing surveillance study conducted by Banach et al., nutrivigilance process was used to monitor the reporting rate and nature of the adverse events suspected to be associated with the company's red yeast rice product (Banach et al., 2021). They found that despite the increase in case reports, the number of reports mentioning serious adverse events due to this product has remained unchanged over the years.

If nutrivigilance is to gain ground as an important means of consumer protection, the movement cannot rely primarily on manufacturers to report adverse effects due to an inherent conflict of interest. For nutrivigilance to succeed, and especially

focused on post-market analysis, there must be a fully committed national surveillance system for nutraceuticals and consumers must have awareness of the spontaneous reporting system.

The regulatory authorities, health providers and patients should observe the adverse effects of the nutraceuticals and they need to proactively report the adverse effects related to their consumption. Everyone has a role in the rational and safe use of these in terms of public health. To increase awareness on the topic, pharmacovigilance and adverse effect reaction reporting must be added to the curriculum of health programs. Additionally, academic institutions, policymakers and companies should collaborate to form public health campaigns to increase consumer awareness.

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Neurocognitive impairment in females with breast cancer treated with endocrine therapy and CDK4/6 inhibitors: a pharmacovigilance study using the World Health Organization's database

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Importance: Endocrine therapies (ETs) and inhibitors of cyclin-dependent kinases-4/6 (iCDK4/6s) are a standard treatment in breast cancer. However, data on potential neurocognitive impacts remain inconsistent for ET and are scarce for iCDK4/6s.

Objective: To evaluate whether ET and iCDK4/6s are associated with neurocognitive impairment (NCI).

Methods: We used observational, real-world cases of NCI from the World Health Organization's database VigiBase® to perform disproportionality analysis. Cases were defined as any symptom of NCI in females treated with ETs or iCDK4/6s. The study period was from the date of the first adverse event reported in VigiBase® with iCDK4/6s (1 January 2014) until the date of data extraction (16 March 2022). In our primary analysis, we calculated the reporting odds ratio (ROR) adjusted for age to identify a potential association between NCI and individual ETs in isolation or in combination with iCDK4/6s. We also performed subgroup analyses by the NCI class.

Results: We identified 2.582 and 1.943 reports of NCI associated with ETs and iCDK4/6s, respectively. NCI was significantly associated with each ET [anastrozole: *n* = 405, aROR = 1.52 (95% CI: 1.37–1.67); letrozole: *n* = 741, aROR = 1.37 (95% CI: 1.27–1.47); exemestane: *n* = 316, aROR = 1.37 (95% CI: 1.22–1.53); tamoxifen: *n* = 311, aROR = 1.25 (95% CI: 1.12–1.40); and fulvestrant: *n* = 319, aROR = 1.19 (95% CI: 1.06–1.33)] and only with palbociclib for iCDK4/6s [*n* = 1,542, aROR = 1.41 (95% CI: 1.34–1.48)].

Conclusion: These findings suggest that in females treated for breast cancer, all ETs may be associated with NCI. However, amongst iCDK4/6s, NCI may be

specific to palbociclib. NCI most frequently involved learning and memory as well as language. Neurocognitive impact of treatments requires better consideration and management.

KEYWORDS

breast cancer, endocrine therapy, cyclin-dependent kinase 4/6 inhibitor, neurocognitive impairment, pharmacoepidemiology

1 Introduction

Endocrine therapies (ETs) have contributed to a significant increase in survival for females with breast cancer. Aromatase inhibitors (AIs) (anastrozole, letrozole, and exemestane), selective estrogen-receptor modulators and degraders (SERMs and SERDs) (tamoxifen, toremifene, and fulvestrant), and gonadotrophin-releasing hormone (GnRH) analogs (leuprorelin, goserelin, and triptorelin) are used in early or metastatic ER-positive breast cancer (Cardoso et al., 2019).

Inhibitors of cyclin-dependent kinases-4/6 (iCDK4/6s) have recently revolutionized the adjuvant and first line treatment of high-risk and metastatic ER-positive breast cancer. They are used in combination to improve the efficacy of ET by acting on the cell cycle checkpoint (Roskoski, 2016). The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have currently approved three iCDK4/6s: abemaciclib, palbociclib, and ribociclib (Ibrance, 2018; Kisqali, 2018; Verzenios, 2018; FDA, 2019a; FDA, 2022; FDA, 2023).

By means of all these therapeutic advances, patients survive longer and are treated for more extended periods of time. Therefore, they are potentially at risk for long-term adverse events (AEs). This raises questions regarding the impact of ET on quality of life and related outcomes (Franzoi et al., 2021; Haggstrom et al., 2022; Siegel et al., 2022). Numerous studies report neurocognitive impairment (NCI) with ET (Hugo and Ganguli, 2014; Haggstrom et al., 2022). However, the literature remains scarce and conclusions inconsistent (Lange et al., 2019; Haggstrom et al., 2022). Limited data are available regarding the impact of iCDK4/6s on cognition. Nevertheless, a recent review suggests that iCDK4/6s may negatively impact cognition (Kjoe et al., 2022).

Using neurocognitive symptoms reported in the World Health Organization's (WHO) pharmacovigilance database VigiBase®, we performed a disproportionality analysis to evaluate the association between NCI and ETs in isolation or in combination with iCDK4/6s. In secondary analyses, we described the clinical features of NCI cases reported with ETs and iCDK4/6s.

2 Methods

2.1 Pharmacovigilance study procedure

We performed a pharmacovigilance study within VigiBase®, the largest pharmacovigilance database with more than 30 million reports received from more than 160 member countries. Vigibase® has been developed to detect potential associations between drugs (including cancer treatments) and AEs (Guerrero et al., 2019; Briggs et al., 2022). AEs can be reported by healthcare or non-healthcare professionals, such as patients or manufacturers. Drugs are coded with the anatomical therapeutic chemical and AEs with the Medical Dictionary for Regulatory Activities (MedDRA). Cases were included when the imputability of NCI symptoms to ET and iCDK4/6s was defined as suspect/interacting/concomitant, using the WHODrug Global dictionary. Serious AE is defined as results in death, life threatening, require inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, or at the judgment of the reporter.

As previously published, our query used the standardized MedDRA query and high-level group terms related to NCI: "dementia," "mental impairment disorders," "cognitive and attention disorders and disturbances," "deliria," "dementia and amnestic condition," and "disturbances in thinking and perception" (Briggs et al., 2022; Gouverneur et al., 2023). In the absence of specific terms that describe drug-induced NCI and in order to avoid inclusion of neurological or psychiatric diseases, we focused our query on symptoms (Supplementary Tables S1A) and excluded all preferred terms (PTs) related to neurological or psychiatric diseases (Supplementary Tables S1B). We also classified (EMM and VLB) each of the PTs included in our study into one of the six NCI patterns defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): social cognition, language, executive function, complex attention, learning and memory, and perceptual motor function (Sachdev et al., 2014).

The analysis included ETs ("letrozole," "anastrozole," "exemestane," "tamoxifen," "toremifene," and "fulvestrant") and iCDK4/6s ("palbociclib," "abemaciclib," and "ribociclib"). One drug may be associated with several PTs. We excluded GnRH analogs due to their multiple non-oncological indications. To minimize the risk of non-breast cancer indications of ETs and iCDK4/6s, the study population was restricted to females.

The protocol was approved by a hospital committee with competency for research not requiring authorization by an institutional review board (University of Caen Normandy, France; reference: 2646, dated 15 July 2021).

2.2 Statistical analysis and outcomes

We performed a pharmacovigilance disproportionality analysis using R version 4.2.1. Disproportionality analysis is performed to compare the proportion of reporting of a specific AE with a drug of interest to the expected proportion assuming the AE with this drug of interest and is independently reported (Faillie, 2019).

In our primary analysis, we first calculated the reporting odds ratio (ROR) adjusted for age to identify a potential association between NCI and each ET. Second, we calculated ROR adjusted for age to identify a potential association between NCI and each iCDK4/6. In the primary

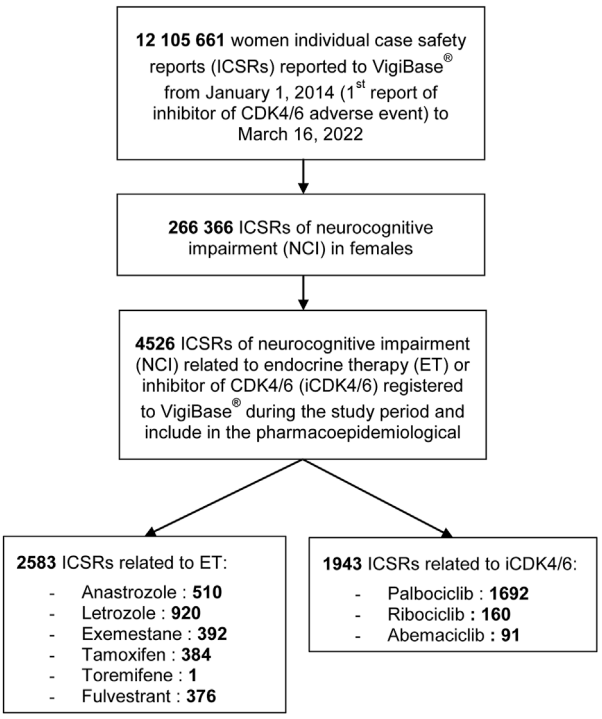

FIGURE 1
Flow chart of the pharmacovigilance study.

analysis, we restricted the period for the extraction of cases and non-cases from the date of the first AE reported in VigiBase® with iCDK4/6s (1 January 2014) until the date of data extraction (16 March 2022). Case characteristics were summarized with means for quantitative variables and proportions for qualitative variables. First, to avoid confounding by the presence of breast cancer in cases, we performed a sensibility analysis where we restricted non-cases to reports that include antineoplastic agents, ET and immunotherapy. Second, to avoid signal induced by reporters other than health care professionals, we repeated the analyses after restricting reports to those from health care professionals. Third, for cases exposed to ETs, to avoid confounding by the co-prescription of an iCDK4/6, we performed an additional analysis where we extracted cases and non-cases from the date of the first AE reported for each ET to the date of the first AE reported with an iCDK4/6. Fourth, a sensibility analysis was also performed after excluding reports with co-illnesses and co-treatments known to cause NCI (Supplementary Table 2).

For the primary and secondary analyses, we report 95% credibility intervals (CIs), with a lower ROR CI bound >1 denoting an association between a drug and an AE. For the effective interpretation of the signal, RORs were only calculated if there were at least five reports for a drug of interest/AE pair.

3 Results

During the study period (1 January 2014 to 16 March 2022), a total of 12,105,661 AEs were reported in Vigibase®. We identified 262,366 reports related to NCI, of which 2,583 concerned ETs and 1,943 concerned iCDK4/6s (Figure 1). A total of 3,400 reports came from the Americas (75%), 971 from Europe (21%), 64 from Eastern Mediterranean (1%), 52 from Asia (1%), and 39 from Africa (<1%). The most reported PTs were "memory impairment" (27%), "amnesia" (9%), "cognitive disorder" (6%), "disturbance in attention" (6%), and "speech disorder (5%) (Supplementary Tables S1A). After excluding cases without age information, we included 2,093 reports concerning ETs and 1,686 reports concerning iCDK4/6s in the age-adjusted primary analysis.

Reports of NCI in patients treated with ET and/or iCDK4/6s concerned all age classes: 23% of females were more than 75 years old ($n = 800$), 26% were between 65 and 74 years old ($n = 884$), 29% were between 45 and 64 years old ($n = 1,009$), and 5% were between 18 and 44 years old ($n = 158$). Age was missing in 17% of reports ($n = 595$). According to the WHO classification, 57% of reports related to NCI were considered serious by reporters. Treatment was interrupted in one-third of patients with serious NCI. Data on time to onset, reversibility after interruption, and treatment rechallenges were not available.

Regarding ET, anastrozole (aROR 1.52; 95% CI: 1.37–1.67), letrozole (aROR 1.37; 95% CI: 1.27–1.47), exemestane (aROR 1.37; 95% CI: 1.22–1.53), tamoxifen (aROR 1.25; 95% CI: 1.12–1.40), and fulvestrant (aROR 1.19; 95% CI: 1.06–1.33) were significantly associated with higher reporting of NCI (Table 1). Only 207 reports were available for toremifene and one included NCI, so no disproportionality was performed.

Regarding iCDK4/6s, only palbociclib (aROR 1.41; 95% CI: 1.34–1.48) was significantly associated with a higher reporting of NCI. No signal was found for ribociclib (aROR 0.73; 95% CI: 0.59–0.91) and abemaciclib (aROR 0.65; 95% CI: 0.51–0.83).

After restricting non-cases to reports that include antineoplastic agents, ET, and immunotherapy, results were broadly consistent with the primary analysis except for tamoxifen (ROR 1.07; 95% CI: 0.96–1.18) and fulvestrant (ROR 1.08; 95% CI: 0.97–1.19), which were no longer statistically significant (Supplementary Table S3). After restricting reports to those from healthcare professionals, the results were broadly consistent with the primary analysis except for tamoxifen (ROR 1.11; 95% CI: 0.96–1.28), exemestane (ROR 1.09; 95% CI: 0.94–1.26), and fulvestrant (ROR 1.07; 95% CI: 0.92–1.23), which were no longer statistically significant (Supplementary Table S4). In the additional analysis that only included reports made prior to the first use of iCDK4/6s, the results were no longer statistically significant for letrozole (ROR 1.10; 95% CI: 0.99–1.23), exemestane (ROR 1.01; 95% CI: 0.86–1.18), and tamoxifen (ROR 0.91; 95% CI: 0.84–0.99) (Supplementary Table S5). Co-illnesses and co-treatments known to be associated with NCI were, respectively, present in 84 and 31 of the 4,524 reports. Due to their low number, sensitivity analyses excluding co-illnesses and co-treatments were not performed.

To better describe the cases of NCI with ETs and iCDK4/6s identified in the primary analysis, we calculated aROR for each of the six NCI patterns (Table 2). Anastrozole was significantly associated with a higher reporting of complex attention (aROR 1.36; 95% CI: 1.15–1.60), language (aROR 1.95; 95% CI: 1.65–2.30), and perceptual motor function impairments (aROR 1.25; 95% CI: 1.03–1.52). Letrozole and exemestane were associated with a higher reporting of language (aROR 2.11; 95% CI: 1.89–2.36 and aROR 2.18; 95% CI: 1.84–2.57, respectively) and learning and memory impairments (aROR 1.54; 95% CI: 1.22–1.94 and aROR 1.78; 95% CI: 1.28–2.48, respectively). Tamoxifen and fulvestrant

TABLE 1 Disproportionality analysis of neurocognitive impairment with individual endocrine therapies and inhibitors of CDK4/6.

	Drug	$N_{observed}$	N_{drug}	ROR	95% CI
AIs	Anastrozole	405	11,729	1.52	(**1.37**–1.67)
	Letrozole	741	23,957	1.37	(**1.27**–1.47)
	Exemestane	316	10,152	1.37	(**1.22**–1.53)
SERM	Tamoxifen	311	11,941	1.25	(**1.12**–1.40)
SERD	Fulvestrant	319	11,706	1.19	(**1.06**–1.33)
iCDK4/6s	Palbociclib	1,542	47,424	1.41	(**1.34**–1.48)
	Ribociclib	81	5,064	0.73	(0.59–0.91)
	Abemaciclib	63	4,343	0.65	(0.51–0.83)

The reporting odds ratio (ROR, adjusted for age) and its 95% credibility interval (CI) lower and upper endpoints evaluate the observed-to-expected ratios of neurocognitive impairment (NCI) cases associated with endocrine therapies and inhibitors of CDK4/6 in VigiBase® (from 1 January 2014 to 16 March 2022). A lower ROR CI endpoint >1 (**in bold**) denotes an association between a drug and an adverse event. Only one case of NCI was identified with toremifene. ROR was not calculable and is therefore not presented in the table.
AIs, aromatase inhibitors; N_{drug}, number of AEs with the drug over the period of interest; $N_{observed}$, number of NCI events with the drug over the period of interest; SERM, selective estrogen-receptor modulator; SERD, selective estrogen-receptor degrader.

were only associated with a higher reporting of language impairment (aROR 1.39; 95% CI: 1.14–1.70 and aROR 1.92; 95% CI: 1.63–2.27, respectively). Palbociclib was significantly associated with a higher reporting of language and learning and memory impairments (aROR 2.74; 95% CI: 2.55–2.94 and aROR 1.31; 95% CI: 1.10–1.57, respectively). No drugs were associated with a higher reporting of executive function or social cognition impairment.

4 Discussion

Using pharmacovigilance data, we identified a significant association between reporting of NCI and AIs, tamoxifen, fulvestrant, and palbociclib. No signal was observed with the other iCDK4/6s. NCI was mainly related to learning and memory as well as language. Reports were not limited to the elderly as one-third concerned females under the age of 65.

4.1 Endocrine therapies

These results provide further evidence that all ET classes may be associated with NCI in females with breast cancer. Our results for AIs are consistent with a meta-analysis of studies that used neurocognitive tests and found the association between AIs and verbal and learning/memory impairments in females with breast cancer (Underwood et al., 2018). Our results suggest that anastrozole and exemestane could also be associated with language impairment. Several studies that used neurocognitive tests support that tamoxifen may negatively impact cognition and language and attention impairments, which is consistent with the findings of our study (Schilder et al., 2010; Boele et al., 2015). Based on neuropsychological assessments of females in randomized clinical trials that compared tamoxifen to AIs, several studies suggest that tamoxifen may lead to NCI more than AIs. In the TEAM trial, females treated with adjuvant tamoxifen had slower information processing speed than those treated with exemestane (p = 0.02; Cohen's d = 0.36) (Schilder et al., 2010). Similarly, overall cognition of females treated with adjuvant tamoxifen in the BIG-1-98 trial was worse than those treated with letrozole (p = 0.04, Cohen's d = 0.40) (Phillips et al., 2010). However, due to discordant results, the impact of AIs and tamoxifen on cognition remains controversial (Lange et al., 2019; Novick et al., 2020). Due to the absence of prior clinical studies aiming to assess the neurocognitive impact of fulvestrant therapy, our study provides relevant data on its neurocognitive consequences (Robertson et al., 2016).

GnRH agonists were not investigated in this study due to their wider range of indications. Data regarding the neurocognitive effect of leuprorelin in females with breast cancer remain scarce. Meta-analyses evaluated the effect of leuprorelin on cognition in men with prostate cancer and showed discordant results (Nead et al., 2017; Sun et al., 2018). Using a similar pharmacovigilance methodology, a recent study highlighted an association between androgen deprivation therapies and NCI in prostate cancer, including leuprorelin (ROR 1.47, 95% CI: 1.34; 1.62) (Briggs et al., 2022).

Estrogen receptors are expressed both on breast cancer cells and the central nervous system. Estradiol is involved in central neurotransmission and could have an impact on axonal growth. ETs may lead to NCI due to decreased estradiol activation in areas involved in cognition functions, such as the hypothalamus, amygdala, or hippocampus (Lange et al., 2019; Haggstrom et al., 2022).

4.2 Inhibitors of cyclin-dependent kinases-4/6

Concerning iCDK4/6s, our study identified a signal of NCI associated with palbociclib, mainly related with language and learning and memory impairments. In the PEARL trial, the cognition subscale of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) favored the palbociclib plus ET arm (hazard ratio = 0.70; 95% CI: 0.54–0.89) (Kahan et al., 2021). However the control arm was capecitabine, which may itself lead to NCI (Lange et al., 2019). In the PALOMA-3 trial, there was no difference in cognitive outcomes between the palbociclib and fulvestrant arms compared to the placebo and fulvestrant arms (Harbeck et al., 2021). However, the

TABLE 2 Analysis of neurocognitive impairment classes with individual endocrine therapies and inhibitors of CDK4/6.

Neurocognitive impairment subtype	Drug	$N_{observed}$	N_{drug}	aROR	95% CI
Complex attention	Anastrozole	145	11,989	1.36	(**1.15**–1.60)
	Letrozole	238	24,460	1.10	(0.97–1.25)
	Exemestane	99	10,369	1.07	(0.88–1.31)
	Tamoxifen	115	12,137	1.20	(0.99–1.44)
	Fulvestrant	105	11,920	0.98	(0.81–1.18)
	Palbociclib	415	48,551	0.94	(0.85–1.03)
	Ribociclib	20	5,125	0.46	(0.30–0.72)
	Abemaciclib	23	4,383	0.61	(0.40–0.91)
Executive function	Anastrozole	8	12,126	1.06	(0.53–2.12)
	Letrozole	21	24,677	1.36	(0.88–2.08)
	Exemestane	6	10,462	0.92	(0.41–2.05)
	Tamoxifen	12	12,240	1.46	(0.83–2.57)
	Fulvestrant	8	12,017	1.07	(0.54–2.15)
	Palbociclib	26	48,940	0.85	(0.58–1.26)
	Ribociclib	4	5,141	NC	NC
	Abemaciclib	4	4,402	NC	NC
Language	Anastrozole	26	12,108	1.95	(**1.65**–2.30)
	Letrozole	71	24,627	2.11	(**1.89**–2.36)
	Exemestane	35	10,433	2.18	(**1.84**–2.57)
	Tamoxifen	27	12,225	1.39	(**1.14**–1.70)
	Fulvestrant	26	11,999	1.92	(**1.63**–2.27)
	Palbociclib	122	48,844	2.74	(**2.55**–2.94)
	Ribociclib	9	5,136	1.10	(0.79–1.55)
	Abemaciclib	3	4,403	NC	NC
Learning and memory	Anastrozole	145	11,989	1.13	(0.77–1.67)
	Letrozole	315	24,383	1.54	(**1.22**–1.94)
	Exemestane	139	10,329	1.78	(**1.28**–2.48)
	Tamoxifen	99	12,153	1.27	(0.87–1.85)
	Fulvestrant	141	11,884	1.14	(0.78–1.68)
	Palbociclib	805	48,161	1.31	(**1.10**–1.57)
	Ribociclib	34	5,111	0.97	(0.50–1.86)
	Abemaciclib	18	4,388	0.37	(0.12–1.14)
Perceptual motor function	Anastrozole	101	12,033	1.25	(**1.03**–1.52)
	Letrozole	115	24,583	0.70	(0.58–0.84)
	Exemestane	50	10,418	0.71	(0.54–0.94)
	Tamoxifen	69	12,183	0.98	(0.77–1.24)
	Fulvestrant	48	11,977	0.58	(0.44–0.78)
	Palbociclib	120	48,846	0.35	(0.29–0.42)

(Continued on following page)

TABLE 2 (*Continued*) Analysis of neurocognitive impairment classes with individual endocrine therapies and inhibitors of CDK4/6.

Neurocognitive impairment subtype	Drug	$N_{observed}$	N_{drug}	aROR	95% CI
	Ribociclib	9	5,136	0.28	(0.15–0.54)
	Abemaciclib	16	4,390	0.56	(0.34–0.92)
Social cognition	Anastrozole	0	12,134	NC	NC
	Letrozole	1	24,697	NC	NC
	Exemestane	1	10,467	NC	NC
	Tamoxifen	0	12,252	NC	NC
	Fulvestrant	1	12,024	NC	NC
	Palbociclib	1	48,965	NC	NC
	Ribociclib	0	5,145	NC	NC
	Abemaciclib	0	4,406	NC	NC

The reporting odds ratio (ROR, adjusted for age) and its 95% credibility interval (CI) lower and upper endpoints evaluate the observed-to-expected ratios of neurocognitive impairment (NCI) cases associated with endocrine therapies and inhibitors of CDK4/6 in VigiBase® (from 1 January 2014 to 16 March 2022). A lower ROR CI endpoint >1 (**in bold**) denotes an association between a drug and an adverse event. Only one case of NCI was identified with toremifene. ROR was not calculable and is therefore not presented in the table.
AIs, aromatase inhibitors; N_{drug}, number of AEs with the drug over the period of interest; NC, not calculable (when the number of reports was less than five); $N_{observed}$, number of NCI events with the drug over the period of interest; SERM, selective estrogen-receptor modulator; SERD, selective estrogen-receptor degrader.

EORTC-QLQ-C30 cognition subscale is only based on two out of thirty questions and concerns self-reported cognitive impairment. The absence of a signal with abemaciclib is concordant with the results of the MONARCH-2 trial (Kaufman et al., 2020). For ribociclib, the EORTC-QLQ-C30 cognition subscale was not published in MONALEESA-3 trial. Finally, abemaciclib and ribociclib are reported more recently, and the number of reports is lower. However, the design of disproportionality analyses enables to detect signals with a low number of AEs (Cellier et al., 2023). Moreover, there was no trend toward significance for abemaciclib and ribociclib that might suggest a lack of power.

Whether iCDK4/6s affect the central nervous system is unknown. Cyclin D inhibition may alter neurogenesis and lead to NCI (Urbach and Witte, 2019; Kjoe et al., 2022). However, this does not explain why the signal in our study was isolated to palbociclib. Considering that abemaciclib has good penetrance into the central nervous system, pharmacokinetic parameters likely do not explain this potential differential effect (Hendrychová et al., 2021). The differential kinase affinity spectrum could explain why NCI may be specific to palbociclib. In contrast to abemaciclib and ribociclib, palbociclib inhibits the tropomyosin receptor kinase (TRK), encoded by the *neurotrophic receptor tyrosine kinase* (*NTRK*) genes (Hendrychová et al., 2021). Binding to the brain-derived neurotrophic factor (BDNF), TRK is a tyrosine kinase receptor which regulates neuronal development, differentiation, and survival, including those in the hippocampus. In *in vitro*, BDNF/TRK deprivation is associated with elevations of the β-amyloid peptide in hippocampal neurons, leading to apoptotic death (Matrone et al., 2008). In mice, deficiency of this pathway is associated with neuro-inflammation and impairment of memory and learning (Wang et al., 2019). In humans, reduced BDNF mRNA expression has been observed during post-mortem examination of patients with Alzheimer's disease (Connor et al., 1997). NTRK fusions are observed in 0.3% of lung cancers and are targeted by two TRK inhibitors approved by the FDA: entrectinib and larotrectinib (Harada et al., 2021). Based on clinical trials, SmPCs of entrectinib and larotrectinib report NCI in, respectively, 27% and 1% of patients. Further studies are needed to determine whether inhibition of the BDNF/TRK pathway mediates NCI in patients treated with palbociclib (FDA, 2019b; FDA, 2019c).

4.3 Strengths and limitations

The present study investigated the association between NCI and ET in isolation or in combination with iCDK4/6s in females with breast cancer using the worldwide pharmacovigilance database Vigibase®, allowing us to isolate 4,526 reports of NCI associated with ET and/or iCDK4/6s. Our primary analysis was adjusted for age and is strengthened by the sensitivity analyses, suggesting that our results are not driven by age or the presence of breast cancer. Sensitivity analysis regarding the type of the reporter was less consistent, probably due to lack of power. Our secondary analysis using DSM-5 neurocognitive patterns allowed a finer description of the NCI symptoms associated with ET and palbociclib. Moreover, we used an original and complementary approach based on pharmacovigilance reports of neurocognitive symptoms rather than neuropsychological tests or self-questionnaires, such as EORTC-QLQ-C30, which are used in clinical trials (Underwood et al., 2018; Kaufman et al., 2020; Harbeck et al., 2021).

Our study had several limitations. Inherent to pharmacovigilance databases is missing data, which did not allow us to more comprehensively describe the reports. Moreover, we were unable to determine the line of treatment, previous chemotherapy, and co-prescribed ET with iCDK4/6, which could have biased the signal. In addition, Vigibase® does not allow access to medical records to confirm the diagnosis of NCI and eliminate differential diagnosis (such as depression and cerebral metastases). To limit non-breast cancer indications, we restricted our analysis to cases in females. It

would be necessary to conduct similar analyses to extend these results to males. Last, disproportionality pharmacovigilance analyses identify new AE signals that require confirmation with the high level of evidence studies (Faillie, 2019). They are also necessary to determine the incidence of NCI.

5 Conclusion

This pharmacovigilance study strengthens the association between ET and NCI in females with breast cancer. We highlighted a new signal for iCDK4/6s isolated to palbociclib, which requires further research. NCI impacted all exposed age groups and mostly involved learning, memory, and language. Neurocognitive impact of breast cancer treatments must be better considered. NCI management involves non-pharmacological approaches that need to be developed.

Data availability statement

Publicly available datasets were analyzed in this study. These data can be found at: public access to overview statistics from VigiBase® can be gained through the VigiAccess website, http://www.vigiaccess.org/.

Ethics statement

The studies involving humans were approved by the Institutional review board: University of Caen Normandy, France; reference: 2646, dated 15 July 2021. 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

RP: data curation, formal analysis, investigation, software, and writing–original draft. BC: conceptualization, formal analysis, methodology, software, and writing–review and editing. E-MM: formal analysis, methodology, software, and writing–review and editing. CD: methodology, software, and writing–review and editing. AD-S, AN, and FJ: writing–review and editing. VL-B: resources and writing–review and editing. EB: conceptualization, formal analysis, investigation, methodology, project administration, supervision, visualization, and writing–original draft.

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Conflict of interest

FJ has received consulting fees from AstraZeneca, GSK, Janssen, and Ipsen and declares honoraria for lectures and scientific boards from AstraZeneca.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1278682/full#supplementary-material

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Big data- and machine learning-based analysis of a global pharmacovigilance database enables the discovery of sex-specific differences in the safety profile of dual IL4/IL13 blockade

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Background: Due to its apparent efficacy and safety, dupilumab, a monoclonal antibody that blocks Interleukin 4 (IL-4) and Interleukin 13 (IL-13), has been approved for treating T-helper 2 (Th2) disorders. However, adverse effects like local injection site reactions, conjunctivitis, headaches, and nasopharyngitis have been reported. Sex differences are known to influence both adaptive and innate immune responses and, thus, may have a bearing on the occurrence of these adverse effects. Nevertheless, the literature lacks a comprehensive exploration of this influence, a gap this study aims to bridge.

Materials and Methods: A comprehensive data mining of VigiBase, the World Health Organization (WHO) global pharmacovigilance database which contains case safety reports of adverse drug reactions (ADRs) was performed to test for sex -specific safety response to dual IL4/IL13 blockade by dupilumab. The information component (IC), a measure of the disproportionality of ADR occurrence, was evaluated and compared between males and females to identify potential sexual dimorphism.

Results: Of the 94,065 ADRs recorded in the WHO global pharmacovigilance database, 2,001 (57.4%) were reported among female dupilumab users, and 1,768 (50.7%) were among males. Immune/autoimmune T-helper 1 (Th1)-, innate- and T-helper 17 (Th17)-driven diseases and degenerative ones were consistently reported with a stronger association with Dupilumab in males than females. Some adverse events were more robustly associated with Dupilumab in females.

Conclusion: Dupilumab has an excellent safety profile, even though some ADRs may occur. The risk is higher among male patients, further studies, including *ad hoc* studies, are needed to establish causality.

KEYWORDS

atopic dermatitis, dual IL4/13 blockade, pharmacovigilance, big data analytics, machine learning, disproportionality analysis, adverse drug reactions, sex medicine

Introduction

The human immune system is not "one-size-fits-it-all", but displays noticeable differences between the sexes (Markle and Fish, 2014; Tokatli et al., 2022). We have defined "sex" as a biological attribute, categorized conventionally as male or female, based on physiological and anatomical distinctions, such as chromosomes, hormone levels, and reproductive/sexual anatomy (Short et al., 2013) This has an impact on various aspects of immunity, including the recognition and components responsible for response, ranging from type 1 to type 3 immunity (Annunziato et al., 2015) and involving both the innate and adaptive systems (Shepherd et al., 2021; vom Steeg and Klein, 2016).

Type 1 immunity protects the body against intracellular microbes by activating mononuclear phagocytes and the oxidative burst. This form of immunity involves T-bet + interferon-gamma (IFN-γ)–producing group 1 innate lymphoid cells or ILCs (ILC1 and natural killer (NK) cells) (Annunziato et al., 2015; Shannon et al., 2021), $CD8^+$ cytotoxic T cells (TC1), and $CD4^+$ T helper type 1 (Th1) cells. These cells produce and release large quantities of IL-2 and lymphotoxin alpha (LT-α) (Annunziato et al., 2015).

Type 2 immunity is composed of GATA-3+ ILC2s (Zhu, 2017; Spinner and Lazarevic, 2020), T_C2 cells, and T-helper 2 (T_h2) cells (Annunziato et al., 2015). Its primary function is to support B-cell production, development, and proliferation, as well as promoting class switching and the release and recruitment of immunoglobulins (Vazquez et al., 2015). Type 2 immunity is crucial in developing helminth infections, allergic/atopic diseases, and airway inflammation observed in asthma patients. This type of immunity is characterized by the molecular signature of IL-4, IL-5 (which stimulate eosinophils and basophils) (Min and Paul, 2008), IL-9, IL-10, and IL-13, along with cytokines produced by epithelial cells such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 (Spellberg and Edwards, 2001; Annunziato et al., 2015; Ochiai et al., 2018; Roan et al., 2019).

At the level of the epithelial barrier, type 3 immunity enables defense against pyogenic extracellular bacteria (such as Streptococci and Staphylococci) and fungi. It comprises type 3 ILCs (ILC3), γδ-T cells, $CD8^+$ αβ-T cells (T_C17), and $CD4^+$ T_h17 cells (Short et al., 2013). Group 3 immunity is involved in the recruitment of neutrophils and is characterized by the following molecular signature: IL-17A, IL-17F, and IL-22, along with high amounts of TGF-beta (Annunziato et al., 2015).

Male sex hormones fine-tune cell-mediated immunity, whereas female sex hormones regulate humoral immunity. As a result, males are predisposed toward the Th1 and Th17 milieu, whereas females have a more pronounced/skewered Th2 phenotypic profile (Klein and Flanagan, 2016). However, the precise effects of hormones, such as testosterone, are still not well understood and appear controversial, with some studies, including the pioneering work by Folstad and Karter (Folstad and Karter, 1992), suggesting that testosterone may negatively impact the immune system, exerting pro-oxidant and immunosuppressive activity (the so-called "immunocompetence handicap hypothesis" or "male susceptible hypothesis") (Stoehr and Kokko, 2006; Nowak-Kornicka et al., 2020). Other studies, on the other hand, have failed to replicate this finding, demonstrating, on the contrary, that testosterone may have immunomodulatory properties.

From a clinical perspective, males are more prone to infectious diseases, particularly more severe phenotypes (such as septicemia/bacteriemia, sepsis, and septic shock) (Annunziato et al., 2015). Females respond better to vaccines but experience a higher incidence of autoimmune disorders (Annunziato et al., 2015).

Atopic dermatitis is a common, relapsing inflammatory skin disease imposing high epidemiological and societal burden, and is characterized by skin barrier impairment, immune dysregulation, and skin dysbiosis. It presents sex-specific differences and worsens during pregnancy (Tuttle et al., 2021).

Limited information exists regarding sexual dimorphism in patients with atopic dermatitis (Tuttle et al., 2021). With the advent of systemic medications like Dupilumab (Dupixent, Regeneron/Sanofi), the pharmacological management of atopic dermatitis as well as other atopic illnesses like asthma and chronic rhinosinusitis with nasal polyps, has undergone a transformation. Dupilumab is a fully-humanized monoclonal IgG4 antibody that functions by blocking IL-4 and IL-13 through the binding of IL-4Rα, a receptor shared by both cytokines (Eichenfield et al., 2022).

Numerous randomized clinical trials (RCTs) have demonstrated the outstanding efficacy and safety profile of Dupilumab. However, it has been suggested that due to sex related differences in both the innate and adaptive immune systems, therapies targeting type 2 immunity, such as Dupilumab, may be more effective in women. Although some RCTs have reported outcomes stratified according to sex, they often neglect to consider a sex based perspective in their discussions of findings, which may result in potential sex bias. This omission could potentially introduce sex bias in clinical conclusions.

With this study, we aim to bridge this gap in knowledge by leveraging data from a global pharmacovigilance database to evaluate the possibility of a sex specific safety response to dual IL4/IL13 blockade by Dupilumab. Our findings may hold potential implications for tailoring treatment strategies to optimize patient outcomes.

Materials and methods

Ethical considerations

In VigiBase, case reports maintain the anonymity of both the patient and the reporter. Each case is referenced using a unique national identification number.

Database

We utilized the global pharmacovigilance database, VigiBase™, developed and maintained by the Uppsala Monitoring Centre (UMC), a Swedish World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. The database contains more than 20 million individual case safety reports (ICSRs) of suspected ADRs that were spontaneously reported by over 140 countries that are part of the WHO Program for International Drug Monitoring, from its inception until 9 March 2021. Although the data is not entirely uniform regarding the relationship between the drug and the reported ADR, it is widely recognized that the comprehensive, data-driven screenings database is crucial for effective pharmacovigilance that can be done quickly.

Disproportionality analysis

Different measures of disproportionality can be calculated to determine the relationship between a drug and a suspected ADR. These measures include the reporting odds ratio (OR), the proportional reporting ratio (PRR), and the information component (IC). The IC measure, which was initially developed using the Bayesian Confidence Propagation Neural Network (Bate, 2007), indicates the strength of the association between the drug and the ADR. If the lower bound of the IC value is positive (or negative), this means that the drug-ADR pair is reported more often (or less often) than expected, based on all the reports available in VigiBase.

$$IC = \left(\frac{N\,observed + 0.5}{N\,expected + 0.5} \right)$$

Where

$$N\,expected = \frac{N\,drug^{*}N\,reaction}{N\,total}$$

In this formula, the term "$N_{expected}$" refers to the expected number of case reports for a specific drug-effect pair, while "$N_{observed}$" refers to the actual number of case reports for the same drug-ADR combination being investigated. "N-drug" represents the total number of case reports for the drug being studied, regardless of the adverse effects reported. On the other hand, "$N_{reaction}$" is the number of case reports for the specific adverse effect under study, irrespective of the type of drug used. Lastly, "N_{total}" refers to the total number of reports in the database.

IC is considered more statistically robust as it is based on data mining techniques that help to reduce the risk of identifying false statistically significant associations. It can provide a conservative measure of association, which is crucial when dealing with ADRs that have very low expected frequencies obtained from a large database like VigiBase. This feature of IC is essential as it helps to avoid drawing incorrect conclusions from the data, which can have serious implications for public health.

ADRs Categorization and Classification

The Medical Dictionary for Drug Regulatory Authorities (MeDRA) ontology at the System Organ Class (SOC) level was used to categorize suspected ADRs related to Dupilumab. We chose the MeDRA ontology for its extensive use in pharmacovigilance and its ability to provide detailed information on ADRs.

Results

The study classified 2,910 probable Dupilumab-related ADR families after analyzing 94,065 ADRs from 37,848 distinct reports in the WHO global pharmacovigilance database. We found that 2,581 (88.7%) of the cases had sex specific information available, with a female-to-male reporting ratio of 1.13:1. Dupilumab-related ADRs reported among females were 2,001 (77.5% of the cases) and those reported among males were 1,768 (68.5% of the cases). Immune/autoimmune (Th1-, innate- and Th17-driven) diseases, as well as degenerative ones, were consistently reported with a stronger association with Dupilumab in males compared with females. Some adverse events were more robustly associated with Dupilumab in females. A few were sex specific and were reported in males or females only.

Table 1 provides a detailed enumeration of these Dupilumab-related ADRs, with Figures 1–5 offering a graphical overview.

Within the immune/autoimmune diseases (Th1-, innate- and Th17-driven), males generally showed higher information component (IC) values than females. For example, males showed an IC of 1.56 for any immune system disorder, compared to a lower IC of 0.58 in females (Table 1; Figure 2).

Other infections

Even if, overall, the risk for any infectious disease did not differ based on sex (IC 0.51 [95%CrI 0.14-0.83] and IC 0.52 [95%CrI 0.22-0.79], in males and females respectively), some specific infections presented sex related differences. Besides the already mentioned communicable disorders, other infections that were significant in males included eye (IC 4.59 [95%CrI 4.22-4.92]) and staphylococcal (IC 1.46 [95%CrI 0.91-1.92]) infections. Streptococcal pharyngitis was, instead, more strongly associated with (Table 1; Figure 3; Figure 4).

Malignancies

Dupilumab administration may favor the progression and the exacerbation of cutaneous T-cell lymphoma. In particular, the risk for cutaneous T-cell lymphoma stage IV was found to be increased

TABLE 1 Sex-specific dupilumab-related ADRs.

Dupilumab-related ADRs	Male			Female		
	IC	IC025	IC975	IC	IC025	IC975
Any immune system disorder	1.56	0.58	2.28	0.29	−0.87	1.12
Th1- and innate-driven disease						
Acne	1.32	0.92	1.67	−0.09	−0.49	0.26
Erythema nodosum	0.34	−2.25	1.70	1.62	0.85	2.22
Vitiligo	1.88	0.50	2.81	0.38	−2.21	1.73
Th17-driven disease						
Psoriasis	0.46	0.07	0.80	0.31	−0.04	0.62
Seronegative arthritis	2.50	0.45	3.69	NA	NA	NA
IL-5 eosinophilic syndrome						
Hypereosinophilic syndrome	2.59	0.54	3.79	1.34	−2.45	2.98
Degenerative disease						
Knee operation	2.47	1.49	3.19	0.96	−0.30	1.84
Malignancy						
Cutaneous T-cell lymphoma IV-stage	2.77	0.72	3.96	NA	NA	NA
Seminoma	2.36	0.31	3.56	NA	NA	NA
Ocular diseases						
Atopic keratoconjunctivitis	3.15	1.41	4.23	NA	NA	NA
Blepharitis	5.86	5.59	6.11	5.07	4.78	5.33
Conjunctivitis	5.72	5.62	5.81	4.96	4.85	5.06
Corneal erosion	2.47	0.42	3.67	1.05	−2.75	2.69
Dry eye	5.71	5.57	5.84	4.79	4.67	4.89
Episcleritis	3.29	1.91	4.22	2.03	−0.02	3.23
Skin diseases						
Acanthosis nigricans	2.56	0.51	3.75	NA	NA	NA
Acarodermatitis	2.42	0.69	3.50	1.81	−0.24	3.003
Alopecia	1.88	1.61	2.13	1.01	0.86	1.15
Alopecia totalis	2.39	0.34	3.58	NA	NA	NA
Dry skin	3.78	3.64	3.92	3.04	2.92	3.15
Erysipelas	1.70	0.44	2.57	−0.96	−4.75	0.68
Other infections						
Eye infection	4.59	4.22	4.92	3.84	3.52	4.13
Staphylococcal infection	1.46	0.91	1.92	0.27	−0.49	0.88
Streptococcal pharyngitis	1.15	−0.38	2.15	1.24	0.39	1.90
Musculoskeletal diseases						
Arthralgia	1.37	1.21	1.51	0.92	0.79	1.04
Back disorder	1.40	0.47	2.10	−1.24	−3.29	−0.04

(Continued on following page)

TABLE 1 (*Continued*) **Sex-specific dupilumab-related ADRs.**

Dupilumab-related ADRs	Male			Female		
	IC	IC025	IC975	IC	IC025	IC975
Respiratory/pulmonary diseases						
Peak expiratory flow rate decreased	NA	NA	NA	2.74	1.21	3.73
Pulmonary congestion	1.17	0.14	1.92	−0.62	−2.67	0.57

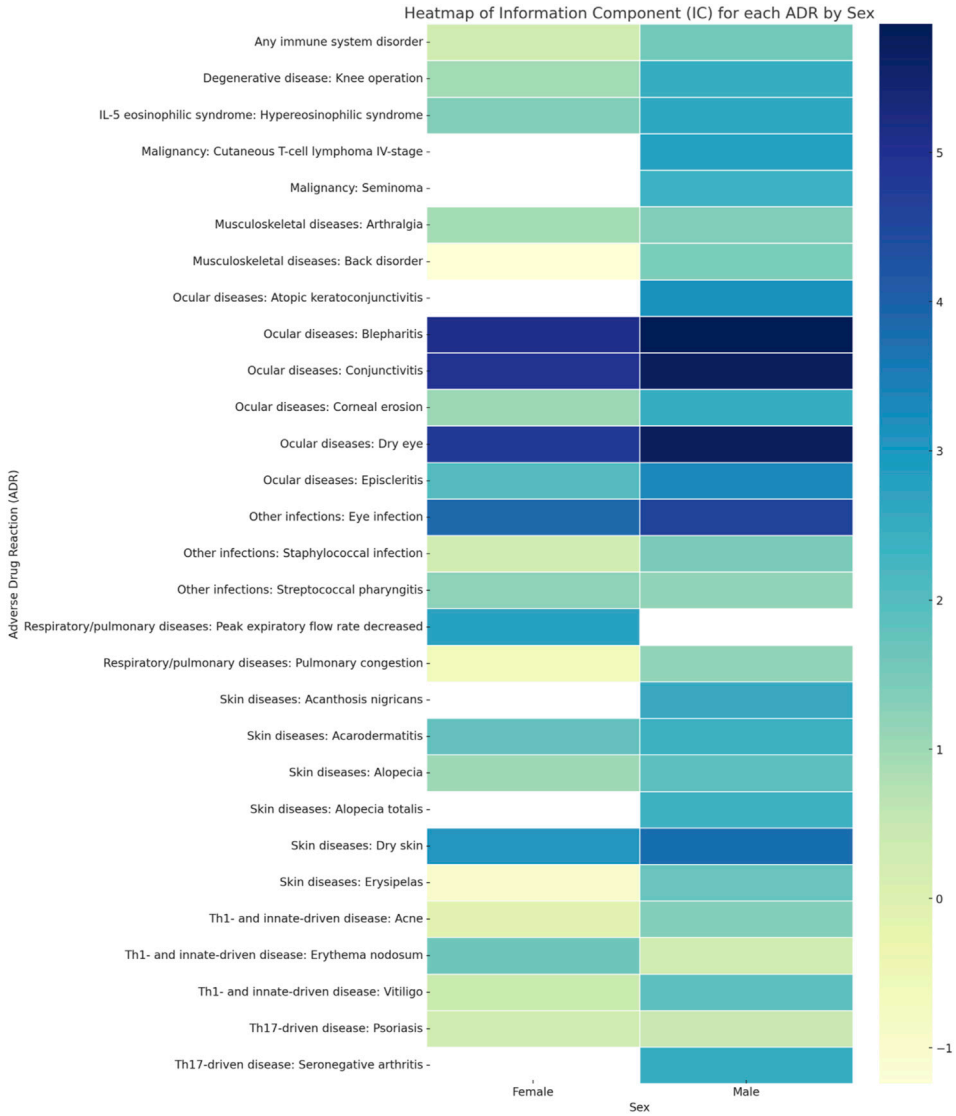

FIGURE 1
Heat map depicting the information component (IC) of each ADR by sex.

in males (IC 2.77 [95%CrI 0.72-3.96]). No sex based differences could be found concerning the other stages. Stage I was not statistically associated with Dupilumab both in males (IC 1.54 [95%CrI −2.26 to 3.18]) and females (IC 1.55 [95% CrI −2.25 to 3.19]). Stage II was reported only in females (IC 1.56 [95%CrI −2.24 to 3.20]) but the association was not significant. Stage III was similarly not associated in males (IC 1.58 [95%CrI −2.22 to 3.22]) as well as in females (IC 1.57 [95% CrI −2.23 to 3.21]). Of note, there was a risk for seminoma (IC 2.36 [95%CrI 0.31-3.56]) (Table 1; Figure 4; Figure 5).

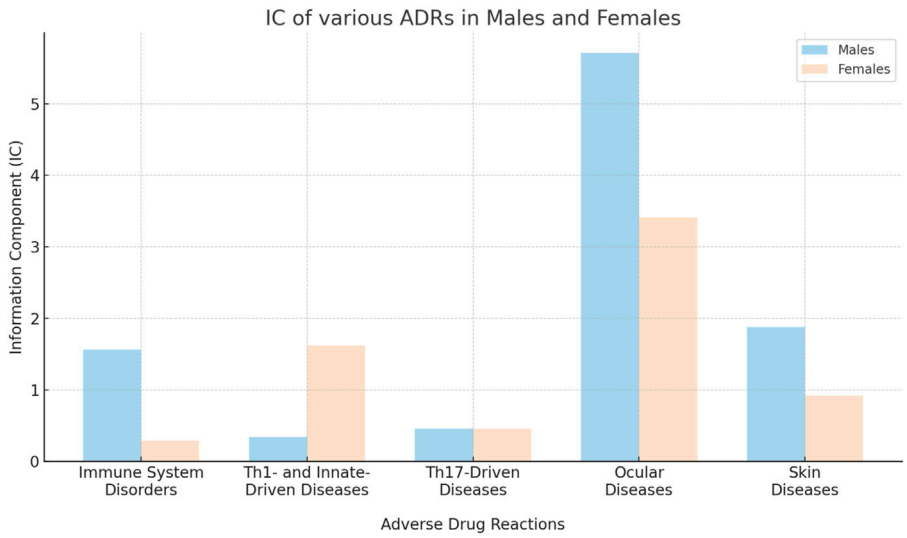

FIGURE 2
Comparative analysis of information component (IC) for various broad category ADRs in males and females.

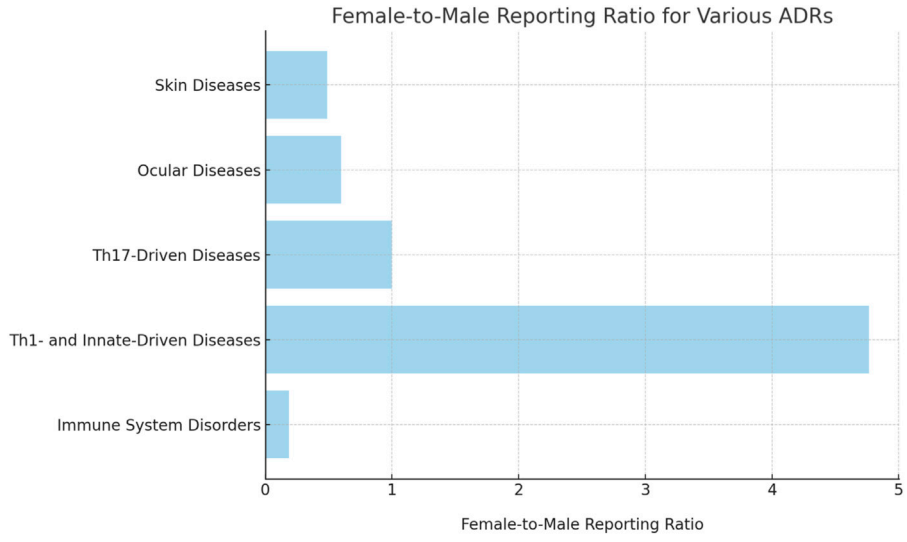

FIGURE 3
Sex-specific reporting ratio for various broad category ADRs.

Ocular diseases

Ocular diseases, including dry eye (IC 5.71 [95%CrI 5.57-5.84]), corneal erosion (IC 2.47 [95%CrI 0.42-3.67]), atopic keratoconjunctivitis (IC 3.15 [95%CrI 1.41-4.23]), blepharitis (IC 5.86 [95%CrI 5.59-6.11]), conjunctivitis (IC 5.72 [95%CrI 5.62-5.81]), and episcleritis (IC 3.29 [95%CrI 1.91-4.22]), exhibited higher ICs in males compared to females (Table 1; Figure 1; Figure 4; Figure 5).

Skin diseases

Alopecia and alopecia totalis, but not alopecia areata (IC 4.09 [95%CrI 3.40-4.64] versus IC 3.41 [95%CrI 2.69-3.99] in males versus females, respectively) were more strongly associated with Dupilumab in males (IC 1.88 [95%CrI 1.61-2.13] and IC 2.39 [95%CrI 0.34-3.58], respectively) (Table 1; Figure 2).

FIGURE 4
Comparative analysis of specific dupilumab-related adverse drug reactions (ADRs) in males and females.

IL-5 eosinophilic syndrome

Hypereosinophilic syndrome was significantly associated with Dupilumab administration among males (IC 2.59 [0.54-3.79]) but not in females (IC 1.34 [-2.45 to 2.98]).

Degenerative diseases

Only the need for undergoing knee operation was significantly associated with Dupilumab in males (IC 2.47 [95%CrI 1.49-3.19]). Other degenerative diseases, including cataract (IC 1.17 [95%CrI 0.60-1.65] versus 0.72 [95%CrI 0.25-1.12] in males and females, respectively) and keratoconus, did not differ stratifying according to sex.

In the respiratory disease category, decreased peak expiratory flow rate stood out in females, with an IC of 2.74, whereas this adverse event was not reported in males (Table 1; Figure 4; Figure 5). Hyposmia was another condition statistically significantly related to Dupilumab use only in females (Table 1; Figure 3).

The sex-specific associations are visually interpreted in a heat map (Figure 1) and in Figure 2, Figure 4, and Figure 5, while the female-to-male reporting ratio for various ADR categories provides a comparative view (Figure 3). These results supply valuable insights into sex specific ADRs associated with Dupilumab.

Discussion

Despite its importance, sex-based medicine is generally overlooked both in research and clinical practice. There is a lack of data concerning the impact of sex on dupilumab-related adverse events. It was observed that adverse drug incidents have a stronger association with Dupilumab in males, despite identifying a female-to-male reporting ratio of 1.13:1, a proportion that is coherent and anticipated as per existing literature (Brabete et al., 2022). We also found that some ADRs were sex-specific, being reported in males or females only.

The finding of a statistically significant association between Dupilumab use and progression/exacerbation of cutaneous T-cell lymphoma may sound surprising and contradict the literature, in that IL4 and IL13 are overexpressed in this malignancy and their dual suppression should inhibit the tumor. It has been, indeed, hypothesized that Dupilumab may be utilized against these types of neoplasm. On the other hand, IL17 has been found to be upregulated in cutaneous T-cell lymphoma and may play a key role in its etiopathogenesis, along with IL23 (Krejsgaard et al., 2013). Another plausible explanation could be an initial misdiagnosis of atopic dermatitis, which exhibits symptoms to those seen in cutaneous T-cell malignancies.

Studies have revealed that sex differences have an impact on various aspects of biologic therapies. For instance, male patients exhibited a better baseline profile than female patients in a large cohort of psoriatic arthritis patients who started TNF inhibitor as their first medication. They had fewer comorbidities, and were more likely to respond to treatment within 3- and 6-month, as well as maintain the treatment for longer periods of time (Højgaard et al., 2018). In contrast, research has shown that females with axial spondyloarthritis have lower response rates and reduced chances of achieving a 12-week response to disease-modifying drugs compared to males (van der Horst-Bruinsma et al., 2013).

The differences between males and females are not only evident in biologic therapies, but also in other treatments like checkpoint inhibitors for cancer. Research shows that in meta-analyses of phase II and III trials of checkpoint inhibitors, both overall survival and progression-free survival improve in both males and females who receive these inhibitors. However, the improvement is significantly greater in males than females for several cancers, such as melanoma, urothelial, and non-small-cell lung cancer (Conforti et al., 2018). In another meta-analysis focusing only on phase III trials, the positive effects of checkpoint inhibitors on overall survival and progression-free survival were more pronounced in males than females. Additionally, male-biased outcomes are more evident in anti-CTLA-4 therapies than in anti-PD-1/PD-L1 therapies (Grassadonia et al., 2018).

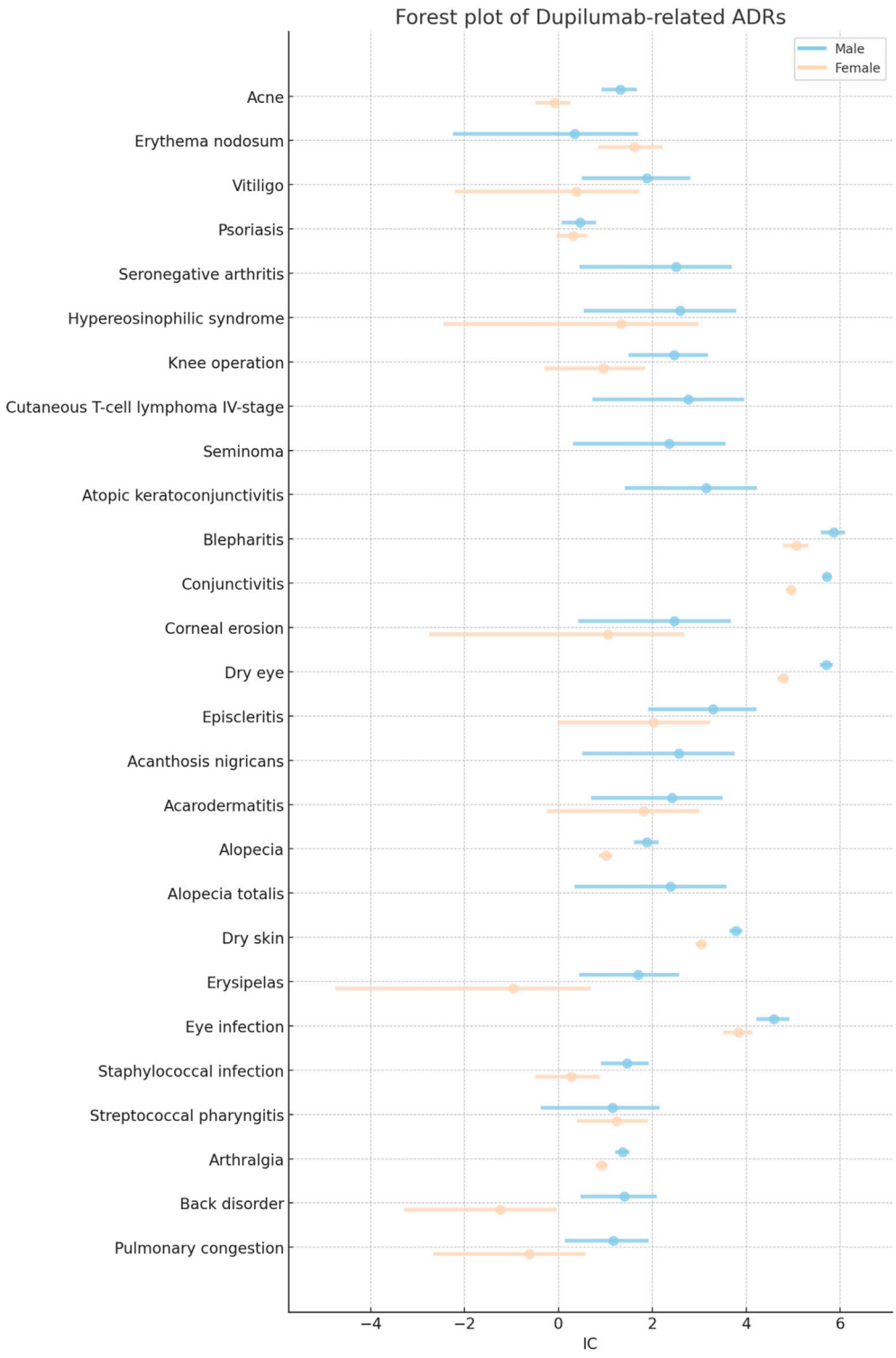

FIGURE 5
Forest plot of sex-based differences in dupilumab-related ADR.

Both the innate and adaptive immune responses exhibit sex-based variations. Research has demonstrated that when compared to their male counterparts, females often display larger counts of resting and activating $CD4^+$ T cells, $CD19^+$ B cells, as well as higher levels of several immunoglobulins, specifically IgE, IgG, and IgM. Additionally, female participants tend to produce more interleukin (IL)-4 and IL-10 in response to phytohemagglutinin-induced polyclonal activation (Girón-González et al., 2000). These variations are assumed to result from acquired (i.e., hormonal) and hereditary causes. Given the above observations, one could

hypothesize that therapies targeting type 2 immunity (such as dupilumab, tralokinumab, lebrikizumab, and nemolizumab) may be more effective in females than males. However, it is important to note that there is currently no published research evaluating the clinical efficacy of these drugs in female patients while controlling for differences in pharmacokinetics.

Concerning the mechanisms specific to ADRs and sex discrepancies, both Tralokinumab and Lebrikizumab, monoclonal antibodies targeting IL-13, have been demonstrated to correlate with elevated risks of conjunctivitis as discerned in phase 2 and 3 clinical trials (Simpson et al., 2018; Wollenberg et al., 2019). Given that androgens, predominantly in males, exhibit distinct interactions with T cells, moderating the synthesis of IL-4 and IL-13 while augmenting the expression of Foxp3, this could elucidate why Dupilumab is more robustly associated with ocular conditions in males. Moreover, the hormones estrogen and progesterone, prevalent in females, significantly influence immune responses, with estrogen fostering a TH2 and T regulatory phenotype and progesterone encouraging a TH2 phenotype and the transformation of fetal T lymphocytes into T regulatory cells. This could clarify why, within immune/autoimmune diseases (Th1-, innate- and Th17-driven), males generally exhibit elevated information component (IC) values than females in conditions like Erythema Nodosum and Seronegative Arthritis."

Dupilumab has not been investigated for its effectiveness or safety in pregnant women. Since dupilumab is a recombinant IgG4 monoclonal antibody and is anticipated to have a high intrauterine exposure starting about mid-gestation (Koren and Ornoy, 2018), it is advised that clinicians refrain from prescribing dupilumab to women who are pregnant, want to become pregnant, or are breastfeeding. However, there have been a few cases of pregnant women with atopic dermatitis who have used dupilumab without any reported negative effects on either the mother or the baby (Mian et al., 2020; Lobo et al., 2021).

Sex is a critical biological variable that needs to be considered in subsequent clinical trials involving biological drugs. In a study exploring sex bias in clinical trials in patients with severe asthma, studies involving omalizumab, benralizumab, reslizumab, mepolizumab and dupilumab in severe asthma was higher (60.4%) than the percentage of men. While sex bias in recruitment was not apparent, the separate analysis by sex of the main variable was carried out in only 5 of the 37 studies included, only 1 of the 37 trials discussed results separated by sex and no study included the concept of gender in the text (Ciudad-Gutiérrez et al., 2021).

This study has notable strengths, such as analyzing a significant number of individual case safety reports and utilizing disproportionality measures to thoroughly evaluate drug-ADR associations. Additionally, Our sample aligns with, and is even more comprehensive than, other studies exploring similar subjects and employing analogous methodologies (Khamisy-Farah et al., 2021; Park et al., 2021).

Nevertheless, the study does possess limitations that need recognition. For example, sex bias in the reporting of adverse drug reactions is a prevalent issue in pharmacovigilance studies, and in our particular case, may be influenced by alterations during the menstrual cycle, or age and ensuing hormonal variations. Furthermore, the diverse database sources could introduce bias that might affect the generalizability of our results. The establishment of a direct causal relationship between Dupilumab use and certain ADRs requires further epidemiological surveys and clinical assessments. Previous data attests to the validity and verification of case reports that are published in VigiBase.

In conclusion, our findings underscore the importance of a personalized approach to Dupilumab therapy despite its excellent safety profile, especially considering the sex-specific differences in adverse drug reactions. This provides an impetus for further research aimed at understanding the implications of such differences in a clinical setting.

Key summary

This study examines the sex-specific safety responses to Dupilumab, an IL-4 and IL-13 blocking monoclonal antibody, by analyzing case safety reports from the WHO global pharmacovigilance database. The results reveal a higher incidence of ADRs with Dupilumab in males, particularly in the context of immune/autoimmune and degenerative diseases, although some ADRs were more robustly associated with females. This underscores the need for further research to establish causality and inform better patient care.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: VigiBase.

Author contributions

KS: Writing–original draft. MO: Methodology, Writing–review and editing. AL: Methodology, Writing–review and editing. YP: Writing–review and editing. HA: Formal Analysis, Validation, Writing–review and editing. GZ: Methodology, Validation, Writing–review and editing. NB: Methodology, Writing–review and editing. AW: Writing–original draft.

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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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Adverse events associated with molnupiravir: a real-world disproportionality analysis in food and drug administration adverse event reporting system

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Molnupiravir, an urgently approved drug during the Coronavirus Disease 2019 (COVID-19) pandemic, serves as the basis for our study, which relies on the Food and Drug Administration Adverse Event Reporting System (FAERS). The objective is to extract adverse event (AE) signals associated with molnupiravir from the FAERS database, thereby providing a reference for post-marketing monitoring of adverse events. Specifically, we extracted individual case safety reports (ICSRs) from the database, focusing on cases with COVID-19 indications and molnupiravir identified as the primary suspect drug. Descriptive analysis of the extracted data was performed, followed by four disproportionality analyses using the reporting odds ratio (ROR) method. These analyses were conducted across four levels, encompassing overall data, reports by health professionals, as well as age and gender differentiations, ensuring the robustness of the analysis results. In total, 116,576 ICSRs with COVID-19 indications and 2,285 ICSRs with molnupiravir as the primary suspect were extracted. Notably, after excluding cases with unknown age or gender, a higher proportion of molnupiravir-related ICSRs were observed among individuals aged 65 years and older (70.07%) and women (54.06%). The most frequently reported adverse events and AE signals were associated with gastrointestinal disorders, as well as skin and subcutaneous tissue disorders. Moreover, individuals aged 65 years and older exhibited a higher risk of cardiac disorders, hepatobiliary disorders, renal and urinary disorders, and vascular disorders. In conclusion, this study found molnupiravir demonstrated a lower risk of serious adverse events compared to other RNA antiviral drugs like remdesivir in patients under 65 years old. However, close monitoring of its safety is still necessary for elderly patients aged 65 years and above. Further studies are warranted to continuously assess the safety profile of molnupiravir as its usage increases, especially in high risk populations.

KEYWORDS

molnupiravir, pharmacovigilance, coronavirus disease 2019, food and drug administration adverse event reporting system, adverse events, safety

1 Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly infectious disease, with a rapid person-to-person transmission rate. According to the WHO Coronavirus (COVID-19) Dashboard, as of 10 February 2023, there have been 760 million confirmed cases of COVID-19 worldwide, resulting in 6.86 million deaths (World Health Organization, 2023). COVID-19 can range from asymptomatic to severe respiratory failure and multi-organ involvement (Huang et al., 2020; Wang et al., 2020). The major symptoms of COVID-19 include fever, cough, and dyspnea (De Vito et al., 2021; Cascella et al., 2023). The minor symptoms are less specific and require comprehensive evaluation. They include anosmia/dysgeusia, headache, diarrhea, vomiting, nausea, sore throat, fatigue, malaise, myalgia, etc (Cheung et al., 2020; Grant et al., 2020; Mao et al., 2020; Vaira et al., 2020). Skin lesions such as vasculitis-like skin eruption can also be seen in COVID-19 patients (Geremia et al., 2020). Although vaccination has significantly reduced the risk of morbidity and mortality (Polack et al., 2020), breakthrough infections remain a concern. Before molnupiravir, remdesivir was the first antiviral against SARS-CoV-2, sharing the same target as molnupiravir. Initially, remdesivir was administered to patients with severe pneumonia and illness (De Vito et al., 2022), but following the PINE-TREE trial, it was also recommended for mild cases to prevent progression (Gottlieb et al., 2022). However, remdesivir requires intravenous infusion, making an oral alternative highly desirable.

Targeting the RNA-dependent RNA polymerase (RdRp), which is a crucial enzyme for SARS-CoV-2 replication, has been proven to be an effective strategy to combat COVID-19, regardless of the variant type. This is because RdRps are widely conserved among all SARS-CoV-2 strains (Rabie, 2022). Molnupiravir is a biologically active prodrug of b-D-N4-hydroxycytidine (NHC, EIDD-1931) that targets RdRp. Upon oral administration, molnupiravir is quickly converted into active NHC in plasma and distributed to various organs. Host kinases then convert it into NHC 5′-triphosphate. This NHC 5′-triphosphate can serve as a competitive alternative substrate for viral RdRp, which integrates into viral RNA and causes the accumulation of mutations in the viral genome, ultimately leading to lethal mutations (Tian et al., 2022). In the MOVE-OUT trial, a phase 3, double-blind, randomized, placebo-controlled trial, molnupiravir demonstrated a 31% relative risk reduction in all-cause mortality compared to placebo. Additionally, the proportion of participants experiencing at least one adverse event was similar in both the molnupiravir and placebo groups, indicating its safety (Jayk Bernal et al., 2022). Being a potential therapeutic option, molnupiravir received emergency use authorization from the Food and Drug Administration (FDA) on 23 December 2021, for the management of mild-to-moderate COVID-19 in adults who are at a heightened risk of developing severe illness (CDER Division of Drug Information, 2023). In addition to the United States, molnupiravir was granted approval in the United Kingdom in November 2021. Furthermore, it received special emergency approval in Japan on 24 December 2021 (Medicines and Healthcare products Regulatory Agency, 2021; Merck & Co, I, 2021). However, the PANORAMIC trial showed no benefits of molnupiravir over placebo in reducing mortality or hospitalization duration for hospitalized COVID-19 patients (Butler et al., 2023). Additionally, the European Medicines Agency's controversial withdrawal of molnupiravir's regulatory application (EMA, 2023) has raised doubts about its efficacy. While the efficacy of molnupiravir remains questionable given these latest trial results and regulatory decisions, some advantages of molnupiravir's safety profile should be considered. Specifically, unlike other antiviral options like remdesivir and nirmatrelvir, molnupiravir has demonstrated a lower potential for clinically significant drug-drug interactions (DDIs) so far (Wanounou et al., 2022; Akhvlediani et al., 2023). The low DDI risk makes molnupiravir an easier oral therapy to administer alongside other medications patients may be taking. Therefore, if the efficacy concerns can be adequately addressed with additional studies, molnupiravir's favorable DDI profile could position it as an alternative oral antiviral option, especially for patients on polypharmacy regimens.

Molnupiravir has not only demonstrated a comparable incidence of adverse reactions in both the molnupiravir and placebo groups during the MOVE-OUT trial but also consistently across all current clinical trials at doses of 200 mg, 400 mg, and 800 mg (Caraco et al., 2022; Fischer et al., 2022; Sinha et al., 2022; Tippabhotla et al., 2022; Zou et al., 2022; Butler et al., 2023; Khoo et al., 2023). Moreover, systematic reviews and meta-analyses suggest that molnupiravir may represent a safe and effective treatment option for patients with COVID-19 (Joseph Mari and Erwin, 2022; Mali et al., 2022; Pitre et al., 2022). Although current clinical trials and systematic reviews indicate that molnupiravir appears to have a favorable safety profile, it is important to note that the safety outcomes in these trials are typically assessed over a limited period of 28–29 days. Therefore, there is still a lack of comprehensive real-world research and post-marketing monitoring for this drug. To address this critical gap, our study aims to gather individual case safety reports associated with molnupiravir from the FDA Adverse Event Reporting System (FAERS) database. By analyzing these reports, we intend to identify potential adverse drug reactions associated with molnupiravir and compare them with other SARS-CoV-2 RNA drugs such as remdesivir, ribavirin, favipiravir, and azvudine. This study aims to contribute to the post-marketing monitoring of molnupiravir and provide valuable insights for its clinical use.

2 Materials and methods

FAERS is a computerized database specifically designed for the spontaneous reporting of adverse events and medication errors involving human drugs and therapeutic biological products. The data structure of FAERS adheres to the International Council for Harmonisation (ICH) guidelines for international safety reporting. Adverse events and therapeutic indications are coded at the "preferred term" (PT) level using the Medical Dictionary for Regulatory Activities (MedDRA).

Access to FAERS data is provided through quarterly data files, which can be obtained from the following link: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. These files are available in two distinct formats: ASCII files and XML files. For our study, we downloaded FAERS data in ASCII format, covering the period from January 2020 to December 2022. We

TABLE 1 2-by-2 contingency table.

	Target adverse event	Other adverse event	Sums
Molnupiravir	a	b	a + b
Other drugs	c	d	c + d
Sums	a + c	b + d	N = a + b + c + d

managed and analyzed the data using Microsoft SQL Server 2019 software. Since the study was an analysis of the third party anonymized publicly available database with pre-existing institutional review board (IRB) approval, IRB approval was exempted by the institutional ethics board of The first Affiliated Hospital Of Jinan University.

To prevent the duplication of multiple report versions, we conducted a deduplication process on the DEMO table. Firstly, we removed identical records, keeping only one instance. Next, if the "CASEID" column was the same, we deleted the duplicate "PRIMARYID" column with the lower value. Additionally, if multiple rows had the same "PRIMARYID" values, we eliminated the earliest "FDA_DT" column to ensure data consistency (Silva et al., 2021).

In order to investigate the adverse event (AE) signals of molnupiravir in COVID-19 prevention and treatment, we utilized the following narrow Standardized MedDRA Query (SMQ) within the "INDI" table: COVID-19, COVID-19 pneumonia, COVID-19 immunization, COVID-19 prophylaxis, COVID-19 treatment, Suspected COVID-19, Asymptomatic COVID-19, SARS-CoV-2 test positive, SARS-CoV-2 carrier, SARS-CoV-2 test false negative, SARS-CoV-2 antibody test positive, SARS-CoV-2 sepsis, SARS-CoV-2 viremia, Occupational exposure to SARS-CoV-2, Exposure to SARS-CoV-2, Coronavirus infection, Coronavirus test positive, Multisystem inflammatory syndrome in children. These queries were employed to extract reports involving COVID-19 from the FAERS database (Wu et al., 2022).

We proceeded to identify cases in the "DRUG" table where the "drugname" and "prod_ai" columns aligned with the regular expression "%MOLNUPIRAVIR%" or "% LAGEVIRIO%", and the "role_cod" column matched the regular expression "PS". These cases represented instances where molnupiravir was administered.

Initially, we examined the attributes of the included Individual Case Safety Reports (ISCRs), which encompassed age, gender, reporter type, reporting country, serious outcomes and dosage. The serious outcomes evaluated encompassed death, life-threatening conditions, interventions, disabilities, congenital anomalies, hospitalizations, and other significant events.

We proceeded with a detailed analysis of the attributes of the ISCRs. Furthermore, a disproportionality analysis was conducted to detect any potential AE signals. To ensure the reliability of the findings, separate disproportionality analyses were performed based on patient age and sex. Additionally, a sensitivity analysis was conducted by restricting the analysis to reports from healthcare professionals as the reporters. In our study, adverse event signals such as "product use issue," "no adverse event," "wrong technique in product usage process," "COVID-19"and similar cases were excluded to enhance the reliability of the findings.

The descriptive statistical analysis encompassed patient age, gender, reporter type, reporting country, dosage and the outcomes of adverse events. The variables are presented as frequencies and percentages.

For the disproportionality analysis, we employed the reporting odds ratio (ROR) method and conducted calculations using a 2-by-2 contingency table (Table 1). In this analysis, reports where molnupiravir was suspected as the causative drug were classified in the target drug group, while reports without molnupiravir as the suspected drug were included in the other drug group. A risk signal was deemed significant if the total number of drugs and adverse events was three or more, and the lower limit of the 95% confidence interval (CI) for the ROR exceeded 1 (Jung et al., 2021; Kim et al., 2021; Rocca et al., 2021).

$$ROR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$ROR95\%CI = e^{\ln\ (ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

3 Results

3.1 Data extraction

A comprehensive analysis was conducted on a dataset of 4,747,645 individual case safety reports (ICSRs) from the FAERS database, spanning January 2020 to December 2022, after removing duplicates. Among them, 116,576 ICSRs indicated COVID-19. For the analysis, 2,285 ICSRs were included in the molnupiravir group, while 114,291 ICSRs were assigned to the other drugs group. More information on ICSR identification can be found in Figure 1.

3.2 Descriptive analysis

The characteristics of the 116,576 ICSRs are presented in Table 2. Notably, the molnupiravir group exhibited a higher proportion (60.96%) of individuals aged 65 years and older, compared to the other drugs group (27.42%). The male-to-female ratio was 0.85 in the molnupiravir group and 0.75 in the other drugs group. Assessing outcomes, the other drugs group reported a higher incidence of life-threatening events (3.40% vs. 2.19%), interventions (0.94% vs. 0.70%), and hospitalizations (20.14% vs. 19.65%) compared to the molnupiravir group. Conversely, the molnupiravir group reported a higher rate of deaths (12.12% vs. 6.99%) compared to the other drugs group. The top 20 drugs

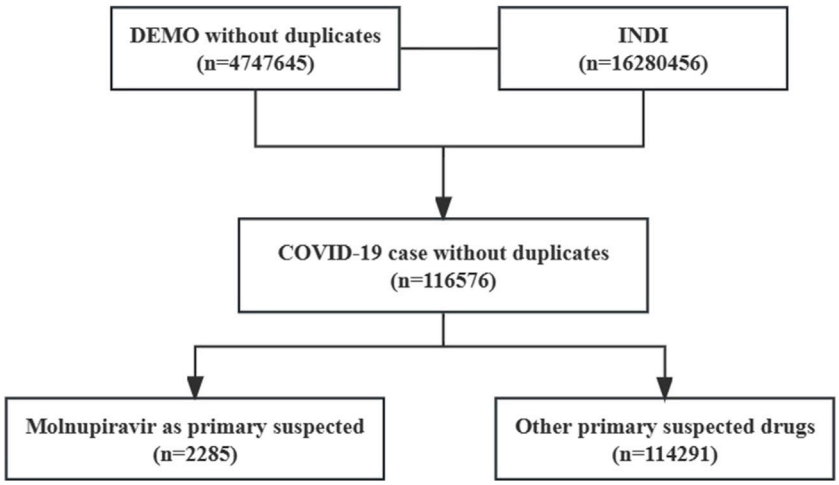

FIGURE 1
Individual case safety reports identification process.

involved in adverse events in the other drugs group are summarized in Figure 2.

The molnupiravir group included 2,285 individual safety case reports (ISCRs) encompassing a total of 4,888 adverse events, while the non-molnupiravir group comprised 114291 ISCRs involving 374575 adverse events. We identified the top 15 AEs based on occurrence and deaths. The most common AEs were Diarrhoea (142, 2.91%), Rash (125, 2.56%), Nausea (97, 1.98%), Dizziness (83, 1.70%) and Vomiting (80, 1.64%); AEs leading to death included, Pneumonia aspiration (23, 0.47%), Respiratory failure (21, 0.43%), Pneumonia (16, 0.33%), Diarrhoea (13, 0.27%) and Dysphagia (11, 0.23%) (Figure 3).

3.3 Disproportionality analysis

3.3.1 Overall

The molnupiravir group comprised 2,285 ICSRs. Using the ROR method, 74 AE signals were identified and classified into 18 System Organ Classes (SOCs). The top 20 AE signals at the preferred term PT level are shown in Table 3. They cover 9 SOCs, with skin/subcutaneous tissue disorders and gastrointestinal disorders (GI) being the most common.

According to the drug labels, the most common adverse events associated with molnupiravir use are diarrhea, nausea, and dizziness, which align with the findings from our analysis (MSD LLC, 2023). These adverse events have been included in our monitoring list. In addition to the adverse events mentioned in the drug labels, we have detected 71 AE signals that are not specifically mentioned.

3.3.2 Reported by health professionals

To ensure reliability, we extracted ICSRs reported by health professionals (physicians, pharmacists, and other healthcare professionals) from the initial pool of 2,285 ICSRs associated with molnupiravir. The health professional group consisted of 1,830 ICSRs related to molnupiravir. Using the ROR method, we identified 52 AE signals in the health professional group. The top 20 AE signals at the PT level are presented in Table 4.

3.3.3 Age

Of the 2,285 ICSRs associated with molnupiravir, 2,042 reported known age and were divided into <65 years and ≥65 years groups. The remaining 243 ICSRs had unknown age. The <65 years group had 595 ICSRs, while the ≥65 years group had 1,393 ICSRs. Using the ROR method, we identified 30 AE signals in the <65 years group and 56 AE signals in the ≥65 years group. It is worth noting that only five signals were common among the top 20 signals in the two age groups. According to Common Terminology Criteria for Adverse Events (CTCAE), in <65 years group, 5 PTs were Grade 3 and 2 PTs were Grade 5 among top 20 adverse events at PT level. In ≥65 years group, 1 PT was Grade 3 and 5 PTs were Grade 5, excluding those not covered by CTCAE (U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, 2017). Overall, adverse events appeared to be more severe in the <65 years group (Figure 4).

3.3.4 Sex

In addition to age sensitivity analysis, we also conducted a sex sensitivity analysis. Of the 2,285 ICSRs associated with molnupiravir, 2,107 reported known gender and were divided into female (1,139 ICSRs) and male (968 ICSRs) groups. The remaining 178 ICSRs had unknown gender. Using ROR, we found 54 AE signals in the female group and 43 AE signals in the male group. RORs with 95% CIs were calculated for each group, and the top 20 adverse drug event signals at the PT level are listed in Figure 5.

It is noteworthy that marasmus (ROR: 408.07, 95% CI: 47.66–3494.22) emerged as the strongest adverse drug event signal in the female group, but it did not appear among the top 20 adverse drug event signals in the male group. The mean time to marasmus onset was 1.75 ± 1.71 days in the molnupiravir group and 16.50 ± 10.60 days in the other COVID-19 drugs group, $p = 0.001$.

TABLE 2 The characteristics of the 116576 COVID-19 ICSRs.

Characteristics	MOLNUPIRAVIR (N = 2,285)		Other COVID-19 drugs (N = 114,291)	
	N	%	N	%
Age (years)				
<18	24	1.05%	1,327	1.16%
18–44	150	6.56%	14,604	12.78%
45–64	421	18.42%	27,827	24.35%
≥65	1,393	60.96%	31,339	27.42%
Unknown	297	13.00%	39,194	34.29%
Sex				
Female	1,139	49.85%	59,484	52.05%
Male	968	42.36%	44,563	38.99%
Unknown	178	7.79%	10,244	8.96%
Type of reporter				
Health professional	1830	80.09%	30,541	26.72%
Non-Health professional	307	13.44%	62,503	54.69%
Unknown	148	6.48%	21,247	18.59%
Reporting country				
United States	360	15.75%	78541	68.72%
Japan	1,667	72.95%	2,717	2.38%
Other countries	258	11.29%	24,466	21.41%
Not Specified	0	0.00%	8,567	7.50%
Outcome				
Death	277	12.12%	7,989	6.99%
Life Threatening	50	2.19%	3890	3.40%
Required Intervention	16	0.70%	1,070	0.94%
Disabled	19	0.83%	961	0.84%
Hospitalizations	449	19.65%	23,021	20.14%
Congenital Anomaly	0	0.00%	118	0.10%
Other Outcomes	701	30.68%	40,316	35.27%
Non-Serious	773	33.83%	36,926	32.31%
Dosage				
Dosage according to the label	1,444	63.19%	\	\
Dosage below the label	201	8.80%		
Dosage above the label	32	1.40%		
Unknown	608	26.61%		

4 Discussion

Molnupiravir, an RNA drug targeting SARS-CoV-2, is being utilized on an emergency basis in numerous countries for the treatment of COVID-19. Various studies have suggested that molnupiravir could be a secure therapeutic option to lower hospitalizations and/or mortality rates among nonhospitalized individuals with COVID-19 (Gao et al., 2023). However, the

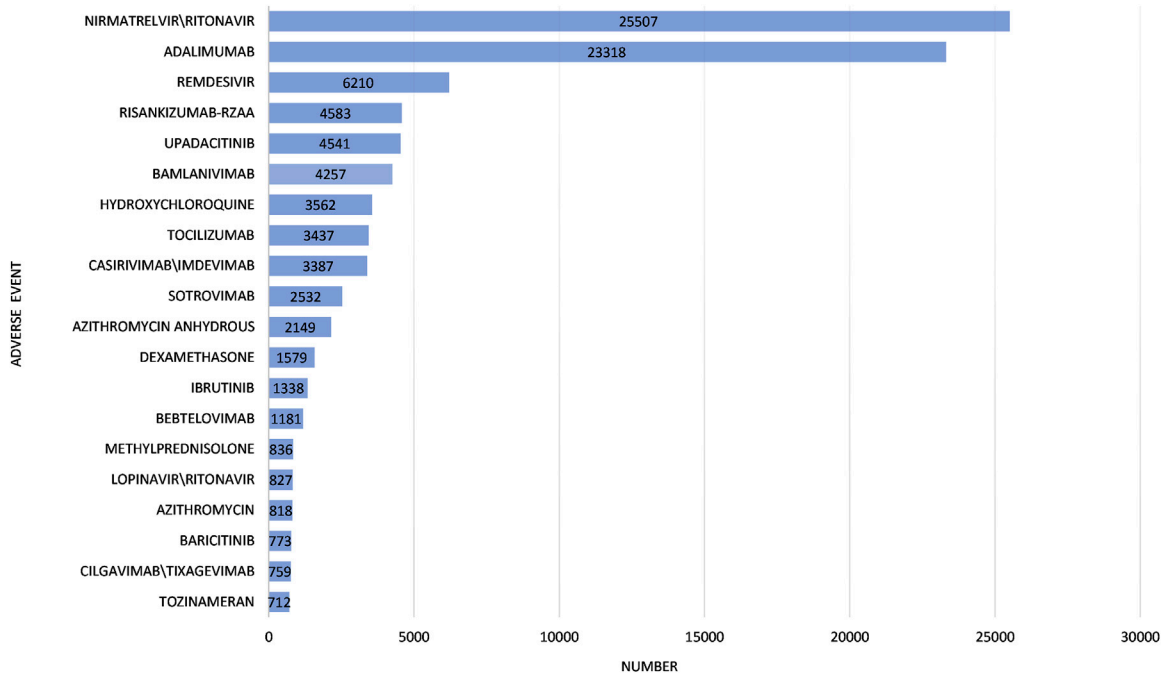

FIGURE 2
Top 20 drugs involved in adverse events in the other Coronavirus Disease 2019 drugs group.

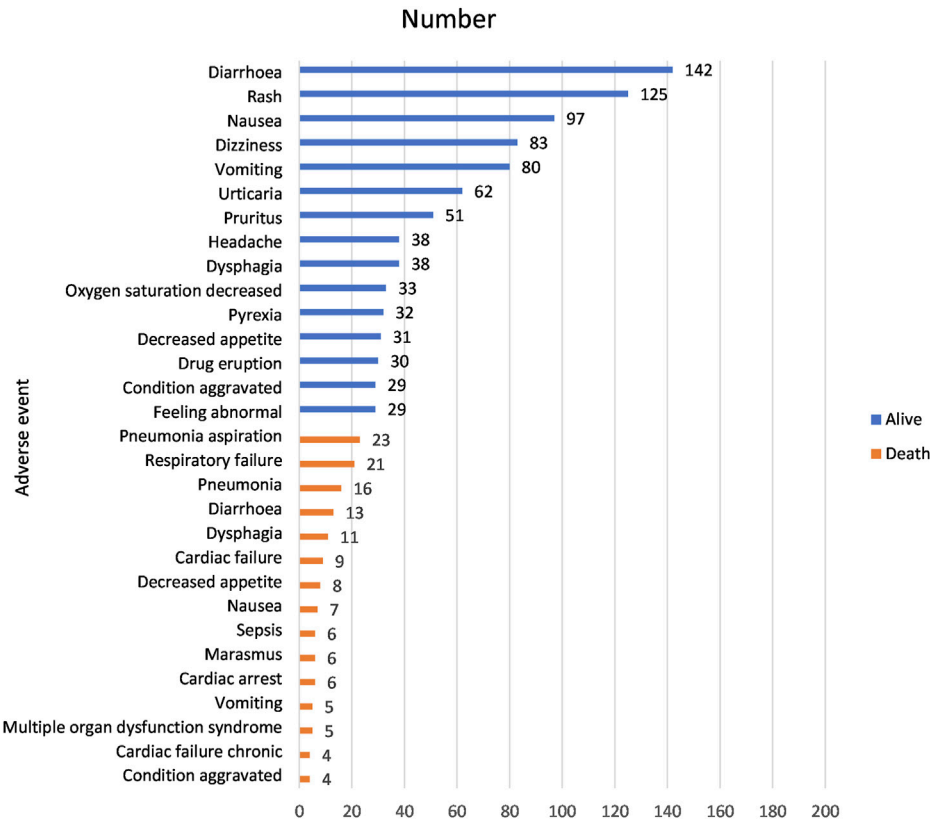

FIGURE 3
Most common adverse events associated with the use of molnupiravir.

TABLE 3 The top 20 AE signals at the PT level.

SOC	AE	N	ROR (95%CI)
Skin and subcutaneous tissue disorders (227)	Drug eruption	30	37.30 (24.10–57.74)
	Toxic skin eruption	10	33.38 (15.88–70.18)
	Rash	125	4.51 (3.76–5.41)
	Urticaria	62	4.47 (3.45–5.78)
Gastrointestinal disorders (73)	Diverticulum intestinal haemorrhagic	3	57.51 (12.87–257.02)
	Faeces soft	9	12.12 (6.00–24.49)
	Melaena	12	10.47 (5.73–19.16)
	Dysphagia	49	6.86 (5.12–9.20)
Infections and infestations (44)	Pneumonia aspiration	44	30.92 (21.77–43.91)
Respiratory, thoracic and mediastinal disorders (19)	Sputum retention	5	63.92 (19.50–209.53)
	Aspiration	8	16.59 (7.72–35.65)
	Lower respiratory tract congestion	3	12.11 (3.58–40.93)
	Asphyxia	3	11.50 (3.42–38.72)
Nervous system disorders (14)	Altered state of consciousness	7	10.53 (4.78–23.22)
	Cerebral infarction	7	8.80 (4.03–19.26)
Psychiatric disorders (13)	Hallucination, visual	8	13.95 (6.57–29.66)
	Abnormal behaviour	5	10.37 (4.07–26.38)
Renal and urinary disorders (12)	Urinary retention	12	7.81 (4.31–14.15)
Metabolism and nutrition disorders (6)	Marasmus	6	153.45 (38.37–613.75)
Cardiac disorders (4)	Cardiac failure chronic	4	15.34 (5.24–44.89)

presence of certain unknown concerns, including teratogenicity, carcinogenicity, mutation, and potential bone and cartilage toxicity, cannot be overlooked (Focosi, 2022). Currently, there is a scarcity of studies investigating the long-term toxicity of molnupiravir. Most of these studies are prospective in nature and have small sample sizes, while there is a lack of retrospective studies with large sample cohorts. In our research, we conducted the first largescale retrospective study utilizing the FAERS database to examine adverse events associated with molnupiravir. Our findings indicate that molnupiravir is associated with an elevated likelihood of gastrointestinal disorders and skin and subcutaneous tissue disorders as adverse events. Moreover, we observed a significant increase in the risk of AEs related to cardiac disorders, hepatobiliary disorders, renal and urinary disorders, and vascular disorders among individuals aged 65 years and older. However, there was no statistically significant difference observed between males and females.

The characteristics of individual safety reports linked to molnupiravir highlight that individuals aged 65 years and older account for over 60% (60.96%) of the reported cases. This observation may be attributed to the approved usage scope of molnupiravir, such as in the United States where LAGEVRIO™ (molnupiravir) is an investigational medicine for treating mild to moderate COVID-19 in adults who have a positive result from a direct-to-consumer SARS-CoV-2 virus test and are at risk of progressing to severe COVID-19. These individuals are typically unable to access or receive clinically suitable FDA-approved or licensed COVID-19 treatment options. Adolescents, on the other hand, tend to possess robust immune systems and generally experience milder illness following severe acute respiratory syndrome coronavirus 2 infection. Additionally, elderly individuals and those at higher risk often receive chronic treatments that may interact with Nirmatrelvir/ritonavir, making molnupiravir a more suitable option for them. The substantial number of elderly individuals using molnupiravir has contributed to the multitude of individual case safety reports, which is one of the factors we suspect. Diarrhea, nausea, and dizziness are the most frequently reported adverse drug events associated with molnupiravir treatment in most clinical trials, aligning closely with the outcomes of our analysis on the common adverse events linked to molnupiravir usage (Sinha et al., 2022). This study validates the effectiveness of utilizing a data mining method for detecting AE signals, making it a valuable reference for clinical applications. However, it should be noted that diarrhea and rash can also manifest as common symptoms of COVID-19 itself, making it difficult to ascertain whether they are truly drug-related adverse events or merely symptoms of the viral infection.

The results of the disproportionality analysis for the molnupiravir group and health professional group showed that adverse events mainly linked to molnupiravir were related to GI disorders and skin/subcutaneous tissue disorders. We found 71 adverse event signals not mentioned in the drug label, with the majority involving skin/subcutaneous tissue disorders. In a phase I, randomized, placebo-controlled study with healthy Japanese participants, toxic skin

TABLE 4 The top 20 AE signals at the PT level of the health professional group.

SOC	AE	N	ROR (95%CI)
Gastrointestinal disorders (176)	Faeces soft	7	19.06 (7.10–51.22)
	Dysphagia	42	8.95 (6.28–12.76)
	Diverticulum intestinal haemorrhagic	3	36.73 (6.13–219.88)
	Haematochezia	11	10.79 (5.31–21.95)
	Diarrhoea	113	3.63 (2.97–4.43)
Skin and subcutaneous tissue disorders (132)	Drug eruption	29	28.60 (16.73–48.88)
	Toxic skin eruption	9	10.51 (4.81–22.96)
	Dermatitis allergic	4	16.33 (4.61–57.88)
	Rash	81	3.98 (3.14–5.04)
	Eczema	9	5.52 (2.67–11.38)
Infections and infestations (44)	Pneumonia aspiration	44	16.50 (11.25–24.20)
Metabolism and nutrition disorders (12)	Marasmus	6	49.01 (12.25–196.05)
	Feeding disorder	6	8.17 (3.24–20.59)
Psychiatric disorders (11)	Hallucination, visual	7	9.03 (3.79–21.49)
	Abnormal behaviour	4	8.91 (2.83–27.98)
Renal and urinary disorders (11)	Urinary retention	11	10.79 (5.31–21.95)
Respiratory, thoracic and mediastinal disorders (8)	Sputum retention	5	61.25 (11.88–315.80)
	Asphyxia	3	12.24 (3.06–48.97)
Nervous system disorders (7)	Altered state of consciousness	7	6.86 (2.97–15.87)
Ear and labyrinth9 disorders (4)	Deafness unilateral	4	32.66 (7.31–145.96)

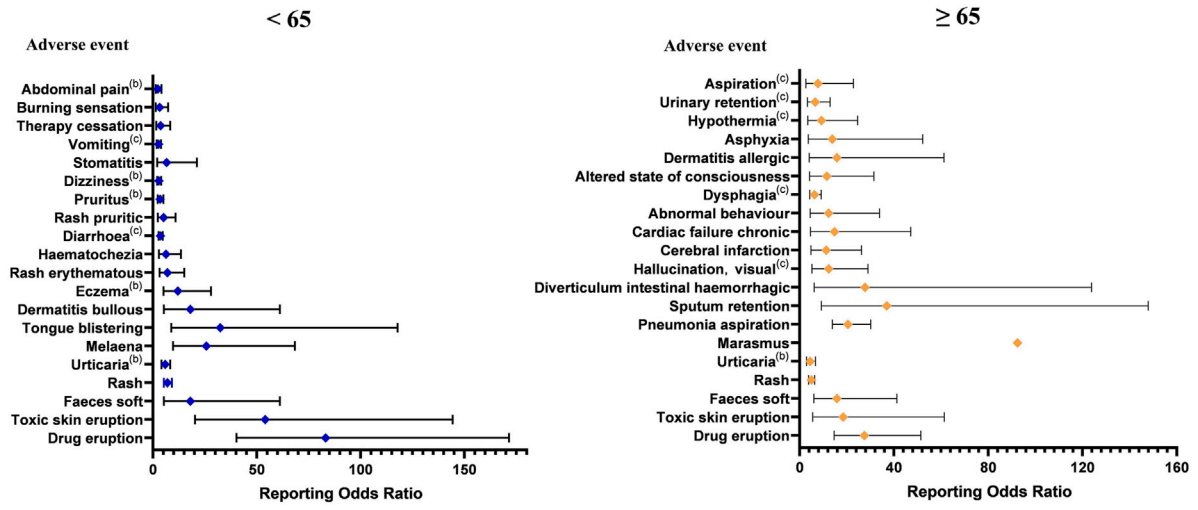

FIGURE 4
The top 20 adverse event signals at the preferred term level base on age. (a The adverse event is up to level 2 in Common Terminology Criteria for Adverse Events. b The adverse event is up to level 3 in Common Terminology Criteria for Adverse Events. c The adverse event is up to level 5 in Common Terminology Criteria for Adverse Events.).

eruption was the most frequently reported adverse event associated with molnupiravir use (Nakamura et al., 2022). In another trial, a similar observation was made where discontinuation of the treatment occurred due to a rash in one participant (Painter et al., 2020). Skin and subcutaneous tissue disorder adverse events were infrequent in some COVID-19 patient studies. However, the ethnic sensitivity of these

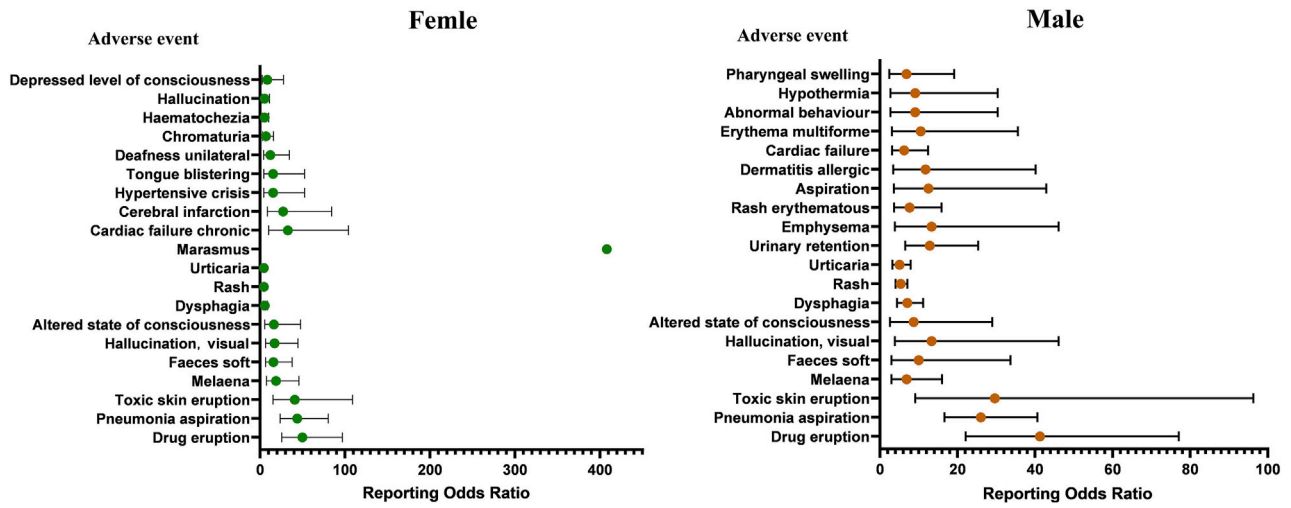

FIGURE 5
The top 20 adverse event signals at the preferred term level base on sex.

findings remains unclear due to the limited scale of our study. Continuous surveillance is crucial to further investigate and monitor these aspects effectively.

Close monitoring of individuals aged ≥65 years is recommended to mitigate serious adverse reactions with molnupiravir. Among the AE signals, 30 were observed in the <65 years group, while 56 were reported in the ≥65 years group, involving 9 SOCs and 14 SOCs, respectively. Notably, the four SOCs related to cardiac disorders, hepatobiliary disorders, renal and urinary disorders, and vascular disorders were exclusively present in the ≥65 years group. These SOCs are associated with more severe PTs not mentioned in the drug labels, such as chronic cardiac failure, abnormal hepatic function, urinary retention, and hypertensive crisis. Additionally, certain clinical trials have reported serious adverse events like cardiac chest pain, haematuria, hypertension, and increased transaminase levels, which are not included in the molnupiravir drug labels (Painter et al., 2020; Fischer et al., 2022). Therefore, increased surveillance of cardiotoxicity, nephrotoxicity, hepatotoxicity, and vascular disease is warranted in elderly patients. Additionally, notable differences exist between the two age groups in the respiratory, thoracic, and mediastinal disorders system. To enhance clarity, we created a heat map (Figure 6). The ≥65 years group showed more signals in respiratory, thoracic, and mediastinal disorders, with the strongest signal being sputum retention (ROR: 36.97, 95% CI: 9.24–147.88). Hence, middle-aged and elderly individuals may require heightened monitoring of adverse events, particularly for cardiac disorders, hepatobiliary disorders, renal and urinary disorders, vascular disorders, and the respiratory, thoracic, and mediastinal disorders system. We also found females ≥65 years old had a higher risk of developing marasmus. Possible mechanisms include appetite and metabolic changes, and direct drug toxicity. Further studies on pathophysiology are warranted. In the interim, clinicians should closely monitor nutritional status and wasting in molnupiravir patients, especially elderly females in the first week. Prompt nutrition and physical therapy support may mitigate progression. The risk of rapid severe marasmus onset should be considered when evaluating molnupiravir's risk-benefit profile.

Molnupiravir has demonstrated excellent safety as an SARS-CoV-2 RNA drug. In comparison, other SARS-CoV-2 RNA drugs have exhibited distinct adverse events in pharmacovigilance studies based on real FAERS database. Remdesivir has shown a significant association with acute kidney injury, with the top three adverse events being elevated liver function test, acute kidney injury, and death. The ribavirin-interferon combination has been linked to an increased risk of anemia, vomiting, neutropenia, diarrhea, and insomnia. Favipiravir has shown side effects such as QTC prolongation, hyperuricemia, abnormalities in liver enzymes, elevation of uric acid, total bilirubin, and liver enzymes, along with gastrointestinal disorders in clinical trials. Conversely, no adverse events were reported in the azvudine group in a clinical trial (Ren et al., 2020; Shan et al., 2020; Wu et al., 2022; Alsuhaibani et al., 2023; Batool et al., 2023). In addition,

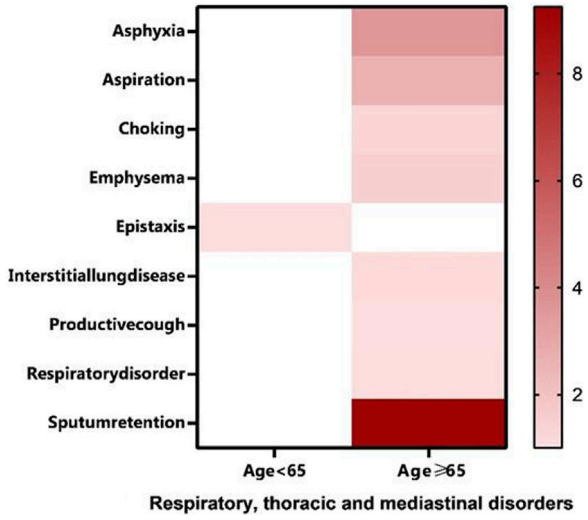

FIGURE 6
Heat map of Respiratory, thoracic and mediastinal disorders.

clinical trials have indicated that Molnupiravir is associated with fewer side effects compared to nirmatrelvir/ritonavir (Mazzitelli et al., 2023). Although GI disorders and skin/subcutaneous tissue disorders are the most common AEs related to molnupiravir, it is essential to enhance safety monitoring in older and medically vulnerable individuals.

Our study has limitations. Firstly, as a spontaneous reporting system, the FAERS database lacks information on patients' baseline characteristics (e.g., age, gender, BMI), onset timing AE severity and so on. These factors limit the predictive ability and detail of our analysis. Secondly, the substantially larger sample size of the non-molnupiravir group compared to the molnupiravir group may lead to baseline imbalance that cannot be readily addressed due to the inherent data source discrepancy. We mention that this could be a limitation in result interpretation. Furthermore, FAERS does not contain information on patient ethnicity, making it impossible to analyze potential differences in adverse events between populations such as Japanese versus Caucasians. The lack of ethnicity data is an important limitation, as previous studies have shown pharmacokinetic differences between ethnic groups (Shimada et al., 1994). In addition, this study did not evaluate the impacts of COVID-19 co-infections with other viruses and medication interactions on adverse events due to data limitations. The lack of COVID-19 co-infection and drug interaction data represents another constraint of this analysis. Lastly, the calculation of the reporting odds ratio (ROR) is sensitive to individual values, and it may be unreliable when one of the theoretical frequencies in the 2 × 2 contingency table is small or the denominator is 0.

5 Conclusion

This pharmacovigilance study used the real FAERS database to assess adverse event risks associated with molnupiravir therapy in COVID-19 patients. However, further clinical studies are needed for confirmation.

Overall, besides common gastrointestinal disorders, skin and subcutaneous tissue disorders were also prevalent. The study found that compared to other RNA antiviral drugs such as remdesivir, molnupiravir demonstrated a lower risk of serious adverse events in individuals under 65 years old. Nonetheless, closer monitoring of drug safety is necessary for individuals ≥65 years old. The adverse events reported in FAERS data align with most clinical trial findings. Ongoing monitoring is vital as the use of molnupiravir increases, enabling a more comprehensive understanding of its safety profile. These findings provided invaluable real-world data for post-marketing surveillance of molnupiravir and impor€tant guidance for its future clinical use.

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.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YL: Methodology, Data curation, Formal Analysis, Investigation, Software, Writing–original draft. LM: Writing–original draft, Conceptualization, Validation. YW: Formal Analysis, Software, Writing–review and editing. JZ: Formal Analysis, Software, Writing–review and editing. LS: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Writing–review and editing. JL: Formal Analysis, Funding acquisition, Methodology, Resources, Validation, Writing–review and editing.

Conflict of interest

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

Publisher's note

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Post-marketing safety surveillance of sacituzumab govitecan: an observational, pharmacovigilance study leveraging FAERS database

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Background and objective: Sacituzumab govitecan (SG), the first antibody-drug conjugate targeting human trophoblast cell-surface antigen 2 (Trop-2), has been approved by the Food and Drug Administration (FDA) for the treatment of advanced or metastatic breast cancer and urothelial cancer. However, there is currently a dearth of information regarding the safety profiles of SG in a large sample cohort. The objective of the present study is to investigate SG-related adverse events (AEs) in real-world settings leveraging the FDA Adverse Event Reporting System (FAERS) database to guide the safety management of clinical medication.

Methods: The FAERS database was retrospectively queried to extract reports associated with SG from April 2020 to March 2023. To identify and evaluate potential AEs in patients receiving SG, various disproportionality analyses such as reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) were employed.

Results: Overall, 2069 reports of SG as the "primary suspect" were identified. Noteworthy, SG was significantly associated with an increased risk of blood lymphatic system disorders (ROR, 7.18; 95% CI, 6.58–7.84) and hepatobiliary disorders (ROR, 2.68; 95% CI, 2.17–3.30) at the System Organ Class (SOC) level. Meanwhile, 61 significant disproportionality preferred terms (PTs) simultaneously complied with all four algorithms were adopted. Therein, anemia, thrombocytopenia, neutropenia, leukopenia, diarrhea, asthenia, alopecia, and electrolyte imbalance were consistent with the common AEs described in the clinical trials and specification of SG. Furthermore, unexpected significant AEs include colitis (ROR, 12.09; 95% CI, 9.1–16.08), heart rate increased (ROR, 5.11; 95% CI, 3.84–6.79), sepsis (ROR, 4.77; 95% CI, 3.59–6.34), cholestasis (ROR, 6.28; 95% CI, 3.48–11.36), blood bilirubin increased (ROR, 4.65; 95% CI, 2.42–8.94) and meningitis (ROR, 7.23; 95% CI, 2.71–19.29) were also be detected. The median time to onset of SG-related AEs was 14 [interquartile range (IQR), 7–52] days, with the majority occurring within the initial month of SG treatment.

Conclusion: Our study validates the commonly known AEs and also found some potentially emerging safety issues related to SG in real-world clinical practice, which could provide valuable vigilance evidence for clinicians and pharmacists to manage the safety issues of SG.

KEYWORDS

sacituzumab govitecan, antibody-drug conjugate, Trop-2, pharmacovigilance, adverse event, FAERS

1 Introduction

Triple-negative breast cancer (TNBC) is a poor prognostic breast cancer subtype characterized by the lack of estrogen and progesterone receptors and the amplification of the human epidermal growth factor receptor 2 (HER2) gene, comprises approximately 15%–20% of invasive breast cancers (Garrido-Castro et al., 2019; Giaquinto et al., 2022). TNBC is associated with higher and earlier recurrence and mortality rates in the operable (I-III) stages and shorter overall survival (OS) in the inoperable (IV) stage (Leon-Ferre and Goetz, 2023). Although immunotherapy has shown promising benefits in first-line clinical treatment, systemic chemotherapy remains the mainstay of standard care for previously treated metastatic TNBC (mTNBC) (Twelves et al., 2016; Winer et al., 2021; Gradishar et al., 2023). However, in second-line or beyond mTNBC setting, single-agent chemotherapy has shown low response rates (10%–15%), short progression-free survival (PFS) (2–3 months), and significant toxicity (Twelves et al., 2016; Khosravi-Shahi et al., 2018; Park et al., 2019). To date, treatment options for mTNBC patients who have received two or more regimens remain limited. Hence, advances in therapeutic options for these breast cancer patients are urgently needed.

Trophoblast cell-surface antigen-2 (Trop-2), a transmembrane calcium signal transducer, is associated with poor outcome in multiple types of malignant epithelial tumors, including TNBC (Goldenberg et al., 2015; Kwapisz, 2022). Sacituzumab govitecan (SG) is an anti-Trop-2 antibody-drug coupling (ADC) consisting of a humanized Trop-2 antibody coupled to SN-38 (the active metabolite of irinotecan) via a proprietary, hydrolyzable linker (Goldenberg et al., 2015; Starodub et al., 2015; Kwapisz, 2022). In a phase 1/2, single-group, basket trial (IMMU-132-01, NCT01631552), clinical anti-tumor activity of SG monotherapy was first observed in the mTNBC patients (n = 108), with an objective response rate of 33.3%, a median PFS of 5.5 months, and median OS of 13.0 months (Bardia et al., 2021a). Subsequently, the clinical benefit of SG was further confirmed by the phase 3 ASCENT study (NCT02574455), which significantly prolonged median PFS (5.6 months vs. 1.7 months) and median OS (12.1 months vs. 6.7 months) in patients with heavily pretreated mTNBC, compared with single-agent chemotherapy of physician's choice (Kwapisz, 2022; Bardia et al., 2021b; Carey et al., 2022; Kathpalia et al., 2023). Based on these impressive results, the Food and Drug Administration (FDA) approved SG (TRODELVY®) as one of the few targeted therapy options currently available for the treatment of mTNBC patients who have received at least two prior therapies (FDA grants regular approval to sacituzumab, 2021).

Despite that, with the knowledge of the SG payload is a cytotoxic ingredient, safety concerns should also be taken into consideration along with its efficacy (Carey et al., 2022). Nevertheless, with the widespread use of SG in clinical practice, limited available information on AEs associated with SG treatment, which mainly comes from clinical trials. According to the safety analyses reported in the previous clinical trial and the instructions of SG, the most common adverse events (AEs) of SG were neutropenia, diarrhea, alopecia, anemia, nausea, fatigue, constipation, and vomiting (Kathpalia et al., 2023; Bardia et al., 2017; Spring et al., 2021; Rugo et al., 2022a). However, the safety profiles of SG therapy in real-world, large sample cohort settings, in particular, time to onset of AEs associated with SG treatment have not been well elucidated to date.

Therefore, we conducted this pharmacovigilance study to evaluate the post-marketing safety profile of SG in real-world settings leveraging the FDA Adverse Event Reporting System (FAERS) database to provide vigilance reference for clinicians and pharmacists to manage the safety issues of SG.

2 Materials and methods

2.1 Study design and data source

This real-world, observational, retrospective pharmacovigilance study, performed from Quarter 2 (Q2) in 2020 to Q1 in 2023, was designed to explore SG related AEs leveraging the FAERS database. The FAERS database is a publicly accessible post-marketing safety surveillance database that including adverse event reports, product quality complaints, and medication error reports submitted by various occupational sources including health professionals, individual patients, pharmaceutical manufacturers, and lawyers (Fang et al., 2023). Despite FAERS is a US-centric database, it receives AE reports from around the global scope. Consequently, the extensive scale and worldwide reach of this open database render it highly appropriate for the evaluation of spontaneous reporting data. The FAERS database includes the following eight types of files: report sources (RPSR), demographic and administrative information (DEMO), drug information (DRUG), indications for use (INDI), start and end dates for reported drugs (THER), adverse events (REAC), patient outcomes (OUTC), and invalid reports (DELETED). All files are available on the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Given that the FAERS databases are accessible to the public and patient records are anonymized and de-identified, neither informed consent nor ethical approval was involved.

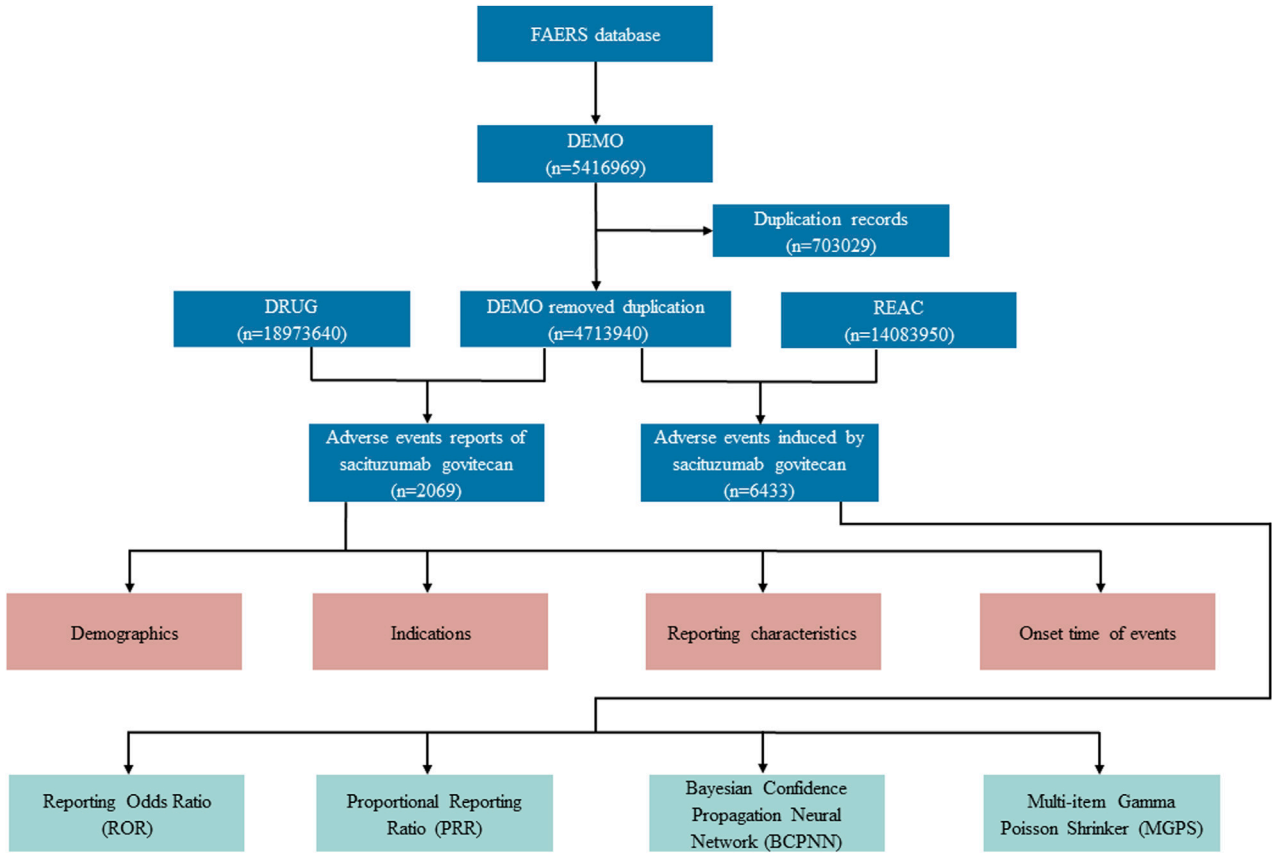

FIGURE 1
Flow diagram for the selection of AEs associated with sacituzumab govitecan from FAERS database.

2.2 Data extraction and mining

The data extraction and mining of the present study is illustrated in Figure 1. Generic names and brand names (sacituzumab govitecan, Trodelvy®) were applied to identify SG-related reports due to two variables, PROD_AI and DRUGNAME. Besides, in the light of FDA's recommendations, we eliminated duplicate reports filed by different people and institutions by choosing the latest FDA_DT when the PRIMARYIDs were the same, and the higher PRIMARYID where the FDA_DT and the CASEID were the same. Generally, drugs reported within FAERS were categorized into four patterns: primary suspect (PS), secondary suspect (SS), concomitant (C), and interacting (I). In our investigations, exposure assessment was only considered when SG was documented as "primary suspect." The AE reports in FAERS database are coded according to Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA). The hierarchical structure of MedDRA allows for PTs to be categorized into the relevant System Organ Class (SOC), which is the highest level of MedDRA. Clinical characteristics, including demographics (age, gender), reporting characteristics (reporting year, region, and occupation of reporters), and indications of reports were collected. Meanwhile, serious outcomes were defined as death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or other important medical event. Additionally, the time to onset of specific AEs induced by SG was also assessed, calculated as the interval between the time of SG dosage initial (START_DT) and the time of AE onset (EVENT_DT) (Shu et al., 2023a). Reports with dates missing or incorrect (drug usage time later than the time of event occurrence) were excluded.

2.3 Statistical analysis

Descriptive analysis was used to characterize all AEs reports in relation to SG treatment. In our investigations, both frequentist methods [reporting odds ratio (ROR) (van Puijenbroek et al., 2002) and proportional reporting ratio (PRR) (Evans et al., 2001)] and Bayesian methods [information component (IC) (Bate et al., 1998) and empirical Bayes geometric mean (EBGM) (Szarfman et al., 2002)] of disproportionality analysis were applied to identify the potential AE signals associated with SG, as a way to confirm our findings and reduce false-positive safety signals. A two-by-two contingency table is the framework for analyses (Supplementary Table S1). Besides, detailed equations and criteria for the four algorithms are presented in Table 1. In the present study, drug-related AE signals were identified based on the inclusion of signals with a minimum of three AE records associated with target drugs, and only AE signals that simultaneously met all four algorithm

TABLE 1 Four major algorithms used for signal detection.

Algorithms	Calculation formulas	Criteria
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	95%CI > 1, a≥3
	$95\%CI = e^{\ln(ROR)\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	PRR≥2, $\chi^2 \geq 4$, a≥3
	$\chi 2 = \frac{(ad-bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$	
BCPNN	$IC = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025 > 0
	$E(IC) = log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(ln2)^2}\left\{[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}] + [\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}] + [\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}]\right\}$	
	$\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$IC025 = E(IC) - 2\sqrt{V(IC)}$	
MGPS	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05 > 2
	$95\%CI = e^{\ln(EBGM)\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	

Abbreviation: ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, bayesian confidence propagation neural network; MGPS, multi-item gamma Poisson shrinker; EBGM, empirical Bayesian geometric mean; CI, confidence interval; χ^2, chi-squared; IC, information component; IC025, the lower limit of the 95% one-sided CI, of the IC; EBGM05, the lower 95% one-sided CI, of EBGM. Equation: a, number of reports containing both the target drug and the target adverse events; b, number of reports containing the target adverse drug reaction with other medications (except the target drug); c, number of reports containing the target drug with other adverse events (except the target adverse events); d, number of reports containing other medications and other adverse events.

standards aforementioned were deemed as significant positive indicators (Shu et al., 2023b). All data processing and statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, United States), Microsoft EXCEL Professional Plus 2013, and the GraphPad Prism 8.0 (GraphPad Software, CA, United States).

3 Results

3.1 Descriptive analysis

During the surveillance period, from April 2020 to March 2023, a total of 4,713,940 reports were documented in the FAERS database, and 2069 (0.04%) reports were associated with SG medication [patient median (interquartile range, IQR) age, 56 (46–66) years]. The specific demographic and clinical details are provided in Table 2. Gender data were available for 1,950 patients, and the proportion of women was 85.40%. Therein, middle-aged patients (18–65 years) tended to have a higher risk of SG related AEs (n = 732, 35.38%). Furthermore, a significant proportion of patients (n = 1,845, 89.17%) experienced serious outcomes, including hospitalizations (616 cases), deaths (544 cases), and life-threatening situations (108 cases) with available follow-up data. From the perspective of reporting sources, 1,823 healthcare professionals-including doctors (52.15%) and pharmacists (35.69%)-submitted 88.11% of the AE reports, as compared to 245 consumers who reported 11.84% of the AEs, and 1unknown person who reported 0.05% of the AEs. According to the data presented in Table 2, the United States of America reported the most number of AE cases, with a total of 744, accounting for 35.96% of the whole. This was followed by France (n = 387, 18.70%), and Canada (n = 245, 11.84%). Besides, the number of reported AEs-related to SG showed a gradual increase from 2020 to 2023. However, it is worth noting that except for 60.75% reported in 2022, the most reported year was the first quarter of 2023 (18.76%).

3.2 AE profiling of sacituzumab govitecan in disproportionality analysis

The proportion of positive signals for SG related AEs at the SOC level were shown in Figure 2. Meanwhile, specific signal strength of SG at the SOC level were described in Table 3. Statistically, we identified 26 organ systems that were involved in SG-induced AEs. In particular, the significant SOCs that met four criteria were investigations (SOC: 10022891, n = 604), blood and lymphatic system disorders (SOC: 10005329, n = 549), metabolism and nutrition disorders (SOC: 10027433, n = 247), hepatobiliary disorders (SOC: 10019805, n = 89), and congenital, familial and genetic disorders (SOC: 10010331, n = 12). Since FAERS is a collection of all medical and health-related PTs, it will also contain some non-drug-related AE signals that may be caused by disease progression or other causes. Therefore, in the present study, neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC: 10029104), injury, poisoning and procedural complications (SOC: 10022117), product issues (SOC: 10077536), surgical and medical procedures (SOC: 10042613) were not included for further analyses of SG-related AEs (Supplementary Table S2).

Furthermore, a total of 61 significant disproportionality PTs that simultaneously comply with the four algorithms is shown in Table 4. In the present study, PTs of neutropenia (PT: 10029354), febrile neutropenia (PT: 10016288), anaemia (PT: 10002034), thrombocytopenia (PT: 10043554), periorbital oedema (PT: 10034545), diarrhoea (PT: 10012735), leukopenia (PT: 10024384), asthenia (PT: 10003549), mucosal inflammation (PT: 10028116), hepatic lesion (PT: 10061998), cholinergic

TABLE 2 Summary of basic demographic and clinical information of reports associated with sacituzumab govitecan based on the FAERS database (From 1 April 2020 to 31 March 2023).

Characteristics	Case number, n	Case proportion, %
Number of events	2,069	
Gender		
Female	1,767	85.40
Male	183	8.84
Unknown	119	5.75
Age		
<18	0	0.00
18≤ and <45	227	10.97
45≤ and <65	505	24.41
≥65	276	13.34
Unknown	1,061	51.28
Indications (Top Five)		
Triple negative breast cancer	1,046	50.56
Product used for unknown indication	388	18.75
Breast cancer metastatic	145	7.01
Breast cancer	118	5.70
Transitional cell carcinoma	74	3.58
AE Severity		
Serious	1,845	89.17
Non-serious	224	10.83
Serious Outcome		
Death	544	26.29
Life-Threatening	108	5.22
Hospitalization - Initial or Prolonged	616	29.77
Disability	27	1.30
Required Intervention to Prevent Permanent Impairment	2	0.10
Other serious medical events	1,506	72.29
Reporting Year		
2020	77	3.72
2021	359	17.35
2022	1,257	60.75
2023Q1	376	18.17
Reported Countries (Top Five)		
United States of America	744	35.96
France	387	18.70
Canada	245	11.84
Germany	82	3.96
Italy	82	3.96

(Continued on following page)

TABLE 2 (*Continued*) Summary of basic demographic and clinical information of reports associated with sacituzumab govitecan based on the FAERS database (From 1 April 2020 to 31 March 2023).

Characteristics	Case number, n	Case proportion, %
Reported Person		
Physician	1,079	52.15
Pharmacist	744	35.96
Consumer	245	11.84
Unknown	1	0.05
Time to onset of SG related AEs		
0-30d	533	25.76
31-90d	145	7.00
91-180d	83	4.01
181-360d	42	2.03
>360d	11	0.53

AE, adverse event; 2023Q1, the first quarter of 2023.

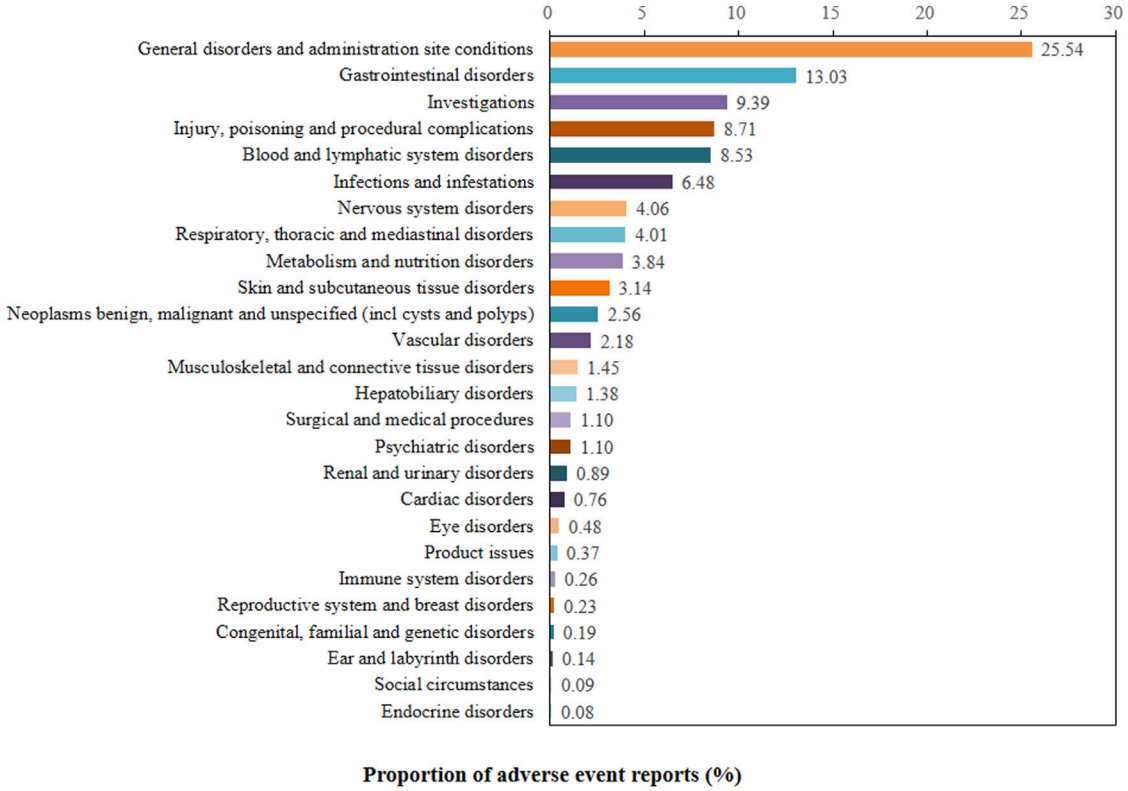

FIGURE 2
Proportion of positive signal for sacituzumab govitecan related AEs at the System Organ Class (SOC) level.

syndrome (PT: 10008674), pleural effusion (PT: 10035598), pneumonitis (PT: 10035742), alopecia (PT: 10001760), hypokalaemia (PT: 10021015), lymphoedema (PT: 10025282) were detected, which were consistent with findings from clinical trials and the label for SG. Noteworthy, some unexpected AEs uncovered in the label of SG were also founded, including colitis (PT: 10009887), heart rate increased (PT: 10019303), cholecystitis acute (PT: 10008614), hepatic cytolysis (PT: 10049199), cholestasis (PT: 10008635), meningitis (PT: 10027199), sepsis (PT: 10040047), blood bilirubin increased (PT: 10005364), prerenal failure (PT: 10072370), and vein collapse (PT: 10074621).

TABLE 3 The signal strength of reports associated with sacituzumab govitecan at the system organ class (SOC) level in FAERS database.

SOC	Case number (n)	ROR (95% CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	1643	2.04 (1.93–2.16)	1.78 (650.36)	0.83 (0.75)	1.78 (1.68)
Gastrointestinal disorders	838	2.24 (2.09–2.41)	2.08 (502.30)	1.06 (0.95)	2.08 (1.94)
Investigations	604	**2.67 (2.46–2.91)**	**2.52 (573.22)**	**1.33 (1.20)**	**2.52 (2.31)**
Injury, poisoning and procedural complications	560	1.01 (0.93–1.10)	1.01 (0.06)	0.01 (−0.11)	1.01 (0.93)
Blood and lymphatic system disorders	549	**7.18 (6.58–7.84)**	**6.65 (2662.35)**	**2.73 (2.59)**	**6.63 (6.08)**
Infections and infestations	417	1.61 (1.46–1.78)	1.57 (90.41)	0.65 (0.50)	1.57 (1.42)
Nervous system disorders	261	0.77 (0.68–0.87)	0.78 (17.91)	−0.37 (−0.55)	0.78 (0.69)
Respiratory, thoracic and mediastinal disorders	258	1.17 (1.04–1.33)	1.17 (6.31)	0.22 (0.04)	1.17 (1.03)
Metabolism and nutrition disorders	247	**3.03 (2.67–3.44)**	**2.95 (321.95)**	**1.56 (1.36)**	**2.95 (2.59)**
Skin and subcutaneous tissue disorders	202	0.85 (0.74–0.98)	0.85 (5.37)	−0.23 (−0.44)	0.85 (0.74)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	165	1.72 (1.48–2.01)	1.70 (48.74)	0.77 (0.54)	1.70 (1.46)
Vascular disorders	140	1.68 (1.42–1.99)	1.67 (37.85)	0.74 (0.48)	1.67 (1.41)
Musculoskeletal and connective tissue disorders	93	0.48 (0.39–0.59)	0.49 (50.79)	−1.03 (−1.32)	0.49 (0.40)
Hepatobiliary disorders	89	**2.68 (2.17–3.30)**	**2.65 (91.96)**	**1.41 (1.07)**	**2.65 (2.15)**
Surgical and medical procedures	71	1.42 (1.13–1.80)	1.42 (8.83)	0.50 (0.15)	1.42 (1.12)
Psychiatric disorders	71	0.47 (0.37–0.60)	0.48 (41.34)	−1.06 (−1.40)	0.48 (0.38)
Renal and urinary disorders	57	0.82 (0.63–1.06)	0.82 (2.25)	−0.28 (−0.66)	0.82 (0.63)
Cardiac disorders	49	0.65 (0.49–0.87)	0.66 (8.93)	−0.61 (−1.01)	0.66 (0.50)
Eye disorders	31	0.48 (0.34–0.69)	0.49 (17.04)	−1.04 (−1.53)	0.49 (0.34)
Product issues	24	0.80 (0.53–1.19)	0.80 (1.21)	−0.32 (−0.89)	0.80 (0.54)
Immune system disorders	17	0.37 (0.23–0.59)	0.37 (18.45)	−1.44 (−2.07)	0.37 (0.23)
Reproductive system and breast disorders	15	3.21 (1.94–5.34)	3.21 (22.79)	1.68 (0.77)	3.21 (1.93)
Congenital, familial and genetic disorders	12	**50.02 (28.21–88.68)**	**49.92 (562.52)**	**5.61 (2.57)**	**48.83 (27.54)**
Ear and labyrinth disorders	9	0.67 (0.35–1.28)	0.67 (1.52)	−0.59 (−1.45)	0.67 (0.35)
Social circumstances	6	0.46 (0.21–1.02)	0.46 (3.83)	−1.12 (−2.10)	0.46 (0.21)
Endocrine disorders	5	0.79 (0.33–1.90)	0.79 (0.28)	−0.34 (−1.47)	0.79 (0.33)

Note: Values in bold indicates significant signals in four algorithms. PRR, proportional reporting ratio; ROR, reported odds ratio; IC, information component; EBGM, the empirical Bayes geometric mean; IC025 and EBGM05, lower limit of the 95% two-sided confidence interval for IC and EBGM, respectively. Signals are detected when all the following criteria are met: PRR ≥ 2 and $\chi 2 > 4$, lower limit of 95% CI of ROR > 1, IC025 > 0, EBGM025 > 2.

3.3 Time-to-onset analysis

There were a total of approximately 814 AE reports that reported time of onset. The mean onset time was 49 days, and the median onset time was 14 (IQR, 7–52) days. Our data showed that the most onset time of SG-related AEs was less than 30 days (n = 533, 65.48%). Of note, AEs might still have occurred after half a year for SG treatment, with a proportion of 2.56% (Table 2). Furthermore, we statistically analyzed the specific time of occurrence of PTs in each report, as detailed in Table 5, the time to onset of commonly reported AEs associated with SG were neutropenia 10.5 (IQR, 6–17) days, diarrhea 12 (IQR, 7–27) days, anemia 13.5 (IQR, 7–21) days, thrombocytopenia 14 (IQR, 6–39) days, respectively. Notably, the median onset time of heart rate increased was somewhat earlier than the other AEs [7 (IQR, 0–43.5) days], whereas pneumonia occurred relatively later [28 (IQR, 15.25–76.25) days].

4 Discussion

Sacituzumab govitecan, a first-in-class ADC targeting Trop-2, showed favorable tolerability and an impressive PFS and OS in patients with heavily pretreated mTNBC (Goldenberg et al., 2015;

TABLE 4 Signal strength of reports associated with sacituzumab govitecan at the Preferred Terms (PTs) level in the FAERS database.

SOC	Preferred terms (PTs)	PT/N	ROR (95%CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
Blood and lymphatic system disorders	Agranulocytosis	7	4.34 (2.07–9.12)	4.34 (17.97)	2.12 (0.59)	4.33 (2.06)
	Pancytopenia	17	3.53 (2.19–5.68)	3.52 (30.67)	1.81 (0.94)	3.52 (2.18)
	Leukopenia	18	3.91 (2.46–6.21)	3.9 (38.73)	1.96 (1.09)	3.89 (2.45)
	Cytopenia	9	5.22 (2.71–10.04)	5.21 (30.58)	2.38 (0.96)	5.2 (2.7)
	Anaemia	61	3.58 (2.78–4.61)	3.55 (112.12)	1.83 (1.4)	3.55 (2.76)
	Thrombocytopenia	48	4.57 (3.44–6.07)	4.54 (132.66)	2.18 (1.67)	4.54 (3.41)
	Haematotoxicity	10	10.15 (5.45–18.89)	10.13 (81.93)	3.33 (1.59)	10.09 (5.42)
	Neutropenia	204	12.78 (11.11–14.7)	12.41 (2132.56)	3.63 (3.34)	12.34 (10.73)
	Febrile neutropenia	117	16.47 (13.7–19.78)	16.18 (1656.42)	4.01 (3.56)	16.07 (13.38)
	Febrile bone marrow aplasia	18	52.81 (33.06–84.33)	52.66 (890.84)	5.68 (3.14)	51.45 (32.21)
Congenital, familial and genetic disorders	Aplasia	10	41.75 (22.32–78.08)	41.68 (389.66)	5.35 (2.26)	40.92 (21.88)
Eye disorders	Periorbital oedema	4	9.79 (3.66–26.14)	9.78 (31.39)	3.28 (0.53)	9.74 (3.65)
Gastrointestinal disorders	Enterocolitis[a]	4	6.2 (2.32–16.55)	6.2 (17.39)	2.63 (0.31)	6.18 (2.32)
	Diarrhoea	255	3.96 (3.49–4.49)	3.84 (540.28)	1.94 (1.74)	3.84 (3.38)
	Large intestine perforation[a]	5	8.23 (3.42–19.82)	8.23 (31.63)	3.04 (0.72)	8.2 (3.41)
	Enteritis[a]	9	13.65 (7.08–26.29)	13.63 (104.69)	3.76 (1.67)	13.55 (7.03)
	Gastrointestinal toxicity	8	15.98 (7.97–32.04)	15.96 (111.37)	3.99 (1.61)	15.85 (7.9)
	Colitis[a]	48	12.09 (9.1–16.08)	12.01 (482.2)	3.58 (2.87)	11.95 (8.99)
	Neutropenic colitis[a]	39	156.97 (113.33–217.42)	156.02 (5607.6)	7.19 (4.51)	145.71 (105.2)
General disorders and administration site conditions	Asthenia	108	3.17 (2.62–3.83)	3.13 (157.38)	1.65 (1.34)	3.13 (2.59)
	General physical health deterioration	44	3.54 (2.63–4.77)	3.53 (79.68)	1.82 (1.31)	3.52 (2.62)
	Death	303	3.45 (3.07–3.87)	3.33 (501.25)	1.74 (1.55)	3.33 (2.97)
	Performance status decreased	3	9.33 (3–29)	9.33 (22.2)	3.22 (0.15)	9.29 (2.99)
	Hyperthermia	5	7.71 (3.2–18.55)	7.7 (29.05)	2.94 (0.68)	7.68 (3.19)
	Mucosal inflammation	17	7.05 (4.38–11.36)	7.03 (87.74)	2.81 (1.71)	7.01 (4.35)
	Vascular device occlusion[a]	3	51.31 (16.33–161.25)	51.29 (144.54)	5.65 (0.45)	50.14 (15.95)
	Disease progression	622	55.73 (51.26–60.59)	50.44 (29520.03)	5.62 (5.39)	49.32 (45.37)
Hepatobiliary disorders	Hepatic lesion	3	6.63 (2.13–20.59)	6.62 (14.28)	2.72 (0.01)	6.61 (2.13)
	Liver disorder	16	3.89 (2.38–6.36)	3.88 (34.21)	1.96 (1.03)	3.88 (2.37)
	Cholecystitis acute[a]	3	7.61 (2.45–23.65)	7.61 (17.16)	2.92 (0.07)	7.58 (2.44)
	Hepatic cytolysis[a]	9	5.01 (2.6–9.64)	5.01 (28.79)	2.32 (0.92)	5 (2.6)
	Cholestasis[a]	11	6.28 (3.48–11.36)	6.28 (48.65)	2.65 (1.29)	6.26 (3.46)
Infections and infestations	Device related infection[a]	6	4.98 (2.23–11.09)	4.97 (19)	2.31 (0.57)	4.96 (2.23)
	Staphylococcal sepsis[a]	3	8.43 (2.71–26.21)	8.43 (19.56)	3.07 (0.11)	8.4 (2.7)
	Meningitis[a]	4	7.23 (2.71–19.29)	7.22 (21.37)	2.85 (0.39)	7.2 (2.7)
	Sepsis[a]	48	4.77 (3.59–6.34)	4.74 (141.67)	2.24 (1.72)	4.73 (3.56)

(Continued on following page)

TABLE 4 (*Continued*) Signal strength of reports associated with sacituzumab govitecan at the Preferred Terms (PTs) level in the FAERS database.

SOC	Preferred terms (PTs)	PT/N	ROR (95%CI)	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
	Septic shock[a]	39	9.64 (7.03–13.22)	9.59 (298.97)	3.26 (2.52)	9.55 (6.97)
	Enterocolitis infectious[a]	5	63.29 (26.01–154.05)	63.25 (297.71)	5.94 (1.27)	61.5 (25.27)
	Neutropenic sepsis[a]	26	38.81 (26.31–57.23)	38.65 (937.19)	5.25 (3.44)	38 (25.77)
Investigations	Weight increased	58	2.65 (2.04–3.43)	2.63 (58.85)	1.4 (0.98)	2.63 (2.03)
	Gamma-glutamyltransferase increased[a]	7	4.63 (2.2–9.72)	4.62 (19.83)	2.21 (0.65)	4.61 (2.2)
	Blood bilirubin increased[a]	9	4.65 (2.42–8.94)	4.64 (25.68)	2.21 (0.85)	4.64 (2.41)
	Weight decreased	92	3.17 (2.58–3.9)	3.14 (134.68)	1.65 (1.32)	3.14 (2.55)
	White blood cell count decreased	50	3.96 (3–5.23)	3.94 (109.57)	1.98 (1.49)	3.93 (2.98)
	Haemoglobin abnormal	6	8.47 (3.8–18.88)	8.46 (39.32)	3.08 (0.94)	8.43 (3.78)
	Heart rate increased[a]	48	5.11 (3.84–6.79)	5.08 (157.09)	2.34 (1.81)	5.07 (3.81)
	Neutrophil count decreased	76	16.4 (13.07–20.58)	16.22 (1078.04)	4.01 (3.42)	16.11 (12.84)
	General physical condition abnormal	26	25.4 (17.24–37.41)	25.3 (599.95)	4.65 (3.17)	25.02 (16.99)
	Neutrophil count abnormal	18	56.27 (35.22–89.89)	56.11 (950.01)	5.77 (3.17)	54.73 (34.26)
Metabolism and nutrition disorders	Hypokalaemia	15	3.59 (2.16–5.96)	3.59 (27.95)	1.84 (0.9)	3.58 (2.16)
	Electrolyte imbalance	9	7.6 (3.95–14.63)	7.59 (51.32)	2.92 (1.28)	7.57 (3.93)
	Cell death	9	44.62 (23.05–86.36)	44.56 (375.59)	5.45 (2.13)	43.69 (22.57)
	Weight fluctuation	93	64.3 (52.24–79.13)	63.38 (5550.43)	5.95 (4.92)	61.62 (50.07)
Nervous system disorders	Cholinergic syndrome	5	90.5 (36.98–221.43)	90.43 (424.65)	6.44 (1.3)	86.88 (35.51)
Renal and urinary disorders	Prerenal failure[a]	3	19.66 (6.31–61.3)	19.66 (52.65)	4.28 (0.34)	19.49 (6.25)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	18	3.55 (2.23–5.64)	3.54 (32.82)	1.82 (0.98)	3.54 (2.23)
	Pneumonitis	26	9.17 (6.23–13.49)	9.14 (187.67)	3.19 (2.25)	9.1 (6.19)
Skin and subcutaneous tissue disorders	Skin tightness	3	7.01 (2.26–21.78)	7.01 (15.4)	2.8 (0.04)	6.99 (2.25)
	Alopecia	86	4.37 (3.53–5.41)	4.33 (220.17)	2.11 (1.74)	4.32 (3.49)
Vascular disorders	Lymphoedema	5	6.47 (2.69–15.57)	6.47 (23.04)	2.69 (0.58)	6.45 (2.68)
	Vein collapse[a]	3	26.81 (8.58–83.72)	26.8 (73.6)	4.73 (0.39)	26.48 (8.48)

[a]Emerging off-label AEs associated with sacituzumab govitecan were identified from the FAERS, database.

Bardia et al., 2021a; Bardia et al., 2021b). Since the favorable results of single-agent SG established in the phase 2 TROPHY-U-01 (NCT03547973) trial and phase 3 TROPiCS-02 (NCT03901339) trial, the FDA has granted fast-track approval to SG for patients with locally advanced/metastatic urothelial carcinoma and unresectable locally advanced/metastatic hormone receptor-positive, HER2-negative BC (Tagawa et al., 2021; Rugo et al., 2022b). Subsequently, the clinical practice and prescriptions of SG will inevitably increase. However, safety evidence of SG was limited to clinical trials, which provide only a narrow opinion of severe or even fatal issues (Bardia et al., 2019; Bardia et al., 2021a; Bardia et al., 2021b; Xu et al., 2023). Thus, the purpose of the present study is to decipher potential AEs associated SG to guide the summary of product characteristics, and to delineate the safety spectrum of SG as a reference for clinical medication.

In the present pharmacovigilance study, as shown in Table 2, SG-related AEs were increased significantly from 2020 to 2023, with the 2022 annual report (n = 1,257) almost four times as many as in 2021 (n = 359). The main reason for the yearly increase in SG-related AE reports may be attributed to the widespread clinical application of SG and the increased awareness of healthcare professionals about post-marketing safety surveillance of drugs. Meanwhile, approximately 88.11% of the AE reports were submitted by health professionals, which might be considered a reliable reporting source. The primary serious outcome of SG is death events, which may be due to the fact that TNBC is the highest recurrence and mortality rates subtype in breast cancer with a 5-year survival 8%–16% (Li et al., 2017; Howard and Olopade, 2021), and therefore mortality events might be more closely related to disease progression.

TABLE 5 Time to onset of AEs associated with sacituzumab govitecan.

AEs	Number[a]	Median (Q1, Q3)
Diarrhoea	130	12 (7, 27)
Neutropenia	94	10.5 (6, 17)
Febrile neutropenia	88	12 (9, 13)
Asthenia	68	14 (5.75, 32.50)
Alopecia	23	6 (0.50, 48.50)
Anaemia	46	13.5 (7, 21)
White blood cell count decreased	34	12 (8, 20.50)
Thrombocytopenia	33	14 (6, 39)
Colitis	41	12 (9, 14)
Neutropenic colitis	29	12 (11,14)
Sepsis	33	12 (10, 21)
Heart rate increased	27	7 (0, 43.50)
Septic shock	30	12 (10, 14.75)
Pneumonitis	14	28 (15.25, 76.25)
Mucosal inflammation	8	11 (7, 51)
Liver disorder	10	10 (4.50, 24.25)
Hypokalaemia	12	7.5 (5.75, 8.75)
Cholestasis	10	10.5 (4.75, 18)

[a]Indicate the number of reports that record the specific time of AEs occurrence. Q1 = Quartile 1; Q3 = Quartile 3.

As described in Tables 3, 4, our disproportionality analyses suggested that the most significant SOCs for SG was congenital, familial and genetic disorders (ROR, 50.02; 95% CI, 28.21–88.68). However, at the SOC level of congenital, familial and genetic disorders, aplasia and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene mutation is the main reported PTs, which were not recorded in the specification of SG or clinical trials, and more likely to be related to the patient's development problems or incomplete documentation of AEs information (TRODELVY). Noteworthy, the ROR for PTs of UGT1A1 gene mutation is 4378.02 (396.92–48289.81) high (Supplementary Table S3), this may be one of the major reasons why the SOC signal of congenital, familial and genetic disorders is so significant. The UGT1A1 enzyme plays a crucial role in the detoxification of SN-38 by glucuronidation, and the metabolites it produces are then eliminated from the body primarily by biliary excretion (Ocean et al., 2017; Nelson et al., 2021). The results of previous studies indicated that patients with UGT1A1 homozygous*28/*28 genotype are at a higher risk of developing neutropenia while on SG therapy, and therefore patients known to have UGT1A1*28 homozygosity should be monitored closely (Bardia et al., 2021a; Rugo et al., 2021; Rugo et al., 2022a).

Besides, "investigations" and "blood and lymphatic system disorders" are also common and significant SOC associated with SG. Interestingly, the majority of PTs belonging to "investigations" were hematological AEs (e.g., white blood cell count decreased, haemoglobin abnormal, neutrophil count decreased), which were consistent with the safety results reported in the previous clinical trials (Bardia et al., 2019; Bardia et al., 2021a; Bardia et al., 2021b). In the ASCENT trials, the incidence of febrile neutropenia, leukopenia, anaemia, neutropenia was 6%, 16%, 34%, and 63%, respectively (Bardia et al., 2021b). According to the SG insert, hematotoxicity is the primary AE, which may be caused by DNA double-strand breaks and apoptosis of hematopoietic cell progenitors due to the topoisomerase inhibition payload (SN-38) of SG. However, its overall incidence and severity were much lower than those observed with irinotecan (D'Arienzo et al., 2023; Mathijssen et al., 2001). For neutropenia, granulocyte colony-stimulating factor prophylaxis can be administered to patients at high risk for febrile neutropenia or a moderate risk but with risk factors (Spring et al., 2021). If not managed properly, severe hematologic AEs may lead to complications such as bleeding and possibly secondary infections up to sepsis. Therefore, clinicians should be vigilant in the early assessment and management of SG-related hematologic toxicity.

As for SOC of metabolism and nutrition disorders, hypokalaemia, electrolyte imbalance, and weight fluctuation are the main significant PT signals (Table 4). Previous reports have shown that severe diarrhea leads to loss of body fluids and electrolytes, which can lead to electrolyte imbalance, dehydration and renal insufficiency, and malnutrition (Do et al., 2022). In addition, nausea and vomiting can also lead to systemic complications metabolic imbalances and nutrient depletion (D'Arienzo et al., 2023). Hence, metabolism and nutrition disorders may be secondary complications due to gastrointestinal

toxicity induced by SG. Based on safety results from clinical trials (Bardia et al., 2021b; Rugo et al., 2022b), diarrhea occurred in about 60% of SG-treated patients, of whom about 10% had grade 3 events, which is thought to be related to the early dissociation of the drug from its antibody (off-target off-tumor toxicity). As per FDA label and clinical guidelines (Bossi et al., 2018; Bardia et al., 2021b; TRODELVY), if a patient develops acute diarrhea or early cholinergic syndrome (abdominal cramps, diarrhea, sweating, or excessive salivation) during or shortly after the infusion, intravenous atropine 0.4 mg every 15 min for two consecutive doses as needed. If ruled negative, loperamide is recommended in standard therapy.

The most commonly reported AEs during the SG treatment in mTNBC clinical trials were diarrhea, neutropenia, leukopenia, nausea, anemia, constipation, fatigue, alopecia, and vomiting (Bardia et al., 2019; Bardia et al., 2021a; Bardia et al., 2021b; Tagawa et al., 2021). In our disproportionality analyses, the significantly reported PTs for SG were anemia, neutropenia, leukopenia, diarrhea, asthenia, alopecia, which were mostly documented in the manufacturer's labeling and clinical trials. Furthermore, no significant disproportionate signals were found for nausea, constipation, and vomiting, several frequently reported adverse effects listed in the SG insert. The reason for these discrepancies may be that AEs are fairly common for all drugs in the FAERS database. The large number of reports of AEs associated with multiple drugs may suppress the signal score. Disproportionality requires that drug-specific AEs be reported more frequently (or less frequently). Thus, the absence of a signal does not mean that there are no associated AEs; it simply indicates that these AEs do not appear to be disproportionate (Sakaeda et al., 2013).

Excitingly, as shown in Table 4, our findings also raise some uncommon safety concerns. First, we detected some rare AEs with significant signals, included periorbital oedema, febrile neutropenia, neutropenic colitis, mucosal inflammation, hepatic lesion, gamma-glutamyltransferase increased, cholinergic syndrome, pleural effusion, pneumonitis, and lymphedema, which were reported in the drug's label and clinical trials (TRODELVY). Second, we found some unexpected PTs with significant signals, including colitis, large intestine perforation, heart rate increased, cholecystitis acute, cholestasis, blood bilirubin increased, meningitis, sepsis, prerenal failure, and vein collapse.

Cardiotoxicity is a known potential AE of HER2-targeting ADC, to date, there were no reports about patients experiencing severe cardiac events related to SG treatment in clinical trials or real-world settings (Bardia et al., 2021a; Bardia et al., 2021b). However, in our disproportionality analyses, the PTs of heart rate increased showed a significant signal (n = 48, ROR = 5.11), suggesting that the risk of cardiac AEs related SG shouldn't be ignored and baseline assessment of risk factors for cardiovascular events remains crucial. On the other hand, anthracycline combined with taxane chemotherapy is the standard adjuvant treatment for TNBC, and cardiotoxicity is the main adverse reaction of anthracyclines (Lee et al., 2021). Thus, the increased heart rate may also be in part a long-term cardiac adverse effect of previous chemotherapy. Anyway, the knowledge of cardiovascular events related SG treatment is urgently needed to be further updated.

In the TROPiCS-02 phase 3 study, neutropenic colitis occurred in 0.5% of patients with hormone receptor-positive/HER2-negative advanced breast cancer, of note, one patient death was related to septic shock from SG associated neutropenic colitis (Rugo et al., 2022d). In the present disproportionality analyses, neutropenic colitis was also detected with a significant signal (n = 39, ROR = 156.97). Besides, off-labeling AEs of colitis (n = 48, ROR = 12.09) and large intestine perforation (n = 5, ROR = 8.23) were detected unexpectedly, which mostly related to the effects of the cytotoxic payload on the mucosal cells (D'Arienzo et al., 2023; Sandmeier et al., 2005). Thus, early recognition and proactive intervention of gastrointestinal toxicity is necessary because these effects can be life-threatening or lead to poor quality of life.

Furthermore, in addition to frequently elevated transaminase, the hepatobiliary toxicity of SG was mainly manifested as acute cholecystitis (ROR, 7.61; 95% CI, 2.45–23.65), cholestasis (ROR, 6.28; 95% CI, 3.48–11.36), blood bilirubin increased (ROR, 4.65; 95% CI, 2.42–8.94) in our present study, which may be related to the excretion of SG through the gallbladder (Ocean et al., 2017). Meanwhile, the meningitis (ROR, 7.23; 95% CI, 2.71–19.29), sepsis (ROR, 4.77; 95% CI, 3.59–6.34), prerenal failure (ROR, 19.66; 95% CI, 6.31–61.3), and vein collapse (ROR, 26.81; 95% CI, 8.58–83.72) were also be detected as potential AEs associated with SG treatment, which may be attributed to the effects of cytotoxic payload to mucosal cells, infection secondary to neutropenia, off-target effects, and infusion reactions, respectively (TRODELVY; D'Arienzo et al., 2023).

The results of the present study indicated that the median time to onset of SG-related AEs was 14 (IQR, 7–52) days, with the majority of AEs occurring within the first month of SG treatment (n = 533, 25.76%), and AEs might still have occurred after half a year (Tables 2, 5). Therefore, longer follow-up periods are needed to observe SG-related AEs in future clinical trials. As described in Table 5, the median onset time of boxed warning AEs, neutropenia, and diarrhea, in a real-world setting was 10.5 (IQR, 6–17) days and 12 (IQR, 7–27) days, respectively. This is similar to the median time to onset of neutropenia and diarrhea reported in the safety analyses results of the phase 3 ASCENT trial (neutropenia and diarrhea was 20 days and 12 days, respectively) (Spring et al., 2021). Taken together, these results suggested that clinicians and pharmacists should pay special attention to the labeled and potential AEs of patients, since which can be life-threatening, especially in the first half month of treatment. A better understanding of the real-world safety profile of SG in patients with mTNBC will lead to better compliance, fewer interruptions, and reflection on the desirable PFS and OS.

The main strength of this study is our ability to detect potential AEs that were not observed during the clinical trial stage for SG. As with previous studies based on pharmacovigilance databases, several limitations of the present study need to be addressed. First, due to the voluntary nature of reporting to FAERS database, the incidence and prevalence of AEs cannot be calculated, and underreporting is expected. Second, the presence of reports in the FAERS database is not causally relevant, so the results of the present study are only indicative of potential AEs, which means that clinicians and pharmacists should be vigilant. Third, multiple unmeasured confounders such as potential drug-drug interactions, comorbidities, and drug combinations, which might affect AEs, were not included in the data analysis. Besides, the disproportionality analysis neither quantified risk nor existed causality, but only estimated signal strength, which was only statistically significant. Therefore, prospective clinical trials are still required to verify their causal connection.

5 Conclusion

In conclusion, based on real-world data leveraging the FAERS, this study comprehensively investigated and identified AEs highly associated with SG by conducting disproportionality analysis. The AEs detected in the present study were generally consistent with the AEs introduced in the label, and some potential AEs, including colitis, large intestine perforation, heart rate increased, cholecystitis acute, cholestasis, blood bilirubin increased, meningitis, sepsis, prerenal failure, and vein collapse were also be revealed. Moreover, the median onset time of labeled and off-label AEs was reported here to provide vigilance reference for clinicians and pharmacists to optimize medication and manage the safety issues of SG. Given the exploratory character of our work, it is imperative to validate our findings in a prospective study and to elucidate the potential mechanisms and risk factors of AEs for improved risk management.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

WL: Data curation, Investigation, Methodology, Software, Visualization, Writing–original draft. QD: Writing–review and editing, Methodology, Supervision. ZG: Formal Analysis, Validation, Writing–review and editing. XY: Writing–review and editing, Formal Analysis, Validation. JL: Conceptualization, Supervision, Writing–review and editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1283247/full#supplementary-material

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A real-world pharmacovigilance study of mepolizumab in the FDA adverse event reporting system (FAERS) database

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Mepolizumab is primarily used in the treatment of asthma, eosinophilic granulomatosis with polyangiitis, eosinophilia syndrome, and chronic rhinitis with nasal polyps. The information about its adverse drug reactions is mainly derived from clinical trials, and there is a shortage of real-world studies with extensive sample sizes. In this study, the U.S. FDA's Adverse Event Reporting System (FAERS) database was analyzed to evaluate the side effects of mepolizumab. A total of 18,040 reports of mepolizumab-associated adverse events were identified from the FDA Adverse Event Reporting System database. Multiple disproportionality analysis algorithms were used to determine the significance of these AEs. The study identified 198 instances of mepolizumab-induced AEs, including some important AEs not mentioned in the product labeling. The time to onset of adverse reactions was also analyzed, with a median time of 109 days. Most AEs occurred within the first month of mepolizumab use, but some may still occur after 1 year of treatment. Gender-specific analysis showed different high-risk AEs for females (digestive and neurological side effects) and males (serious adverse effects leading to hospitalization and death). The findings mentioned provide valuable insights on optimizing the use of mepolizumab, enhancing its effectiveness, and minimizing potential side effects. This information will greatly contribute to the practical implementation of the drug in clinical settings.

KEYWORDS

mepolizumab, adverse drug event, FAERS, real-world study, asthma

1 Introduction

Asthma, a long-term inflammatory condition of the respiratory passages, is characterized by indications like coughing, wheezing, difficulty breathing, and tightness in the chest (Hammad and Lambrecht, 2021). It has a global impact, affecting approximately 300 million individuals of diverse ages and ethnic backgrounds, and tragically causing around 250,000 deaths annually. When individuals with asthma continue to experience uncontrolled symptoms despite receiving appropriate treatment, they are now recognized as having severe asthma, which imposes a significant financial burden on healthcare providers. As per the guidelines established by the European Respiratory Society (ERS) and the American Thoracic Society, severe asthma is characterized as asthma that necessitates the use of high-dose corticosteroid medication, along with another controller, to attain control, or asthma that persists uncontrolled despite this treatment (Chung et al., 2014). Approximately 5%–10% of asthma patients are believed to suffer

from severe asthma, which places a significant burden on healthcare resources (Schoettler and Mary, 2020).

Eosinophilic inflammation in the airways is closely linked to the severity of asthma, with tissue and blood eosinophil counts directly influencing the frequency of asthma attacks and the risk of irreversible airway obstruction (Khalfaoui et al., 2022). The development, maturation, and survival of eosinophils in tissues are closely linked to disease severity and airway eosinophilia, with Interleukin-5 (IL-5) playing a vital role (Hassani and Koenderman, 2018). To target IL-5, a significant driver of eosinophilic inflammation, mepolizumab, a humanized monoclonal anti-IL-5 antibody, has been developed. The FDA has approved this medication as an additional maintenance treatment for severe asthma in patients aged 12 years and older, effectively decreasing blood eosinophil counts (approved by the FDA in November 2015) (Castillo et al., 2017). Mepolizumab has been approved in different parts of the world for treating eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and chronic rhinosinusitis with nasal polyps (Pavord et al., 2022). Numerous randomized controlled experiments have shown that mepolizumab is a viable and easily tolerated choice for treatment. Studies have demonstrated that it decreases the occurrence of asthma flare-ups in individuals suffering from severe eosinophilic asthma, resulting in better management of symptoms and improved overall quality of life (Pavord et al., 2012; Ortega et al., 2014). Furthermore, mepolizumab has demonstrated the ability to decrease the size of polyps and relieve nasal blockage in individuals with chronic rhinosinusitis accompanied by nasal polyps, irrespective of the presence of asthma or Aspirin-exacerbated respiratory disease (Roufosse et al., 2020).

Despite the extensive use of mepolizumab in clinical settings, there has been a gradual increase in reports of related adverse events (AEs) (Corren, 2019; Aldajani et al., 2022). Injection site reactions, diarrhea, pruritus, headache, gastrointestinal disorders, musculoskeletal disorders, nasopharyngitis, sinusitis, bronchitis, and upper respiratory tract infections were frequently reported as treatment-emergent adverse events in phase II and phase III clinical trials of mepolizumab. Several severe adverse events were documented, such as deterioration of symptoms related to hypereosinophilic syndrome, infection caused by M.abscessus, eosinophilic gastroenteritis, and peripheral T-cell lymphoma. This information was reported by F. Roufosse et al. in a phase III, randomized, placebo-controlled trial assessing the efficacy and safety of mepolizumab in hypereosinophilic syndrome (Gleich et al., 2021). Nevertheless, the effectiveness and safety information for mepolizumab over an extended period has primarily been documented through case reports, clinical trials, and meta-analyses (Henriksen et al., 2018; Domingo Ribas et al., 2021). The research has concentrated on particular systems or included relatively limited sample sizes and specific criteria for selection. As a result, comprehensive safety data from large samples and real-world cohorts are currently lacking. To assess the safety of mepolizumab in real-world scenarios, this pharmacovigilance analysis was performed due to the extensive clinical utilization and the necessity for adverse event evaluations.

The FAERS database, which is open to the public, is a spontaneous reporting system (SRS) that contains a wide range of case reports documenting adverse drug events. These reports are submitted by healthcare professionals, pharmacists, manufacturers, and other individuals(Yu et al., 2021). FAERS, being the biggest worldwide pharmacovigilance repository, functions as a valuable resource for detecting adverse events linked to drug usage(Fusaroli et al., 2022). The aim of this research was to assess the AEs of mepolizumab by analyzing post-marketing data from FAERS. Our main objective in these findings is to offer valuable perspectives for clinical surveillance and the detection of possible hazards linked to mepolizumab.

2 Materials and methods

2.1 Data source

FAERS, also known as the FDA Adverse Event Reporting System, is a comprehensive database where adverse event reports, prescription errors, and complaints regarding product quality that have led to AEs are stored. More information about FAERS can be found at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers. The database aids in the FDA's monitoring of the safety of pharmaceutical and therapeutic biologic products after they have been approved for marketing. The FAERS database consists of seven datasets that cover different types of data, including patient demographic and administrative information (DEMO), drug information (DRUG), adverse event coding (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start and end dates for reported drugs (THER), and indications for drug administration (INDI).

The research included the examination of AEs information associated with mepolizumab, which was acquired from the FAERS database. Data extraction was performed from the fourth quarter of 2015 (2015 Q4) through the first quarter of 2023 (2023 Q1). The Statistical Analysis System (SAS) 9.4 was utilized for data gathering and preprocessing. Initially, the FAERS database yielded a grand total of 12,691,282 reports. Nevertheless, because of the regular updates of the database, it became imperative to reanalyze the data to remove any redundant instances of previous public reports. Before conducting statistical analysis, a deduplication procedure was carried out in accordance with the guidelines provided by the FDA. To accomplish this, the most recent FDA_DT was chosen when the CASEID values were identical, and the PRIMARYID with a higher value was selected when both CASEID and FDA_DT were a match (Shu et al., 2022a; Shu et al., 2022b). After going through this deduplication procedure, incomplete, incorrect, and duplicate reports were excluded and the total count of reports decreased to 10,773,842. Both the trademarks and generic names were utilized to identify records associated with etoposide. The search involved the use of 'Mepolizumab' and 'NUCALA' in this particular study. The drugs reported in FAERS were categorized into four modalities: PS (primary suspect), SS (second suspect), C (concomitant), and I (interacting). To enhance the precision of the analyses and eliminate the influence of concurrent medications, the AEs role code was preserved exclusively for instances where the PS drug was identified as 'mepolizumab' (Zhang et al., 2023). The highest level of terminology used for coding all AEs in the report is the System Organ Class (SOC) based on the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). We screened a grand total of 63,047 terms related to mepolizumab, which were categorized as preferred terms (PTs). During the period of this research, we identified totally 18,040 AEs reports of etoposide as the PS drug. To reduce confounding, in the disproportionality analysis at PT level, we removed PTs associated with the mepolizumab indication (Tang et al., 2022). Figure 1 displays the flow chart of the investigation.

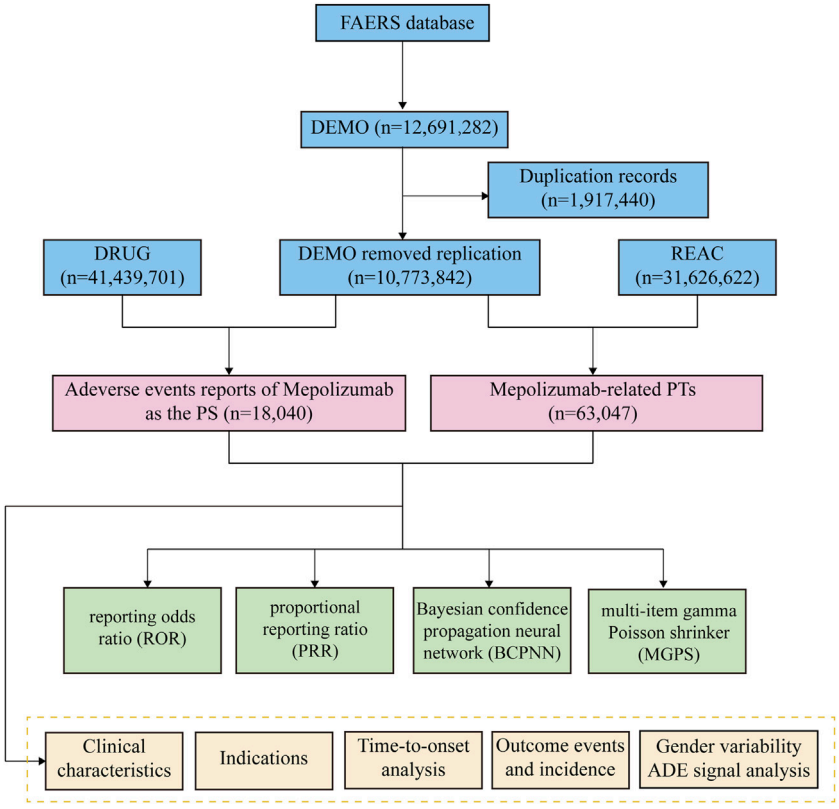

FIGURE 1
The process of selecting mepolizumab-associated AEs from FAERS database.

2.2 Statistical analysis

Disproportionate analysis is a tool for hypothesizing possible causal relationships between drugs and adverse reactions, with subsequent clinical assessment of underlying case reports (Caster et al., 2020). It is based on a comparison of the observed and expected number of reports for any given combination of drug and adverse event and is often recommended for vigilance analyses of adverse drug reactions in large spontaneous reporting databases (Montastruc et al., 2011). Reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN) and Multi-item gamma Poisson shrinker (MGPS) are common algorithms for disproportionality analysis and are currently widely used by the Healthcare Products Regulatory Agency (MHRA), the Netherlands Pharmacovigilance Centre, the World Health Organization (WHO) and the FDA (Sakaeda et al., 2013). The ROR and PRR algorithms are frequentist (non-Bayesian) algorithms, and the advantage of ROR is that it corrects for bias due to the low number of reports of certain events compared to PRR (Rothman et al., 2004). The advantage of PRR over ROR is that it is less affected by omission of adverse events (Evans et al., 2001). In conclusion, the non-Bayesian method (frequency method) is simple to calculate and has high sensitivity, but when the number of adverse events is small, the likelihood of false positives is high (Wu et al., 2023). BCPNN and MGPS algorithms are Bayesian algorithms. BCPNN is excellent in integrating data from multiple sources and cross validation, MGPS has the advantage that it is able to detect signals from rare events (Bate et al., 1998; Kubota et al., 2004). The Bayesian approach is stable. It accounts for the uncertainty in the disproportionate rate when the reports are small, reduces the likelihood of false positives, and is used for pattern recognition in higher dimensions, but it is computationally complex and has a relatively lagged signal detection time (Tang et al., 2022). Therefore, this study adopts the joint use of multiple algorithms, makes reasonable use of the advantages of different algorithms, expands the detection range, and verifies the results from multiple perspectives in order to detect more comprehensive and reliable safety signals (Sakaeda et al., 2013; Noguchi et al., 2018; Zhou et al., 2023). PTs with reported counts ≥3 were selected for the initial screening in this study (Jiang et al., 2023). The signal detection thresholds for each algorithm are set according to authoritative methods (Bate et al., 1998; Evans et al., 2001; Szarfman et al., 2002; van Puijenbroek et al., 2002), and the specific formulas and thresholds are detailed in Table 1.

Additionally, the time to onset (TTO) of mepolizumab-induced AEs was defined as the interval between EVENT_DT (date of onset of AEs, in the DEMO file) and START_DT (date of initiation of mepolizumab, in the THER file). Deleted data include inaccurate or missing date inputs and EVENT_DT being earlier than START_DT.

Microsoft EXCEL 2019, SAS 9.4 (2013; SAS Institute Inc., Cary, North Carolina, United States), R software (version 4.2.1) are primarily employed for data processing and analysis. We used the "ggplot2" package in the R software for data visualization.

TABLE 1 The specific formulas for the four algorithms are as follows. Notes: Equation: a, number of reports containing both the target drug and the target adverse drug reaction; b, number of reports containing other adverse drug reactions of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. The MGPS employs an empirical Bayesian approach, whereby a prior distribution is obtained by maximum likelihood estimates, and the prior and likelihood are subsequently combined to obtain a posterior distribution. The fifth percentile of the posterior distribution is denoted by "EBGM05" and is interpreted as the one-sided 95% confidence lower bound for the EBGM. Abbreviations: 95% CI, 95% confidence interval; N, the number of reports; χ2, chi-squared; IC, information component; IC025, the lower limit of the 95% CI of the IC; E (IC), the IC expectations; V (IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, empirical Bayesian geometric mean lower 95% CI for the posterior distribution.

Algorithms	Equation	Criteria
ROR	ROR = ad/bc	Lower limit of 95% CI > 1, N ≥ 3
	95%CI = $e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)\hat{}0.5}$	
PRR	PRR = [a(c+d)]/[c(a+b)]	PRR ≥ 2, χ^2 ≥ 4, N ≥ 3
	χ^2 = [(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	
BCPNN	IC = $\log_2$a(a+b+c+d)/[(a+c)(a+b)]	IC025 > 0
	95%CI = E(IC) ± 2[V(IC)]^0.5	
MGPS	EBGM = a(a+b+c+d)/[(a+c)(a+b)]	EBGM05 > 2
	95%CI = $e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)\hat{}0.5}$	

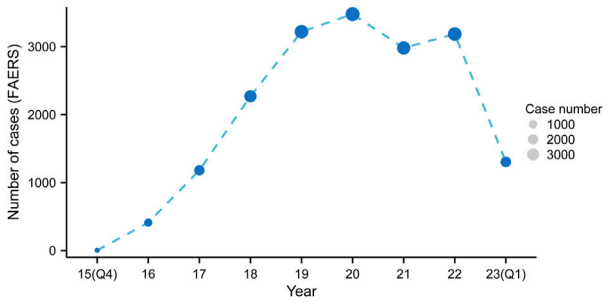

FIGURE 2
The annual distribution of mepolizumab-related AEs reports from 2015 to 2023.

3 Results

3.1 Descriptive analysis

Upon eliminating duplicates, a grand total of 18,040 adverse event reports were discovered, wherein mepolizumab was classified as the primary suspect drug. These reports corresponded to a collection of 63,047 mepolizumab-related preferred terms (PTs) (Figure 1). From 2015 to 2022, there was a steady rise in the reporting of AEs associated with mepolizumab, with the latest available information being the data for the first quarter of 2023 (Figure 2).

The AEs reported for mepolizumab are presented in Table 2, showcasing their characteristics. The largest proportion of reports (1.51%) originated from the elderly population (aged >64 years), while females (55.76%) accounted for a higher proportion compared to males (26.21%). The majority of reported weights were around 80 kg (3.94%). The majority of reports (73.69%) were provided by consumers, with health professionals accounting for around a quarter of the submissions (25.14%). In terms of geography, America had the largest percentage of reports (53.92%), with Canada (27.31%), Japan (2.87%), the United Kingdom (2.68%), and Australia (2.54%) following closely behind. Among the reported outcomes, serious outcomes (56.38%) were the most frequently documented, followed by hospitalization (34.18%) and death (7.55%). In 25.66% of cases, the utilization of Mepolizumab for unspecified purposes was documented, with asthma (64.72%) being the most frequently reported indication.

3.2 Signal of system organ class

Table 3 presents the signal intensities of mepolizumab-associated AEs categorized by SOCs. A total of 27 organ systems were impacted by adverse events associated with mepolizumab, as indicated by our statistical analysis. Among these, several significant SOCs were identified based on meeting the criteria of at least one of the four indices used for analysis. The significant SOCs included respiratory, thoracic, and mediastinal disorders (case = 12,574, ROR 5.20[95%CI 5.10–5.30]); general disorders and administration site conditions (case = 11,309, ROR 1.01[95%CI 0.99–1.03]); injury, poisoning, and procedural complications (case = 8,185, ROR 1.16[95%CI 1.13–1.19]); infections and infestations (case = 6,366, ROR 1.97[95%CI 1.92–2.02]); surgical and medical procedures (case = 1726, ROR 2.06[95%CI 1.96–2.16]); immune system disorders (case = 894, ROR 1.17[95% CI 1.10–1.25]); and social circumstances(case = 752, ROR 2.66[95%CI 2.47–2.86]). These findings highlight the specific organ systems where mepolizumab-induced AEs were most frequently reported and indicate areas that warrant further attention and investigation.

3.3 Signal of preferred terms and subgroup analysis

All the four algorithms combined identified a total of 198 cases of AEs caused by mepolizumab, encompassing 20 System Organ Classes (SOCs) as shown in Supplementary Table S1. Table 4 presents a summary of reported PTs with a minimum of 20 occurrences. This table includes 63 PTs, corresponding to 11 SOCs. Importantly, our data mining revealed several significant AEs that were not explicitly mentioned in the mepolizumab product label. The unexpected AEs consist of PTs such as discharge of fluids, nonspecific response, recurrence of symptoms, discomfort in the chest, incomplete

TABLE 2 Clinical characteristics of reports with mepolizumab from the FAERS database.

Characteristics	Case number, n	Case Proportion, %
Number of events	18,040	
Age		
<18	6	0.03
18–64	187	1.04
>64	273	1.51
Unknown	17,574	97.42
Gender		
Female	10,060	55.76
Male	4,728	26.21
Unknown	3,252	18.03
Weight		
<80	710	3.94
80–100	363	2.01
>100	220	1.22
Unknown	16,747	92.83
Reported Person		
Health professional	4,536	25.14
Consumer	13,295	73.69
Unknown	209	11.57
Reported Countries (top five)		
America	9,728	53.92
Canada	4,927	27.31
Japan	517	2.87
United Kiongdom	483	2.68
Australia	458	2.54
Serious Outcomes	n = 14,110	
Death (DE)	1,066	7.55
Life-threatening (LF)	152	1.08
Hospitalization (HO)	4,823	34.18
Disability (DS)	106	0.75
Other serious outcomes	7,955	56.38
Unknown	8	0.06
Indications (top five)		
Asthma	11,676	64.72
Product used for unknown indication	4,665	25.86
Eosinophilic granulomatosis with polyangiitis	542	3.00
Hypereosinophilic syndrome	121	0.67
Nasal polyps	89	0.49

(Continued in next column)

effectiveness of the therapeutic product, multiple allergies, infected sputum, COVID-19 infection, pneumonia, chronic inflammation of the sinuses, inflammation of the nasal passages, infection caused by *pseudomonas*, suspected COVID-19, exposure through contact with the skin, accidental exposure to the product, issue of missing product dose, inadequate dosage, reduced peak expiratory flow rate, abnormal count of eosinophils, increased level of immunoglobulin E in the blood, abnormal breathing sounds, abnormal oxygen saturation, reduced results of pulmonary function tests, abnormal complete blood count, increased respiratory rate, loss of sense of smell, sleep disorder due to a general medical condition, severe asthma attack, discolored sputum, congestion in the lungs, increased production of sputum, pain in the lungs, cough syndrome in the upper airways, sensation of choking, chronic obstructive pulmonary disease (COPD), congestion in the sinuses, disorder in the sinuses, abnormal lung sounds, loss of independence in daily activities, isolation of the patient, quarantine, sinus surgery, emergency medical care, hospitalization, and cataract surgery. Our analysis has identified additional AEs that emphasize and enhance the overall comprehension of mepolizumab's safety profile.

We then conducted subgroup analyses, which can to some extent reduce the confounding of the results by demographic characteristics (de Vries et al., 2020). Among the two subgroups aged 18–64 and >64 years, the PT with the highest number of reported cases was product dose omission issue (subgroup ages <18 was exclude because of insufficient case reports). Additionally, when analyzing the top 15 reported AEs in each subgroup, we found that signals reported only among 18–64 subgroup included "condition aggravated", "urticaria", "chest pain", "device use error", and "sinusitis". On the other hand, "malaise", "cough", "Inappropriate schedule of product administration", "wheezing", and "blood pressure increased" appeared to be more common in ages>64 subgroup (Supplementary Figure S1).

Similarly, subgroup analyses were performed for gender (Supplementary Figure S2), weight (Supplementary Figure S3), and reported person (Supplementary Figure S4) to analyze and compare similarities and differences in signals across subgroups. This information is essential for more refined clinical management, guiding clinical decision makers to adjust treatments based on the characteristics of specific subgroups.

3.4 Time to onset of mepolizumab-associated adverse events

The provided database furnished us with data concerning the initiation periods of adverse events associated with mepolizumab. Out of all the reported adverse events, a grand

TABLE 3 Signal strength of reports of mepolizumab at the System Organ Class (SOC) level in FAERS database. Notes: Red are those that follow the algorithm.

System Organ Class (SOC)	Case Numbers	ROR (95% Two-Sided CI)	PRR	χ2	IC (IC025)	EBGM(EBGM05)
Respiratory, thoracic and mediastinal disorders	12,574	5.20(5.10–5.30)	4.36	33,876.31	2.12(0.45)	4.33(4.26)
General disorders and administration site conditions	11,309	1.01(0.99–1.03)	1.01	1.09	0.01(−1.65)	1.01(0.99)
Injury, poisoning and procedural complications	8,185	1.16(1.13–1.19)	1.14	153.85	0.19(−1.48)	1.14(1.12)
Infections and infestations	6,366	1.97(1.92–2.02)	1.87	2714.94	0.90(−0.77)	1.87(1.83)
Nervous system disorders	3,432	0.68(0.66–0.70)	0.7	489.38	−0.52(−2.19)	0.70(0.68)
Musculoskeletal and connective tissue disorders	3,034	0.92(0.88–0.95)	0.92	22.73	−0.12(−1.79)	0.92(0.89)
Investigations	2,525	0.67(0.64–0.70)	0.68	398.91	−0.55(−2.22)	0.68(0.66)
Skin and subcutaneous tissue disorders	2,482	0.67(0.65–0.70)	0.69	374.6	−0.54(−2.21)	0.69(0.66)
Gastrointestinal disorders	2369	0.43(0.41–0.45)	0.45	1715.95	−1.14(−2.81)	0.45(0.44)
Surgical and medical procedures	1726	2.06(1.96–2.16)	2.03	912.07	1.02(−0.65)	2.03(1.95)
Psychiatric disorders	1,360	0.39(0.37–0.41)	0.40	1264.2	−1.31(−2.97)	0.40(0.39)
Cardiac disorders	971	0.74(0.70–0.79)	0.75	86.09	−0.42(−2.09)	0.75(0.71)
Immune system disorders	894	1.17(1.10–1.25)	1.17	22.74	0.23(−1.44)	1.17(1.11)
Product issues	888	0.82(0.77–0.88)	0.83	32.99	−0.27(−1.94)	0.83(0.78)
Eye disorders	790	0.65(0.60–0.69)	0.65	151.4	−0.62(−2.29)	0.65(0.61)
Social circumstances	752	2.66(2.47–2.86)	2.64	765.33	1.40(−0.27)	2.63(2.48)
Vascular disorders	740	0.60(0.56–0.64)	0.6	196.54	−0.73(−2.39)	0.60(0.57)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	679	0.32(0.30–0.35)	0.33	958.4	−1.60(−3.27)	0.33(0.31)
Metabolism and nutrition disorders	536	0.41(0.38–0.45)	0.42	439.58	−1.25(−2.92)	0.42(0.39)
Renal and urinary disorders	419	0.32(0.29–0.36)	0.33	591.42	−1.61(−3.28)	0.33(0.30)
Blood and lymphatic system disorders	260	0.25(0.22–0.29)	0.26	567.39	−1.96(−3.62)	0.26(0.23)
Ear and labyrinth disorders	238	0.86(0.76–0.98)	0.87	4.99	−0.21(−1.87)	0.87(0.78)
Hepatobiliary disorders	153	0.30(0.26–0.35)	0.30	250.67	−1.73(−3.40)	0.30(0.26)
Reproductive system and breast disorders	143	0.29(0.25–0.34)	0.29	247.74	−1.78(−3.44)	0.29(0.25)
Endocrine disorders	119	0.73(0.61–0.88)	0.73	11.56	−0.45(−2.11)	0.73(0.63)
Congenital, familial and genetic disorders	58	0.34(0.26–0.44)	0.34	74.05	−1.55(−3.22)	0.34(0.28)
Pregnancy, puerperium and perinatal conditions	45	0.18(0.13–0.24)	0.18	168.85	−2.47(−4.14)	0.18(0.14)

total of 3,263 included comprehensive and precise details regarding the time of occurrence. The AEs had a median onset time of 109 days, with an IQR of 7–469 days. In Figure 3, it can be seen that most AEs (1,134 or 34.75%) happened within the initial month of mepolizumab usage, as shown by the distribution of AE onset times. AEs were least likely to occur during the second to third month of treatment, with rates of 7.88% and 5% respectively, but significantly rose afterwards. Significantly, our data revealed that a considerable 30.95% of AEs remained possible following a year of mepolizumab treatment. These findings emphasize the importance of monitoring patients for potential AEs throughout the course of mepolizumab therapy, even beyond the initial months.

3.5 Signal of preferred terms gender difference risk

Females who have symptoms like queasiness, diarrhea, throwing up, exhaustion, discomfort, infection site discomfort, chest uneasiness, flu-like sickness, walking difficulty, flu, bronchitis, urinary tract infection, exposure through skin contact, back discomfort, muscle pain, muscle cramp, head pain, cough,

TABLE 4 Signal strength of reports of mepolizumab at the PT level in the FAERS database. Notes: *, AEs that are not mentioned in the drug label. PT, Preferred Terms.

SOC Name	Preferred terms (PTs)	Case Numbers	ROR(95%CI)	PRR	χ2	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	Secretion discharge*	117	8.43(7.02–10.12)	8.41	751.95	3.05(1.39)	8.29(7.12)
	Nonspecific reaction*	27	5.89(4.03–8.60)	5.88	108.21	2.54(0.88)	5.83(4.24)
	Symptom recurrence*	31	5.44(3.82–7.75)	5.44	111.08	2.43(0.76)	5.39(4.01)
	Ill-defined disorder	219	4.48(3.92–5.12)	4.47	584.14	2.15(0.48)	4.43(3.97)
	Chest discomfort*	411	4.23(3.84–4.66)	4.21	998.29	2.06(0.40)	4.18(3.85)
	Therapeutic product effect incomplete*	510	3.33(3.05–3.64)	3.31	820.21	1.72(0.06)	3.30(3.07)
	Polyp	23	3.24(2.15–4.89)	3.24	35.43	1.69(0.02)	3.23(2.29)
Immune system disorders	Multiple allergies*	46	5.60(4.19–7.49)	5.6	171.7	2.47(0.80)	5.54(4.35)
Infections and infestations	Sputum purulent*	29	40.12(27.48–58.58)	40.11	1023.8	5.22(3.55)	37.21(27.11)
	Coronavirus infection*	78	7.16(5.72–8.95)	7.15	406.92	2.82(1.15)	7.06(5.86)
	Respiratory tract infection	158	5.88(5.02–6.88)	5.87	630.69	2.54(0.87)	5.81(5.09)
	Pneumonia*	1,654	4.90(4.67–5.15)	4.8	4957.5	2.25(0.59)	4.76(4.57)
	Chronic sinusitis*	25	6.40(4.32–9.50)	6.4	112.52	2.66(1.00)	6.33(4.55)
	Herpes zoster	266	4.27(3.79–4.82)	4.26	658.64	2.08(0.42)	4.23(3.83)
	Lower respiratory tract infection	203	4.03(3.51–4.63)	4.02	457.34	2.00(0.33)	4.00(3.56)
	Rhinitis*	37	4.45(3.22–6.16)	4.45	98.16	2.14(0.48)	4.42(3.37)
	Pseudomonas infection*	33	4.23(3.00–5.96)	4.23	80.64	2.07(0.40)	4.20(3.15)
	Suspected COVID-19*	24	3.95(2.64–5.90)	3.95	52.43	1.97(0.31)	3.93(2.80)
	Viral upper respiratory tract infection	27	3.67(2.51–5.35)	3.67	51.95	1.87(0.20)	3.65(2.66)
Injury, poisoning and procedural complications	Exposure via skin contact*	600	151.10(137.88–165.58)	149.67	68,217.54	6.85(5.18)	115.45(106.94)
	Wrong technique in device usage process	560	10.41(9.57–11.32)	10.33	4625.01	3.34(1.68)	10.14(9.45)
	Accidental exposure to product*	578	5.73(5.27–6.22)	5.68	2209.48	2.49(0.83)	5.63(5.26)
	Product dose omission issue*	2170	3.67(3.52–3.84)	3.58	4050.28	1.83(0.17)	3.56(3.44)
	Product preparation issue	30	4.59(3.20–6.57)	4.59	83.41	2.19(0.52)	4.55(3.37)
	Underdose*	306	3.35(2.99–3.74)	3.33	497.49	1.73(0.06)	3.32(3.02)
Investigations	Peak expiratory flow rate decreased*	22	57.99(37.29–90.17)	57.97	1103.87	5.70(4.02)	52.06(35.98)
	Eosinophil count abnormal*	31	33.11(23.02–47.62)	33.09	904.96	4.96(3.29)	31.10(22.94)
	Coronavirus test positive*	51	29.57(22.30–39.23)	29.55	1328.47	4.81(3.14)	27.96(22.07)
	Eosinophil count decreased*	41	23.91(17.48–32.71)	23.9	858.47	4.51(2.85)	22.85(17.58)
	Blood immunoglobulin E increased*	36	13.26(9.52–18.46)	13.25	397.29	3.69(2.03)	12.94(9.81)
	Breath sounds abnormal*	47	9.50(7.12–12.68)	9.5	350.62	3.22(1.56)	9.34(7.33)
	Oxygen saturation abnormal*	24	7.49(5.00–11.21)	7.49	132.89	2.89(1.22)	7.39(5.27)
	Pulmonary function test decreased*	31	5.51(3.86–7.84)	5.5	113.01	2.45(0.78)	5.45(4.06)
	Full blood count abnormal*	173	4.62(3.98–5.37)	4.61	484.74	2.19(0.53)	4.58(4.04)

(Continued on following page)

TABLE 4 (*Continued*) Signal strength of reports of mepolizumab at the PT level in the FAERS database. Notes: *, AEs that are not mentioned in the drug label. PT, Preferred Terms.

SOC Name	Preferred terms (PTs)	Case Numbers	ROR(95%CI)	PRR	$\chi 2$	IC (IC025)	EBGM (EBGM05)
	Respiratory rate increased*	26	3.34(2.27–4.92)	3.34	42.37	1.73(0.07)	3.33(2.41)
Nervous system disorders Product issues	Anosmia*	35	3.38(2.42–4.71)	3.37	58.11	1.75(0.08)	3.36(2.54)
	Product complaint	646	23.12(21.36–25.03)	22.89	12,940.72	4.46(2.79)	21.94(20.53)
	Product availability issue	74	3.42(2.72–4.29)	3.41	125.38	1.76(0.10)	3.40(2.80)
Psychiatric disorders	Sleep disorder due to a general medical condition*	282	19.56(17.36–22.04)	19.48	4758.68	4.23(2.57)	18.78(17.00)
Respiratory, thoracic and mediastinal disorders	Asthmatic crisis*	474	114.39(103.51–126.43)	113.54	43,103.42	6.54(4.87)	92.74(85.29)
	Sputum discoloured*	203	18.03(15.67–20.74)	17.97	3141.96	4.12(2.45)	17.39(15.46)
	Pulmonary congestion*	97	8.51(6.97–10.41)	8.5	631.61	3.07(1.40)	8.38(7.08)
	Sputum increased*	21	8.87(5.76–13.65)	8.86	143.98	3.13(1.46)	8.73(6.08)
	Pulmonary pain*	30	7.90(5.51–11.34)	7.9	178.02	2.96(1.30)	7.79(5.76)
	Nasal congestion	248	4.17(3.68–4.73)	4.16	590.46	2.05(0.38)	4.13(3.72)
	Upper-airway cough syndrome*	43	4.63(3.43–6.25)	4.63	121.21	2.20(0.53)	4.60(3.57)
	Choking sensation*	24	4.63(3.10–6.92)	4.63	67.61	2.20(0.53)	4.59(3.28)
	Chronic obstructive pulmonary disease*	186	3.71(3.21–4.28)	3.7	364.1	1.88(0.21)	3.68(3.26)
	Sinus congestion*	49	3.91(2.95–5.18)	3.91	105.18	1.96(0.29)	3.88(3.07)
	Sinus disorder*	76	3.53(2.82–4.42)	3.53	136.7	1.81(0.15)	3.51(2.91)
	Rales*	23	3.98(2.64–5.99)	3.97	50.81	1.98(0.32)	3.95(2.80)
	Oropharyngeal discomfort	35	3.63(2.60–5.06)	3.63	66.1	1.85(0.18)	3.61(2.73)
	Dyspnoea	2,490	4.60(4.42–4.79)	4.46	6,680.8	2.15(0.48)	4.43(4.28)
	Rhinitis allergic	21	5.10(3.32–7.84)	5.1	68.55	2.34(0.67)	5.06(3.53)
	Bronchospasm	93	7.51(6.12–9.22)	7.5	516.58	2.89(1.22)	7.41(6.24)
Social circumstances	Social problem	116	33.06(27.39–39.89)	33	3376.76	4.96(3.29)	31.02(26.50)
	Loss of personal independence in daily activities*	472	6.06(5.53–6.64)	6.02	1954.58	2.58(0.91)	5.96(5.52)
Surgical and medical procedures	Patient isolation*	28	76.63(51.48–114.07)	76.6	1811.94	6.06(4.38)	66.57(47.72)
	Quarantine*	23	60.95(39.53–93.96)	60.92	1208.56	5.77(4.09)	54.42(37.88)
	Sinus operation*	45	19.22(14.27–25.89)	19.21	747.95	4.21(2.54)	18.53(14.45)
	Emergency care*	21	6.21(4.04–9.55)	6.21	90.6	2.62(0.95)	6.14(4.28)
	Hospitalisation*	614	3.53(3.26–3.82)	3.5	1093.89	1.80(0.14)	3.49(3.26)
	Cataract operation*	20	3.95(2.54–6.13)	3.95	43.63	1.97(0.30)	3.92(2.71)

asthma attack, throat pain, itching, and more, were found to have high-risk signals during the signal detection analysis conducted at the PT level. In contrast, males had high-risk indicators that encompassed drug inefficacy, inadequate therapeutic outcomes, death, chest discomfort, lung infection, unapproved usage, difficulty breathing, and admission to the hospital (Figure 4).

In order to examine gender disparities in the findings of adverse event signal mining for mepolizumab, a visual representation known as a 'volcano map' was employed. The volcano map uses the -Log10*p*-value scale on the vertical axis and the Log2ROR value scale on the horizontal axis. Every point on the map indicates a pairing of the medication and negative reaction. Pink dots indicate potential adverse event signals in female patients, while green dots indicate potential adverse event signals in male patients. Furthermore, Figure 5 highlights significant adverse event signals that exhibit noteworthy Log2ROR and -Log10*p* values. The visual

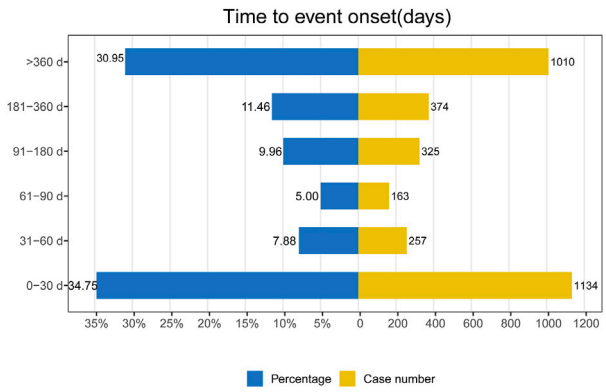

FIGURE 3
Time to onset of mepolizumab-related AEs.

depictions offer valuable information on potential adverse event signals specific to gender related to mepolizumab, emphasizing the variations in reported AEs among males and females.

4 Discussion

Due to the scarcity of preclinical data, it is essential to gather pharmacovigilance data from post-marketing systems that report adverse events, which would greatly enhance drug specifications. Furthermore, it should be emphasized that information obtained from clinical trials may not precisely depict the actual circumstances in the real world, which encompasses a wide range of patients and comorbidities. The examination showed a consistent rise in the quantity of documented adverse events in recent times (Figure 2), possibly as a result of the increasing utilization of mepolizumab. The results highlight the significance of ongoing surveillance for adverse events. Based on our current understanding, this study on adverse events related to mepolizumab using the FAERS database is the most extensive pharmacovigilance investigation. It offers a comprehensive and methodical overview of worldwide reports regarding mepolizumab-associated adverse events in FAERS.

Based on the information from the baseline profile, it was observed that females (55.76%) experienced a higher occurrence of negative responses to mepolizumab in comparison to males (26.21%), which is

SOC	PT	Female/Male	ROR (95% CI)
Gastrointestinal disorders	Nausea	239/46	2.32(1.69–3.19)
Gastrointestinal disorders	Diarrhoea	153/40	1.71(1.20–2.42)
Gastrointestinal disorders	Vomiting	138/40	1.54(1.08–2.19)
General disorders and administration site conditions	Drug Ineffective	660/353	0.83(0.73–0.95)
General disorders and administration site conditions	Fatigue	599/218	1.23(1.05–1.44)
General disorders and administration site conditions	Malaise	559/180	1.39(1.17–1.65)
General disorders and administration site conditions	Pain	324/112	1.29(1.04–1.60)
General disorders and administration site conditions	Injection Site Pain	271/69	1.76(1.35–2.29)
General disorders and administration site conditions	Therapeutic Product Effect Incomplete	257/186	0.61(0.51–0.74)
General disorders and administration site conditions	Chest Discomfort	255/83	1.37(1.07–1.76)
General disorders and administration site conditions	Death	251/258	0.43(0.36–0.51)
General disorders and administration site conditions	Chest Pain	126/76	0.74(0.55–0.98)
General disorders and administration site conditions	Influenza Like Illness	102/27	1.69(1.10–2.58)
General disorders and administration site conditions	Illness	99/25	1.77(1.14–2.74)
General disorders and administration site conditions	Gait Disturbance	93/27	1.54(1.00–2.36)
Infections and infestations	Pneumonia	841/506	0.73(0.66–0.82)
Infections and infestations	Influenza	202/68	1.33(1.01–1.75)
Infections and infestations	Bronchitis	142/35	1.81(1.25–2.62)
Infections and infestations	Urinary Tract Infection	96/15	2.86(1.66–4.92)
Injury, poisoning and procedural complications	Exposure Via Skin Contact	439/144	1.36(1.13–1.65)
Injury, poisoning and procedural complications	Accidental Exposure To Product	428/135	1.42(1.17–1.72)
Injury, poisoning and procedural complications	Wrong Technique In Device Usage Process	409/134	1.36(1.12–1.66)
Injury, poisoning and procedural complications	Underdose	224/64	1.56(1.18–2.06)
Injury, poisoning and procedural complications	Off Label Use	96/62	0.69(0.50–0.95)
Musculoskeletal and connective tissue disorders	Back Pain	389/113	1.54(1.25–1.90)
Musculoskeletal and connective tissue disorders	Myalgia	148/44	1.50(1.07–2.10)
Musculoskeletal and connective tissue disorders	Muscle Spasms	112/33	1.51(1.03–2.23)
Nervous system disorders	Headache	617/159	1.74(1.46–2.08)
Product issues	Product Complaint	442/151	1.31(1.09–1.57)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1355/682	0.88(0.80–0.97)
Respiratory, thoracic and mediastinal disorders	Cough	753/283	1.19(1.04–1.37)
Respiratory, thoracic and mediastinal disorders	Asthmatic Crisis	156/46	1.51(1.09–2.10)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal Pain	123/38	1.44(1.00–2.08)
Skin and subcutaneous tissue disorders	Pruritus	281/85	1.48(1.16–1.88)
Surgical and medical procedures	Hospitalisation	283/154	0.82(0.67–1.00)

FIGURE 4
Reporting odds ratios (ROR) with 95% CI for all positive gender-related AEs. CI, confidence interval. The ROR here is not a strictly defined ROR in pharmacoepidemiological perspective.

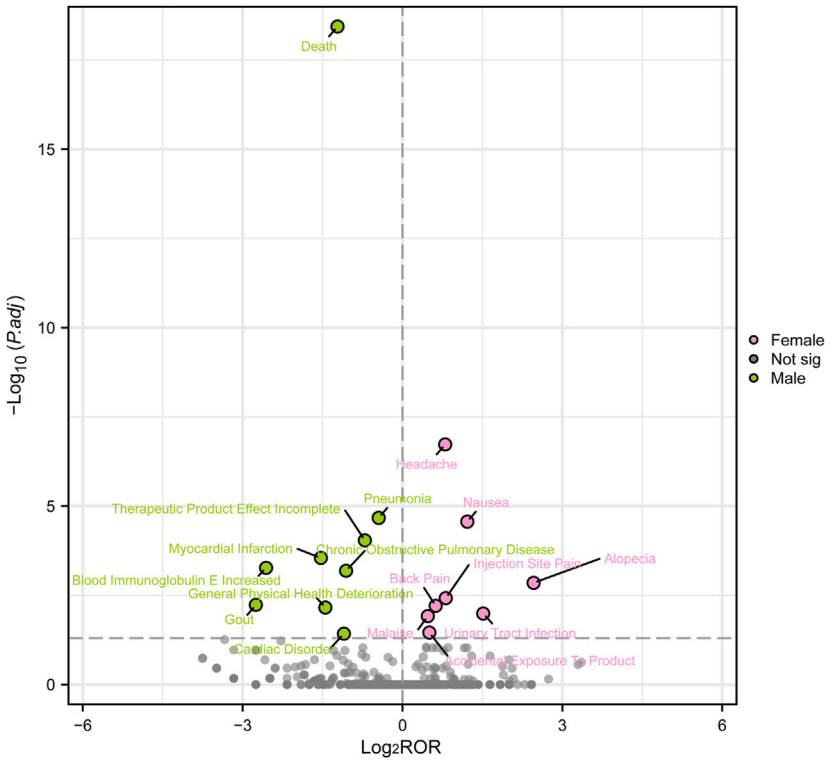

FIGURE 5
Volcanic map of gender difference risk signal for mepolizumab. ROR, reporting odds ratios; *P*.adj, the *p*-value is adjusted with false discovery rate (FDR) method.

consistent with asthma epidemiological research. Additionally, adverse reactions were less common in individuals below the age of 18 receiving mepolizumab. These observations are consistent with the primary target population of mepolizumab, which is additional treatment for patients with poorly controlled asthma. It is worth noting that patients with asthma before the age of 10 have a higher likelihood (up to 60%) of achieving asthma remission, whereas the remission rate in adults with asthma ranges from 5% to 15%(De Marco et al., 2002; Rönmark et al., 2007). Moreover, the higher prevalence of women among adults experiencing severe asthma could be attributed to the greater abundance of ILC2 in female individuals with asthma compared to their male counterparts(Cephus et al., 2017; Porsbjerg et al., 2023). Increased levels of type 2 innate lymphoid cells (ILC2 cells) may contribute to an intense allergic airway inflammation, resulting in insufficient management of asthma symptoms. Our reported findings indicate that mepolizumab is mainly linked to adverse events in female individuals, which is consistent with this observation.

Our analysis of disproportionality revealed that mepolizumab had significant AEs in SOCs, including Respiratory, thoracic and mediastinal disorders; General disorders and administration site conditions; Injury, poisoning and procedural complications; Infections and infestations; Surgical and medical procedures; and Social circumstances. Mepolizumab, in the context of infectious and infestations within the SOC, was frequently linked to pneumonia (n = 1,654), herpes zoster (n = 266), and lower respiratory tract infection (n = 203). The commonly reported adverse events related to respiratory, thoracic, and mediastinal disorders were dyspnea, asthma, cough, and wheezing. Notably, asthmatic crisis exhibited a strong correlation, with a significant signal strength of ROR 114.39 (103.51–126.43), PRR 113.54, IC 4.86, and EBGM 85.29. In previous clinical trials, headache and nasopharyngitis have consistently been identified as the most frequent AEs, while asthma crisis has been recognized as a significant and severe adverse event(Ortega et al., 2014; Pavord et al., 2017; Wechsler et al., 2017; Han et al., 2021). However, our study diverges in that the most prevalent adverse reactions were dyspnea, pneumonia, hospitalization, skin contact, and asthma crisis. These adverse reactions can have grave consequences. Significantly, the identical mepolizumab employed during phase III clinical studies, albeit administered at different quantities, has been associated with a heightened susceptibility to pneumonia in individuals with eosinophilic chronic obstructive pulmonary disease (Pavord et al., 2017). The main uses of mepolizumab include treating asthma, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and nasal polyps. It is worth mentioning that dyspnea, one of the recognized side effects linked to the utilization of mepolizumab in our study, could also originate from the primary illness.

Previous studies have shown that mepolizumab is primarily used for treating asthma. These studies have also identified common side effects such as headache and nasopharyngitis (Pavord et al., 2012; Khurana et al., 2019). However, our analysis has revealed a lower occurrence and weaker signals of sinus dysfunction, sinus congestion, and nasal congestion as potential side effects. The COSMEX study found that asthma worsening was the second most common negative outcome observed during mepolizumab therapy, occurring after

nasopharyngitis, especially in individuals with severe eosinophilic asthma. Furthermore, asthma exacerbation emerged as the most commonly reported severe adverse incident, impacting 10% of individuals. Notably, patients who experienced treatment intervals longer than 12 weeks reported a deterioration in asthma symptoms. This highlights the potential risk of asthma exacerbation with the use or discontinuation of the monoclonal antibody. Encouragingly, the majority of clinical trials have not identified any significant adverse reactions associated with mepolizumab. Long-term monotherapy with mepolizumab appears to contribute to maintaining stable asthma control.

In our study, the most common infection type was purulent sputum, followed by helminthic infection, pharyngitis caused by fungi, allergic aspergillosis in the bronchopulmonary system, bacterial infection in the lower respiratory tract, fungal infection in the respiratory tract, and viral infection in the lower respiratory tract. Additionally, upper respiratory tract infection was also a common infection, consistent with our findings. It is important to note that asthma itself does not increase the risk of SARS-CoV-2 infection. However, it is worth mentioning that our results indicate a correlation between infections with coronaviruses not explicitly stated, such as COVID-19. It is crucial to highlight that viral infections serve as the primary risk factor for acute asthma exacerbations(Busse et al., 2010; Satia et al., 2020). An increase in ACE2 receptor expression was observed in a subset of individuals with asthma who exhibited elevated Th1 and reduced Th2 epithelial gene expression. The heightened manifestation of ACE2 receptor could potentially enhance the likelihood of negative consequences in pneumonia resulting from coronaviruses(Camiolo et al., 2020). Consistently, there was an inverse association between ACE2 gene expression and Th2 gene expression(Bradding et al., 2020). Furthermore, in a national cohort study conducted in Korea, YANG and colleagues(Yang et al., 2020) found that individuals with non-allergic asthma faced an increased likelihood of testing positive for SARS-CoV-2 and experiencing severe clinical outcomes associated with neocoronary pneumonia. Mepolizumab has the potential to modify the host immune response by inhibiting IL-5 expression, which can increase susceptibility to SARS-CoV-2 infection by suppressing Th2 responses. However, it is reassuring to highlight that the majority of clinical studies have demonstrated the safety of biologics, including mepolizumab(Cheng et al., 2004). There were notable decreases in eosinophil counts among patients receiving biologics, which were not linked to an elevated severity of neocoronaryngitis or increased mortality rates (Adir et al., 2021).Nevertheless, the observation from our study regarding the potential association between the use of mepolizumab and coronavirus infection should be taken seriously. Further investigations are warranted to assess this relationship in real-world settings.

The analysis of TTO showed that the median time for mepolizumab-related adverse events to occur was 109 days, with most cases happening within the initial month (n = 1,134, 34.75%) following mepolizumab treatment. Furthermore, we noticed a swift rise in the likelihood of AEs following the third month, eventually reaching an approximate 30% rate within a year. Moreover, the likelihood of encountering at least one worsening during the duration of the therapy rose from 24.2% (95% CI, 21.0%–27.7%) at week 16%–49.1% (95% CI, 45.2%–53.1%) at week 52, as stated in the preceding COSMOS study(Khurana et al., 2019). The findings indicated the importance of closely monitoring the AEs experienced by patients throughout the entire duration of treatment.

According to the data presented in Table 2, there was a greater occurrence of adverse drug reactions among female patients in comparison to male patients. It is essential to consider gender-biased analyses when evaluating the safety of drugs due to this observed difference in gender(Fuseini and Newcomb, 2017). To further investigate the correlation between gender and negative drug reactions, we performed gender-based subgroup analysis. According to Figure 4, it can be observed that females are more prone to encountering gastrointestinal and nervous system adverse reactions, including queasiness, bowel movements, throwing up, migraines, in addition to discomfort in the back, muscular discomfort, and muscular contractions. Infections can occur in both genders, but it is notable that pneumonia is more likely to occur in males, while influenza, bronchitis, and urinary tract infections are more common in females. Interestingly, males have a higher probability of experiencing chest pain, dyspnea, and serious adverse effects leading to hospitalization and death compared to females. Conversely, women are more frequently linked to asthmatic episodes. In order to enhance our comprehension of the correlation between gender and adverse drug reactions, we conducted additional validation of our findings through the adjustment of the *p*-values. Male patients exhibited a higher prevalence of mortality, pneumonia, heart attack, COPD, elevated blood immunoglobulin E levels, gout, decline in overall health, and cardiovascular disease in comparison to their female counterparts. On the other hand, female patients experienced a higher prevalence of headache, nausea, hair loss, pain at the injection site, back pain, fatigue, urinary tract pain, and unintentional exposure to the product. Although several clinical trials conducted in asthma, chronic rhinitis, and eosinophilic chronic obstructive pulmonary disease did not report any deaths associated with drug therapy, post-marketing data revealed that deaths accounted for 7.55 percent of serious adverse reactions, with at least 1,066 cases(Pavord et al., 2012; Chupp et al., 2017; Pavord et al., 2017; Han et al., 2021; Jackson et al., 2022). Males exhibited a higher likelihood of experiencing deaths in comparison to females. The occurrence of this could be ascribed to environmental elements like tobacco use, alcohol consumption, and other detrimental behaviors commonly seen in males, potentially resulting in coexisting conditions like pneumonia. Consequently, it reminds us that male patients undergoing treatment with mepolizumab may have a poorer prognosis. Furthermore, male patients are more susceptible to acute myocardial infarction and cardiac diseases. Although previous clinical studies did not report any drug-related serious cardiovascular AEs, it serves as a reminder to be cautious and warn about the symptoms of chest pain, especially in male patients presenting with such symptoms during the use of the drug. During a prior clinical trial examining the efficacy of mepolizumab in treating resistant eosinophilic asthma, a single instance of chest discomfort was documented in the experimental group, whereas the control group did not report any incidents of chest pain (Haldar et al., 2009). Furthermore, there was a case study detailing the occurrence of noncardiogenic chest discomfort linked to mepolizumab in a 66-year-old male individual (Korbitz et al., 2020). Earlier research has found a connection between the category of adverse events and the age at which they occur, indicating that headaches are more prevalent during the initial stages of asthma (Khatri et al., 2019). Moreover, this research contributes to the current understanding by emphasizing the correlation between the category of adverse events and gender, particularly noting that women experience headaches more

frequently. Therefore, it is important to closely observe the usage of this medication in young females to detect any instances of headaches. Curiously, a female patient, aged 32, experienced hair loss after 4 months of receiving mepolizumab. The dermatology department assessed the condition as reversible alopecia caused by biologic therapy (Nixon et al., 2020). This finding aligns with our analyses, which also determined that women are more susceptible to hair loss. Moreover, as a result of the distinct physiological traits of females, infections caused by drugs mainly appear as urinary tract infections. These findings emphasize the importance of focusing on adverse reactions in clinical practice among patients of different genders. Nevertheless, it is essential to emphasize that additional clinical evidence is required to verify these findings.

To investigate and examine the adverse reaction signals linked to mepolizumab, we employed the FAERS database in our study. The method possesses robust extrapolation capability and efficiently overcomes the constraints of limited sample sizes and brief observation periods in clinical trials. Our analysis focused on AEs associated with mepolizumab, along with other pertinent and significant AEs. The objective was to offer valuable perspectives for the surveillance and improvement of clinical drug safety. Nevertheless, it is important to be aware that in spontaneous reporting systems (including FAERS), adverse event reports are voluntary and come from a variety of sources, so varying degrees of underreporting, delayed reporting, and misreporting to incomplete information may introduce bias into the measurement of the disproportionality report (Alomar et al., 2020; Khan et al., 2020; Noguchi et al., 2021). Furthermore, even when the reports are complete, it is seldom possible to enumerate the denominator or potential user population, so neither incidence nor risk can be calculated (Crisafulli et al., 2023). Finally, the signals of adverse reactions identified using the disproportionality method partially reflect the existence of a statistical correlation between a particular drug and the corresponding adverse reaction, but do not establish causality (Xia et al., 2023). Considering the above shortcomings and other potential confounders and biases, we need to interpret the results of these analyses more cautiously and further clinical study evaluations are required to confirm these associations. Although the FAERS database has its limitations in pharmacovigilance studies, our thorough analysis of the adverse event signals associated with mepolizumab and the discovery of unforeseen adverse event signals could lay the groundwork for future clinical research on this medication.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: All data come from the FAERS database, which is available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

FZ: Conceptualization, Formal Analysis, Writing–original draft, Writing–review and editing. CZ: Formal Analysis, Visualization, Writing–original draft. SL: Writing–original draft. ZC: Conceptualization, Formal Analysis, Visualization, Writing–original draft. DW: Writing–original draft. YO: Writing–original draft. LW: Writing–original draft. JC: Writing–original draft. YL: Funding acquisition, Writing–original draft.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1320458/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Age-based subgroup analysis of mepolizumab-related AEs.

SUPPLEMENTARY FIGURE S2
Gender-based subgroup analysis of mepolizumab-related AEs.

SUPPLEMENTARY FIGURE S3
Weight-based subgroup analysis of mepolizumab-related AEs.

SUPPLEMENTARY FIGURE S4
Reported person-based subgroup analysis of mepolizumab-related AEs.

SUPPLEMENTARY TABLE S1
Signal strength of reports of mepolizumab at the Preferred Terms (PT) level in the FAERS database (ranked by EBGM05 value).

SUPPLEMENTARY TABLE S2
Gender-based disproportionate analysis of linezolid-related AEs. **(A)**, number of reports of target AE in female; **(B)**, number of reports of other AEs in female; **(C)**, number of reports of target AE in male; d, number of reports of other AEs in male. Therefore, the ROR here is not a strictly defined ROR in pharmacoepidemiological perspective; we just use this algorithm for signal value calculation of gender-based signal strength differences.

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Enhancing antidepressant safety surveillance: comparative analysis of adverse drug reaction signals in spontaneous reporting and healthcare claims databases

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Background/Objective: Spontaneous reporting systems (SRS) such as the Korea Adverse Event Reporting System (KAERS) are limited in their ability to detect adverse drug reaction (ADR) signals due to their limited data on drug use. Conversely, the national health insurance claim (NHIC) data include drug use information for all qualifying residents. This study aimed to compare ADR signal profiles for antidepressants between KAERS and NHIC, evaluating the extent to which detected signals belong to common ADRs and labeling information.

Materials and Methods: ADR signal detection in KAERS and NHIC databases, spanning January to December 2017, employed disproportionality analysis. Signal classes were determined based on System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA). Also, Common ADR Coverage (CAC), the proportion of detected signals deemed common ADRs, and labeling information coverage (LIC) represented by mean average precision (mAP) were calculated. Additionally, protopathic bias and relative risk (RR) evaluation were performed to check for signal robustness.

Results: Signal detection revealed 51 and 62 signals in KAERS and NHIC databases, respectively. Both systems predominantly captured signals related to nervous system disorders, comprising 33.3% (N = 17) in KAERS and 50.8% (N = 31) in NHIC. Regarding the type of antidepressants, KAERS predominantly reported signals associated with tricyclic antidepressants (TCAs) (N = 21, 41.2%), while NHIC produced most signals linked to selective serotonin reuptake inhibitors (SSRIs) (N = 22, 35.5%). KAERS exhibited higher CAC (68.63% vs. 29.03%) than NHIC. LIC was also higher in KAERS than in NHIC (mAP for EB05: 1.00 vs. 0.983); i.e., NHIC identified 5 signals not documented in drug labeling information, while KAERS found none. Among the unlabeled signals, one (Duloxetine-Myelopathy) was from protopathic bias, and two (duloxetine-myelopathy and tianeptine-osteomalacia) were statistically significant in RR.

Conclusion: NHIC exhibited greater capability in detecting ADR signals associated with antidepressant use, encompassing unlabeled ADR signals, compared to KAERS. NHIC also demonstrated greater potential for identifying less common ADRs. Further investigation is needed for signals detected exclusively in NHIC but

not covered by labeling information. This study underscores the value of integrating different sources of data, offering substantial regulatory insights and enriching the scope of pharmacovigilance.

KEYWORDS

signal detection, drug safety surveillance, spontaneous reporting system, healthcare claim database, antidepressant, adverse drug reaction, pharmacovigilance

1 Introduction

Pharmacovigilance relies on robust data sources to detect adverse drug reaction (ADR) signals and ensure patient safety. Spontaneous reporting systems (SRS) have traditionally been a cornerstone of pharmacovigilance, with the Korea Adverse Event Reporting System (KAERS) serving as a vital repository for adverse event reports. (van Puijenbroek et al., 2002; Van Puijenbroek et al., 2003; Bate and Evans, 2009). However, SRS, including KAERS, have a fundamental limitation—they lack comprehensive data on drug utilization, hindering their ability to detect ADR signals effectively (Hazell and Shakir, 2006).

In contrast, national health insurance claim (NHIC) databases, such as the extensive claims data from the Korean National Health Insurance Review & Assessment (HIRA) database, document records of prescription drug use for all qualifying residents in Korea (Kim et al., 2017). This presents a unique opportunity to augment traditional SRS data with information on a full set of drug exposures, potentially enhancing the detection of ADR signals.

Globally, comprehensive electronic healthcare data sources have emerged as a valuable resource for pharmacovigilance (Liu et al., 2013). In US, the Food and Drug Administration (FDA)'s Sentinel System has combined electronic health records (EHR), claims from insurance providers, pharmacy records, and patient registries from over 300 million individuals in the United States, providing a comprehensive representation of real-world healthcare practice (Carnahan et al., 2014). In Europe, the EU-ADR Project has combined electronic health records (EHR) from European countries such as UK, Italy, Denmark and Netherlands to enable large-scale drug safety monitoring (Trifiro et al., 2009; Coloma et al., 2011). While quite a many studies have utilized these databases to perform pharmacovigilance, comparing ADR signal profiles between the electronic health database to SRS is rare due to the challenges of accessing and analyzing data from multiple sources; only one study compared signal detectability between EU-ADR and FAERS (Patadia et al., 2015)

In Korea, many studies utilized the NHIC data for pharmacoepidemiologic studies (Choi et al., 2010; Kim et al., 2011a; Choi et al., 2011). However, few studies compared signal detection between NHIC and KAERS. This study aimed to compare ADR signal profiles, including signal numbers and classes for system organ class (SOC) and antidepressants between KAERS and NHIC, and to determine the extent to which detected ADR signals correspond to common ADRS and labeling information in both systems.

Given antidepressants are a widely prescribed class of medications with substantial safety issues (Uher et al., 2009), a comprehensive understanding of their ADR signals from two different data sources is essential for effective clinical decision-making. Ultimately, this research would underscore the value of combining both healthcare claims and spontaneous reporting systems, offering valuable regulatory insights.

2 Materials and methods

2.1 Data source

KAERS Data was sourced from the Korea Adverse Event Reporting System (KAERS) for the year 2017. KAERS is operated by the Korea Institute of Drug Safety and Risk Management (KIDS). We specifically selected reports containing information on the usage of antidepressants, encompassing patient demographics, drug classifications using the Anatomical Therapeutic Chemical (ATC) code, recorded adverse drug reactions (ADRs), and causality assessments based on World Health Organization-Uppsala Monitoring Centre (WHO-UMC). ADRs were cataloged following the World Health Organization-Adverse Reaction Terminology (WHO-ART).

NHIC Data are from the 2017 Health Insurance Review Agency's National Patient Data (HIRA-NPS). HIRA-NPS is derived from a 3% random sample of the entire Korean patient population and consists of healthcare claims submitted by providers for reimbursement (Kim et al., 2011b). This dataset encompasses all prescriptions for antidepressants reported to the HIRA during the year 2017. ADRs in this dataset were identified based on patient diagnoses using the Korean Standard Classification of Diseases (KCD) codes for drug-induced disorders. The identification of antidepressants was determined through the main ingredient codes listed in each prescription. Supplementary Material provide a detailed list of identified ADRs and main ingredient codes.

In the KAERS database, we identified a total of 3,957 reports that contained antidepressants (ATC code: "N06A") within the timeframe of 1 January 2017, to 31 December 2017 (Figure 1A). Initially, we excluded reports with the reason for follow-up listed as "report cancellation" and then selected only spontaneous reports. Among these, we retained reports classified as having "certain," "probable," and "possible" causality assessment based on WHO-UMC, resulting in 2,242 reports encompassing 5,992 drug-ADR pairs.

As for the NHIC database, it provided drug usage information for 1,473,083 patients during the specified time period (Figure 1B). We first identified patients who had taken antidepressants, which amounted to 90,228 patients. By narrowing down to those who had experienced a drug-induced disorder within 12 weeks after taking an antidepressant, we identified a subset of 1,613 patients. From this subset, we selected after-antidepressant ADRs and subsequently

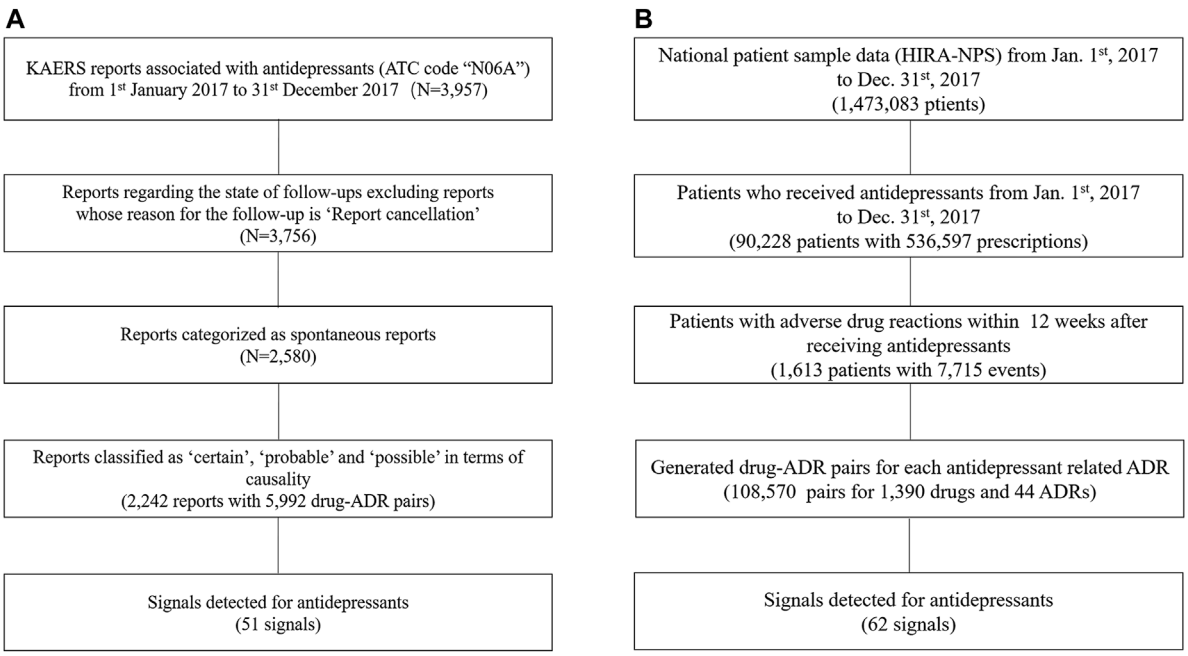

FIGURE 1
Flow Chart for Data Preparation; **(A)** KAERS data preparation; **(B)** NHIC data preparation; Abbreviation: KAERS, Korea adverse event reporting system; ATC code, Anatomical Therapeutic Chemical code; ADR, adverse drug reactions; HIRA-NPS, Health Insurance Review Agency's National Patient Data.

generated drug-ADR pairs, resulting in a total of 108,570 pairs involving 1,390 drugs and 44 ADRs.

Given the absence of explicit links between ADRs and drug exposure in the NHIC, we employed a systematic approach to establish these drug-ADR pairings (Figure 2).

- We initially extracted after-antidepressant ADRs, defined as ADRs occurring within 12 weeks following the last prescription of antidepressants.
- For each after-antidepressant ADR, we conducted a retrospective pairing, connecting any drugs utilized in the 12 weeks leading up to the ADR occurrence.
- Two occurrences of the same ADR (X1 and X2) within 12 weeks after taking a drug (A) were retained as A-X1 and A-X2, while different ADRs (e.g., X and Y) occurring within 12 weeks after taking different drugs (e.g., A and B) were paired as distinct drug-ADR pairs (e.g., A-X, A-Y, B-X, B-Y).
- Identical drug-ADR pairs for the same patient were considered as one to mitigate any bias arising from multiple duplications.
- We selected the 12-week time window based on established antidepressant treatment patterns and recognized practices in healthcare database studies (Choi et al., 2010; Dipiro et al., 2014).

2.2 Signal detection algorithms

For the detection of ADR signals, we conducted disproportionality analyses using various statistical measures, including the proportional reporting ratio (PRR), confidence interval of proportional reporting ratio (PRRCI), reporting odds ratio (ROR), and confidence interval of reporting odds ratio (RORCI). Additionally, data-mining techniques such as the information component (IC), empirical Bayesian geometric mean (EBGM), and the lower 5% point of empirical Bayesian geometric mean (EB05) were employed (Madigan et al., 2010). Table 1 presents a standard 2 × 2 contingency table for each indicator, along with the corresponding formula. The thresholds were selected in accordance with the criteria utilized in international and national SRS databases (Sciences, 2010).

2.3 Comparison of detected signals

Following signal detection, all identified signals in both KAERS and NHIC were categorized and compared at the System Organ Class (SOC) level using the Medical Dictionary for Regulatory Activities (Brown et al., 1999). Additionally, signals were evaluated to determine whether they corresponded to common adverse drug reactions (ADRs) associated with antidepressants, as defined by the IBM Micromedex® database, the Korea Pharmaceutical Information Center database (KPIC), as well as labeling information from the FDA in the United States and the Ministry of Food and Drug Safety (MFDS) in South Korea (IBM, 2021; KPIC, 2021). Common ADRs were considered those with an incidence rate exceeding 1% for a specific ADR related to a particular antidepressant. The proportion of common ADRs among all detected signals was calculated to assess the common ADR coverage (CAC).

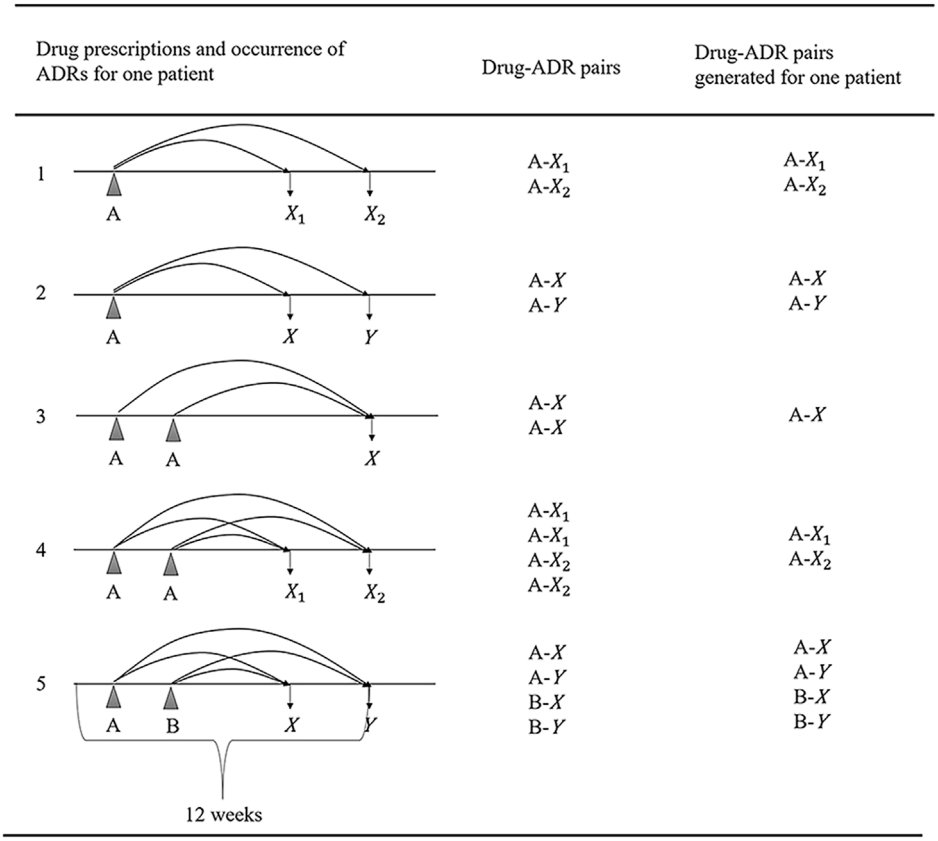

FIGURE 2
Generating algorithm for drug-ADR pairs; (A, B: Indicating different drugs; X, Y: Denoting various adverse drug reactions (ADRs); X1, X2: Indicating the same ADR occurring at different times; Abbreviation: ADR, adverse drug reaction.

The labeling information coverage (LIC) was assessed using the Mean Average Precision (mAP), a commonly used metric in information retrieval (Schuemie and safety, 2011). This metric evaluates how effectively a system ranks signals, giving higher priority to ranking true positive items. A higher mAP score signifies greater accuracy in detecting signals that align with the labeling information. It is determined by calculating the number of highly ranked signals that are true positives at the true positive point (Table 2). While there was no definitive gold standard for verifying the validity of the detected signals, the labeling information sourced from both the FDA of the United States and the MFDS of South Korea was regarded as truth in this study.

2.4 Evaluation protopathic bias and relative risk in national health insurance claim

During the signal detection process, false positive signals can emerge due to something called protopathic bias. This bias happens when a drug is prescribed to treat a disease or an early sign of a disease before that event is recorded in the database. We used a method called Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD) to mitigate protopathic bias (Schuemie and safety, 2011). This method compares the number of prescriptions before and after a specific ADR occurs within a set time frame. If there is an increase in prescriptions after the ADR event, it suggests that the drug might be treating the ADR rather than causing it, which signifies a protopathic bias.

Additionally, we computed the Relative Risk (RR) along with its confidence interval for each drug-ADR combination to assess the robustness of the detected signals. This calculation was based on the comprehensive prescription data available in the NHIC database. Initially, number of exposures and outcomes required for the 2*2 table were organized (Table 3), and from this organized data, we computed the RR and its corresponding confidence interval. If the lower bound of the RR was greater than 1, it indicated that the risk of a particular drug causing a specific ADR was statistically significant.

All statistical analyses were conducted using SAS® software (version 9.4) and R Statistical Software (version 4.0.3). Specifically, R packages such as "PhViD," "openEBGM," and "RCOR" were utilized for signal detection and evaluation (Sing et al., 2005; Ahmed and Poncet, 2013; Canida and Ihrie, 2017).

3 Results

3.1 Descriptive analysis of databases

In the KAERS database, the majority of reports (49.29%) originated from individuals aged 60 and above (Table 4). Of

TABLE 1 Calculation and threshold for data-mining indicators.

2 × 2 contingency table			
	Specific ADR	All other ADRs	Total
Specific drug	A (n11)	B (n12)	A + B (n10)
All other drugs	C (n21)	D (n22)	C + D (n20)
Total	A + C (n01)	B + D (n02)	A + B + C + D (n)
Corresponding formulas			
Signal detection indicators	Calculation	Thresholds	
PRR	(n11/n10)/(n21/n20)	PRR≥2, χ^2 (†)≥4, n11 ≥ 3	
ROR	(n11/n12)/(n21/n22)	ROR≥2, χ^2 ≥4, n11 ≥ 3	
PRRCI	(n11/n10)/(n1/n20)	PRR–1.96SE > 1, n11 ≥ 3	
RORCI	(n11/n12)/(n21/n22)	ROR - 1.96SE > 1, n11 ≥ 3	
IC	IC = $log_2 \frac{N_{ij}}{E_{ij}}$ (*)	IC–2SD > 0, n11 ≥ 3	
EBGM	DuMouchel (1999)	EBGM≥2.5, n11 ≥ 3	
EB05	DuMouchel (1999)	EB05 ≥ 1.8, n11 ≥ 3	

Abbreviations: ADR, adverse drug reaction; PRR, proportional reporting ratio; PRRCI, confidence interval of proportional reporting ratio; ROR, reporting odds ratio; RORCI, confidence interval of reporting odds ratio; IC, information component; EBGM, empirical Bayes geometric mean; EB05, the lower 5% point of empirical Bayes geometric mean; * N_{ij}: observed frequency of drug-ADR pairs, E_{ij}: expected frequency of drug-ADR pairs; † χ^2: chi-square value.

these reports, 65.7% were contributed by females, while 32.87% came from males. In terms of the types of antidepressants involved, the highest number of reports were associated with selective serotonin reuptake inhibitors (SSRIs, 39.47%), followed by tricyclic antidepressants (TCAs, 31.80%), noradrenergic and specific serotonergic antidepressants (NaSSAs, 7.00%), serotonin-norepinephrine reuptake inhibitors (SNRIs, 6.47%), serotonin antagonist and reuptake inhibitors (SARIs, 5.44%), and serotonin receptor agonists (SRAs, 3.21%).

Similarly, in the NHIC database, the largest proportion of patients (46.87%) were aged 60 and older, and 61.20% of patients were female. The most commonly prescribed antidepressants were TCAs (51.82%) and SSRIs (48.32%), followed by SARIs (17.30%), SNRIs (5.70%), NaSSAs (4.93%), and SRAs (2.17%).

Among all the selected reports in KAERS, the most frequently reported ADRs were dizziness (16.15%), followed by nausea (13.38%), somnolence (12.85%), mouth dry (8.39%), and constipation (7.54%). Meanwhile, in NHIC, the most common after-antidepressant ADRs were tremor (38.83%), followed by unspecified toxic liver disease (16.54%), myoclonus (4.61%), epileptic seizures (4.23%), and mental disorders (4.15%).

3.2 Comparison detected signals between Korea adverse event reporting system and national health insurance claim

In the KAERS database, a total of 51 signals related to antidepressants were detected among 5,992 drug-ADR pairs. Notably, all of these signals corresponded to labeled adverse effects of antidepressants, as confirmed by both the FDA of the United States and the MFDS of South Korea. The antidepressant nortriptyline had the highest number of detected signals (8 signals), followed closely by amitriptyline and escitalopram (6 signals each). PRRCI generated the most signals (51 signals), closely followed by RORCI, which yielded similar results (49 signals). In contrast, EBGM and EB05 produced fewer signals, accounting for only 5 and 2 signals, respectively.

In the NHIC database, signal detection produced 62 signals. The highest number of detected signals was associated with duloxetine, which had 7 signals. Tianeptine followed with 6 signals, and amitriptyline had 5 signals. Similar to KAERS, PRRCI and

TABLE 2 The calculation of the mean average precision (mAP).

Drug	ADR	Indicator value	Rank by indicator	Labeling information	Precision
A	X	10	1	Yes	1/1 = 1
B	Y	9	2	No	
C	X	8	3	Yes	2/3 = 0.67
A	Z	7	4	No	
D	Y	6	5	Yes	3/5 = 0.6
mAP=(1 + 0.67+0.6)/3 = 0.76					

TABLE 3 Data arrangement for relative risk calculation.

	Occurrence of specific ADR	Nonoccurrence of specific ADR	Total
Patients who took a specific antidepressant	x1	n1-x1	n1
Patients who didn't take specific antidepressants	x2	n2-x2	n2

Abbreviations: ADR, adverse drug reaction.

TABLE 4 Description of KAERS and NHIC databases.

Characteristics	KAERS	NHIC	
	Reports associated with antidepressants	Patients receiving antidepressants	Patients with ADRs
Total	2,242 (100.00%)	90,228 (100.00%)	1,613 (100.00%)
Age			
0–19	52 (2.32%)	2,891 (3.20%)	33 (2.05%)
20–39	274 (12.22%)	14,182 (15.72%)	190 (11.78%)
40–59	679 (30.29%)	30,866 (34.21%)	576 (35.71%)
60+	1,105 (49.29%)	42,289 (46.87%)	814 (50.46%)
unknown	132 (5.89%)	0 (0.00%)	0 (0.00%)
Gender			
Male	737 (32.87%)	35,008 (38.80%)	656 (40.67%)
Female	1,473 (65.70%)	55,220 (61.20%)	957 (59.33%)
unknown	32 (1.43%)	0 (0.00%)	0 (0.00%)
Types of antidepressants			
SSRI	885 (39.47%)	43,596 (48.32%)(*)	837 (51.89%)(*)
TCA	713 (31.80%)	46,758 (51.82%)	751 (46.56%)
NaSSA	157 (7.00%)	4,447 (4.93%)	129 (8.00%)
SNRI	145 (6.47%)	5,140 (5.70%)	136 (8.43%)
SARI	122 (5.44%)	15,607 (17.30%)	365 (22.63%)
SRA	72 (3.21%)	1,958 (2.17%)	32 (1.98%)
other	148 (6.60%)	30 (0.03%)	0 (0.00%)
Top 5 most frequently reported ADRs in KAERS		Top 5 most after-antidepressant ADRs in NHIC	
Dizziness	362 (16.15%)	Tremor	2996 (38.83%)
Nausea	300 (13.38%)	Unspecified toxic liver disease	1276 (16.54%)
Somnolence	288 (12.85%)	Myoclonus	356 (4.61%)
Mouth dry	188 (8.39%)	Epileptic seizures	326 (4.23%)
Constipation	169 (7.54%)	Mental disorders	320 (4.15%)

Abbreviation: KAERS, korea adverse event reporting system; NHIC, national health insurance claim data; ADR, adverse drug reaction; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; SRA, serotonin receptor agonist; (*): Percentages may total more than 100% due to multiple prescriptions for the same patient.

RORCI were the primary indicators responsible for generating most of the signals (62 signals), while IC demonstrated similar results with 57 signals. PRR and ROR produced comparable outcomes, each resulting in 43 and 45 signals, respectively. EBGM and EB05 generated fewer signals compared to other indicators but much higher compared to KAERS, yielding only 28 and 22 signals, respectively. Out of all the detected signals, 57 were consistent with labeling information from both the FDA of the United States and the MFDS of South Korea. However, five ADRs had not yet been labeled. All the detected signal information in KAERS and HIRA is included in Supplementary Material.

Analyzing the profiles of the detected signals, in the KAERS database, the majority of signals were associated with nervous system disorders (N = 23, 45.1%), followed by gastrointestinal system disorders (N = 14, 27.5%), and psychiatric disorders (N = 13, 25.5%) (Figure 3). Regarding drug types, TCAs exhibited the most signals (N = 21, 41.2%), followed by SSRIs (N = 16, 31.4%), SNRIs (N = 6, 11.8%), NaSSAs (N = 3, 5.9%), SRAs (N = 3, 5.9%), and SARIs (N = 2, 3.9%).

While in NHIC database, the majority of detected signals being related to nervous system disorders (N = 31, 50.8%), followed by hepatobiliary disorders (N = 11, 18.0%), skin and appendages disorders (N = 8, 12.9%). In terms of drug types, SSRIs exhibited the most signals (N = 22, 35.5%), followed by TCAs (N = 18, 29.0%), SNRIs (N = 11, 17.7%), SARIs (N = 4, 6.5%), NaSSAs (N = 4, 6.5%), and SRAs (N = 3, 4.8%).

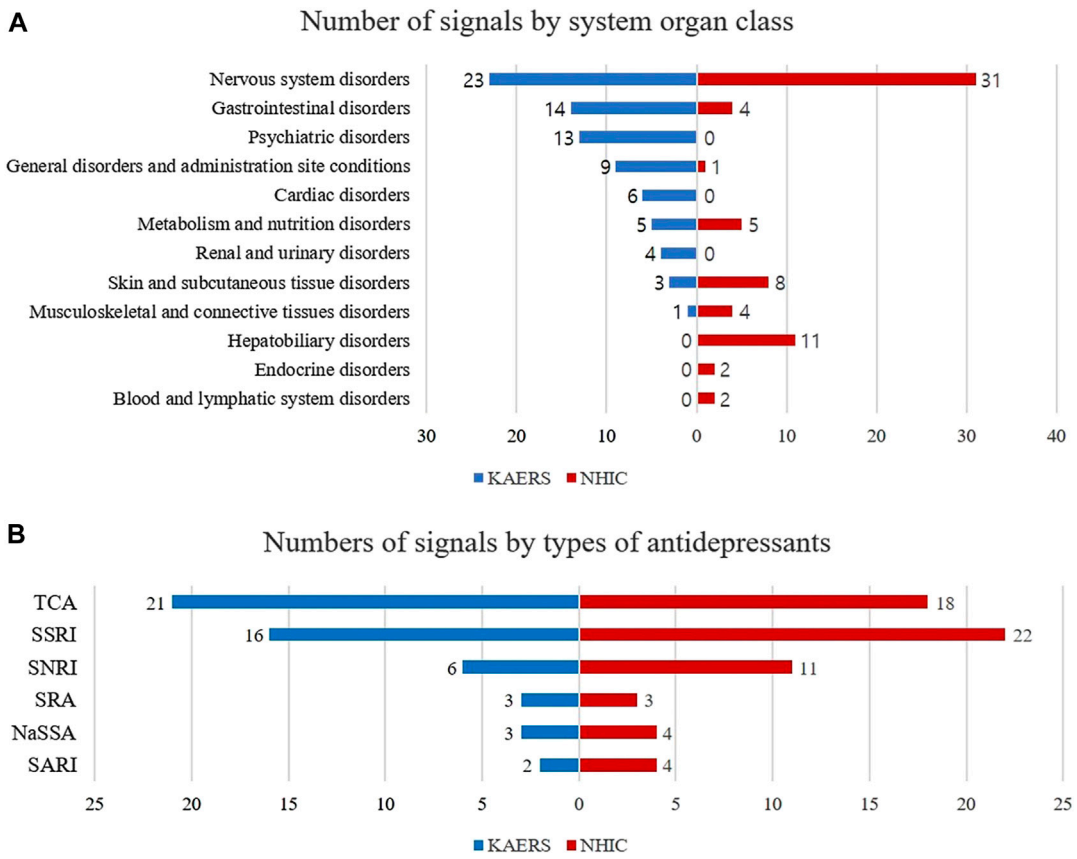

FIGURE 3
Comparison of signal profiles between KAERS and NHIC; **(A)** Number of signals by system organ class; **(B)** Number of signals by type of antidepressants; Abbreviation: KAERS, Korea adverse event reporting system; NHIC, national health insurance claim data; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; SRA, serotonin receptor agonist.

3.3 Comparison of CAC (common ADR coverage) and labeling information coverage

The common ADR coverage (CAC) of detected signals was assessed in both the KAERS and NHIC systems using information from the IBM Micromedex® database, the Korea Pharmaceutical Information Center database, and collected labeling information. In PRRCI, the indicator that yielded the highest number of signals in both systems, 68.63% (35 out of 51 signals) of the signals detected in KAERS were associated with common ADRs (Figure 4). In contrast, in NHIC, only 29.03% (18 out of 62 signals) of the signals were related to common ADRs.

Additionally, an assessment of labeling information coverage (LIC) was conducted to compare the two databases. In KAERS, no unlabeled signals were detected, resulting in a perfect mAP score of 1.00 for all indicators (Table 5). Conversely, in NHIC, which detected 5 unlabeled signals, EB05 exhibited the highest accuracy with a mAP of 0.983, while PRRCI and IC showed slightly lower accuracy with mAP scores of 0.936 and 0.933, respectively, according to labeling information.

3.4 Evaluation of signal robustness in national health insurance claim

The Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD) method was employed to address potential protopathic bias in unlabeled detected signals (Table 6). For each unlabeled drug-ADR combination, the number of prescriptions 12 weeks before the first occurrence of the ADR and 12 weeks after the ADR were tallied along with a one-tailed binomial test. Notably, the combination of duloxetine and myelopathy is likely influenced by protopathic bias. After data processing, it was found that 34 prescriptions of duloxetine were initiated 12 weeks before the onset of myelopathy, while 44 prescriptions were created 12 weeks later. This observed significant increase ($p < 0.05$) in prescription numbers before and after the ADR strongly suggests that the signal is likely due to protopathic bias.

In the NHIC database, for each drug-ADR combination, the Relative Risk (RR) along with its confidence interval and ADR incidence were calculated. A total of 68 combinations showed statistically significant risk compared to other antidepressants, including two of the five unlabeled signals: duloxetine-myelopathy and tianeptine-osteomalacia. A detailed list of drug-

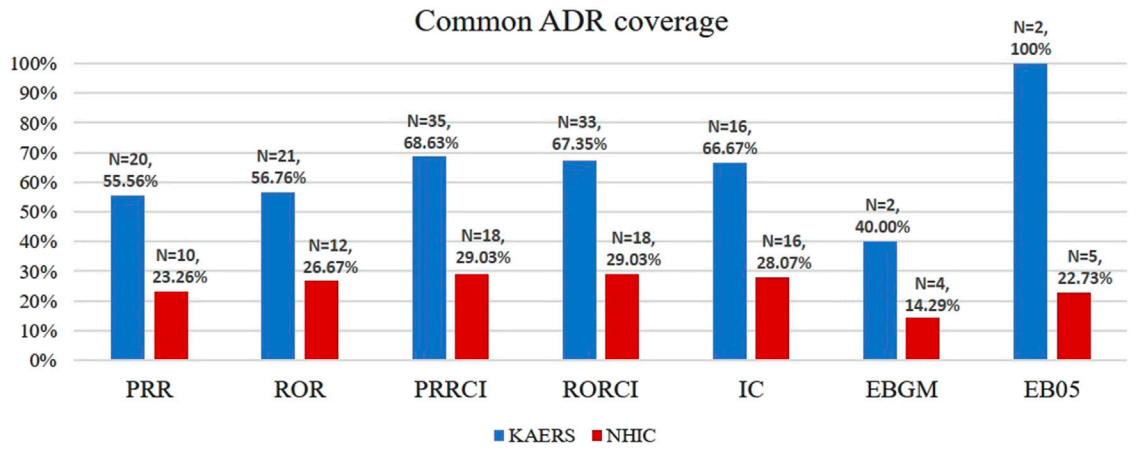

FIGURE 4
Common ADR number and common ADR coverage; Abbreviations: KAERS, Korea adverse event reporting system; NHIC, national health insurance claim data; ADR, adverse drug reaction; PRR, proportional reporting ratio; ROR, reporting odds ratio; PRRCI, confidence interval of proportional reporting ratio; RORCI, confidence interval of reporting odds ratio; IC, information component; EBGM, empirical Bayes geometric mean; EB05, the lower 5% point of empirical Bayes geometric mean.

TABLE 5 Numbers of signal detected and corresponding mAP scores.

Indicators		PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
KAERS	**Detected signals number**	36	37	51	49	24	5	2
	Labeled signals number	36	37	51	49	24	5	2
	mAP	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NHIC	**Detected signals number**	43	45	62	62	57	28	22
	Labeled signals number	39	41	57	57	52	26	20
	mAP	0.944	0.955	0.936	0.947	0.933	0.951	0.983

Abbreviations: KAERS, korea adverse event reporting system; NHIC, national health insurance claim data; mAP, mean average precision; PRR, proportional reporting ratio; ROR, reporting odds ratio; PRRCI, confidence interval of proportional reporting ratio; RORCI, confidence interval of reporting odds ratio; IC, information component; EBGM, empirical Bayes geometric mean; EB05, the lower 5% point of empirical Bayes geometric mean.

TABLE 6 LEOPARD and reporting situation for unlabeled signals.

Drug	ADR	Number of patients	Prescriptions before ADR	Prescriptions after ADR	*p*-value
Amitriptyline	Myoclonus	30	54	65	0.1797
Duloxetine	Myelopathy	13	34	44	0.01026
Tianeptine	Ulcer of oesophagus	17	24	27	0.3899
	Gastroenteritis and colitis	4	4	3	0.7734
	Osteomalacia	2	3	1	0.9375

Abbreviations: LEOPARD, longitudinal evaluation of observational profiles of adverse events related to drugs; ADR, adverse drug reaction.

ADR combinations with a lower bound greater than 1 can be found in the Supplementary Material.

4 Discussion

In this study, we observed variations in the number of safety signals detected between the KAERS and NHIC databases, with 51 signals in KAERS and 62 in NHIC based on PRRCI. Notably, when we used EBGM and EB05 for signal detection, KAERS yielded a relatively smaller number of signals compared to NHIC. This discrepancy may be attributed to the significant shrinkage of the estimator in KAERS when the adverse event cell count for a specific drug is less than about 10, as reported by Madigan (Madigan, 1999).

Both KAERS and NHIC identified the majority of safety signals within the System Organ Class (SOC) of nervous system disorders,

accounting for 33.3% and 50.8%, respectively. This aligns with expectations, given that most antidepressants exert their effects on neurotransmitters or their receptors, potentially leading to nervous system disorders (Khushboo and Sharma, 2017). Furthermore, antidepressants were associated with the second-highest number of safety signals in the SOC of gastrointestinal disorders (14 signals), followed by SOCs such as psychiatric disorders (13), general disorders (9), cardiac disorders (6), metabolism and nutrition disorders (5), and renal disorders (4) in KAERS. These findings are consistent with a previous meta-analysis by Correll et al., 2015, which reported increased safety risks associated with antidepressants, including obesity, dyslipidemia, diabetes mellitus, thyroid disorders, hyponatremia, and various other medical conditions.

However, NHIC exhibited a different signal profile by SOC, except for nervous system disorders. This divergence can be explained by the limitations of KCD codes used in NHIC to identify drug-induced adverse reactions. KCD codes may not adequately capture psychiatric and cardiac disorders induced by drug use, and they may also lack codes for common disorders like constipation, diarrhea, fatigue, anorexia, and dry mouth. Additionally, mild diseases such as fever, which may not prompt a clinic visit, could be missed in NHIC's safety signal detection within the SOC of general disorders.

When we classified the signals by the types of antidepressants, KAERS showed the highest number of signals associated with TCA antidepressants (N = 21, 41.2%), followed by SSRIs (N = 16, 31.4%). In contrast, NHIC detected more signals related to SSRI antidepressants (N = 22, 35.5%) than TCAs (N = 18, 29.0%). This variation between the two databases may be influenced by differences in healthcare practices and reporting mechanisms. It's essential to note that TCAs and SSRIs are commonly prescribed classes of antidepressants, which could explain their prevalence in detected signals in both databases.

NHIC exhibited a lower Common ADR Coverage (CAC) compared to KAERS (29.03% vs. 68.63%), indicating that the safety signals detected in KAERS are more likely to consist of common adverse reactions. This substantial difference in CAC suggests that the conditions identified in NHIC based on KCD codes may not encompass many common disorders. It could also imply that NHIC has a greater potential to detect rare adverse reactions compared to KAERS. However, it could have occurred simply because the KCD codes derived from ICD codes to document medical conditions are limited in identifying drug-induced common disorders such as constipation, diarrhea, fatigue, anorexia, and dry mouth (Hohl et al., 2014).

Regarding Labeling Information Coverage (LIC), measured by the extent to which detected safety signals are mentioned in the labeling information approved by regulatory agencies, KAERS and NHIC had mAP values of 1.00 and 0.93, respectively, in EB05. NHIC notably identified 5 safety signals that were not found in the drug labeling information, including amitriptyline-myoclonus, duloxetine-myelopathy, tianeptine-ulcer of oesophagus, tianeptine-gastroenteritis and colitis, and tianeptine-osteomalacia. Among these signals, one (duloxetine-myelopathy) was attributed to protopathic bias, as duloxetine is used to treat neuropathic pain (Swidan, 2005; Hall et al., 2006). The remaining 4 signals were supported by existing literature.

For instance, the signal of amitriptyline-myoclonus was documented in a study revealing that 30 out of 98 patients who underwent cyclic antidepressant therapy experienced drug-associated myoclonus (Garvey and Tollefson, 1987). This signal was also reported in a Korean study in 2006 (Choi et al., 2006). The safety signals of ulcer of oesophagus, gastroenteritis and colitis associated with tianeptine are frequently observed in patients who have taken antidepressants (Choi et al., 2006; Kelly et al., 2008; Wang et al., 2018). The safety signal of osteomalacia, resulting from bone loss, is also documented in French and Spanish pharmacovigilance databases (Dardonville et al., 2019).

The integration of healthcare claim data with SRS data, as demonstrated in this study, offers a promising approach to enhancing the safety of antidepressant use. It enables more accurate signal detection, proactive risk management, and improved patient care, ultimately leading to safer and more effective antidepressant treatments.

4.1 Limitations

This study has several limitations worth noting. First, our analysis was constrained to a 12-month timeframe from the NHIC database, which necessitated limiting the KAERS data to the same 12-month period. Extending the observation period could have potentially yielded more safety signals.

Second, it's essential to acknowledge the fundamental differences in how these two systems identify safety issues. KAERS relies on voluntary and anonymous safety reports, which are associated with a higher likelihood of under-reporting and can be influenced by reporting biases driven by media coverage, financial incentives, and the duration a drug has been available on the market. In contrast, NHIC identifies drug-induced disorders based on KCD codes recorded during patients' clinic visits, where the causality assessment between the drug and the disorders may not be as certain as in KAERS. This means that unless a patient seeks medical attention for a particular disorder and that disorder is specifically coded as drug-induced in the KCD system, it may not be captured as a safety problem in NHIC. However, prior research using NHIC for signal detection has demonstrated a relatively high positive predictive value (PPV); i.e., 80% for statin-specific adverse events, 32% for rosuvastatin-specific adverse events (Choi et al., 2010).

Lastly, while we compared the signals identified in both systems with labeling information, there is no universally accepted gold standard to definitively determine which system offers more accurate results. Therefore, direct comparisons between the two systems can pose challenges. Nevertheless, it's important to recognize that both systems provide valuable insights and play distinct roles in enhancing post-market drug surveillance efforts.

5 Conclusion

The NHIC exhibited greater signal detection capabilities, encompassing unlabeled ADR signals, compared to KAERS. Additionally, NHIC demonstrated a lower CAC, indicating potential for capturing more intricate signals. Further investigation is needed for signals detected exclusively in NHIC

but not covered by labeling information. Integrating safety signal detection from both healthcare claims and SRS databases enhances the safety of antidepressants use and provides valuable regulatory insights for pharmacovigilance.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Seoul National University Institutional Review Board (IRB No. E2104/002-002). 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

TK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing–original draft, Writing–review and editing. XJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing–original draft, Writing–review and editing. YN: Conceptualization, Formal Analysis, Project administration, Writing–review and editing, Methodology, Writing–original draft. MK: Conceptualization, Formal Analysis, Methodology, Project administration, Writing–original draft, Writing–review and editing. SH: Conceptualization, Formal Analysis, Investigation, Project administration, Supervision, Writing–review and editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1291934/full#supplementary-material

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Adverse event reporting of four anti-Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: a real-world study based on the FDA adverse event reporting system

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Background: Anti-Calcitonin gene-related peptide monoclonal antibodies (anti-CGRP mAbs) have shown significant efficacy in preventing migraine. However, there have been limited reports of adverse events (AEs) after marketing, particularly for eptinezumab launched in 2020. The study aimed to mine and analyze the AE signals with four anti-CGRP mAbs from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to gain insights into the safety profile of these medications post-marketing.

Methods: All AE reports on the four anti-CGRP mAbs (erenumab, galcanezumab, fremanezumab, and eptinezumab) were retrieved from the FAERS database from the first quarter (Q1) of 2018 to Q1 of 2023. Disproportionality analysis was measured by reporting odd ratio (ROR) and Bayesian confidence propagation neural network (BCPNN) to identify potential AE signals. Comparisons were made between the four drugs in terms of AEs.

Results: A total of 38,515 reports of erenumab, 19,485 reports of galcanezumab, 5,332 reports of fremanezumab, and 2,460 reports of eptinezumab were obtained, mostly reported in the second to third year after launch in the market. The common AEs to erenumab included constipation (17.93%), injection site pain (14.08%), and alopecia (7.23%). The AEs that occurred more frequently with galcanezumab included injection site pain (24.37%), injection site erythema (5.35%), and injection site haemorrhage (4.97%). Common AEs related to fremanezumab were injection site pain (13.10%), injection site erythema (7.02%), and injection site pruritus (5.47%). Fatigue (13.54%), throat irritation (9.02%), and pruritus (8.20%) were the most common AEs with eptinezumab. In addition, there are new AEs that were not listed in the drug instructions but occurred concurrently with multiple drugs, such as Raynaud's phenomenon, weight increase, menstrual disorders, throat tightness, and paraesthesia oral.

Conclusion: Common AE signals of the four anti-CGRP mAbs and new AE signals were found to provide a reference for clinical drug selection in clinical practice.

KEYWORDS

Calcitonin gene-related peptide, adverse events, migraine, FDA adverse events reporting system, safety

1 Introduction

Calcitonin gene-related peptide (CGRP), a peptide neurotransmitter, and its receptors are widely distributed in the trigeminal vascular system and the central nervous system (Liu et al., 2022). The release of CGRP increases during migraine attacks, and CGRP levels are positively correlated with headache severity (Goadsby et al., 1988). Four monoclonal antibodies (mAbs) targeting the CGRP have been approved by the United States Food and Drug Administration (FDA) for the prevention of episodic and chronic migraine, including one anti-CGRP receptor mAb (Eerenumab) and 2 anti-CGRP ligand mAbs (fremanezumab and galcanezumab) available in 2018 and 1 anti-CGRP ligand mAb (eptinezumab) available in 2020. These mAbs can significantly prevent episodic or chronic migraine, as shown by reduced numbers of migraine days per month and days on acute medication, with a good safety profile.

Currently, due to the better preventive effect of CGRP antibodies and the cyclical nature of migraine attacks, German and European guidelines recommend that migraine patients undergo a treatment break after 9–12 months of CGRP antibody therapy (Diener et al., 2020). However, current real-world data suggests that migraine headaches will appear an increasing deteriorating trend during the 3 months of discontinuing CGRP antibodies in most patients (Pavelic et al., 2022). More data are needed on the benefits of treatment interruption.

The majority of studies support good effectiveness and tolerability of anti-CGRP-mAbs in the real world (Pavelic et al., 2022). However, there is not much data on these drugs' post-marketing safety, and many available papers are real-world single-center studies with limited sample sizes (Alex et al., 2020; Kanaan et al., 2020; Viudez-Martinez et al., 2022). Furthermore, since eptinezumab is a newly marketed anti-CGRP mAb, there are few reports of relevant adverse events (AEs). By comparing the AEs of other anti-CGRP mAbs, the potential AEs of eptinezumab might be identified more quickly and provide recommendations for clinical use.

The FDA Adverse Event Reporting System (FAERS) is an important source of data about AEs in the real-world setting. The FAERS database is a public, voluntary, and spontaneous reporting system that contains information on AEs and medication error reports submitted by health professionals, consumers, and drug manufacturers, thus reflecting, to some extent, the occurrence of drug AEs in the real world.

Therefore, this study aimed to mine AEs on the four anti-CGRP mAbs for migraine prophylaxis from the FAERS database. By comparing the similarities and differences of AEs among four anti-CGRP mAbs, undetected AEs were explored to provide forewarning for clinical drug selection. The results should provide reference to clinicians and promote further research in the real world.

2 Methods

2.1 Data source

The FAERS database was summarized quarterly and contains AE reports, medication errors, and product quality issues. As erenumab, fremanezumab and galcanezumab were all launched in 2018, the data retrieval started from the first quarter (Q1) of 2018 to Q1 of 2023, and a total of 21 quarterly ASCII data packages were extracted from the FAERS database and imported into the SAS 9.4 software for data cleaning and analysis. Data were cleaned by deduplication and excluding missing values. According to the FDA's recommendations, we selected the latest FDA_DT (date FDA received the case) when the PRIMARYIDs (a unique number for identifying a FAERS report) were the same, and chose the highest PRIMARYID when the FDA_DT and the CASEID (a number for identifying a FAERS case) were the same, to remove duplicate reports submitted by various individuals and institutions. FAERS reported drugs are arbitrary, so the generic names and brand names were used as keywords for data extraction. The AEs were classified and standardized based on the preferred terms (PTs) and system organ classes (SOCs) in the Medical Dictionary for Regulatory Activities (MedDRA).

TABLE 1 Calculation formulas.

	AEs of interest	All other AEs	Total
Drugs of interest	a	b	a+b
All other drugs in FAERs	c	d	c + d
Total	a+c	b + d	N = a+b + c + d

Note: FAERS: FDA adverse event reporting system; AEs: adverse events.

Reporting odds ratio (ROR) = $\frac{ad}{bc}$.

ROR 95%CI = $e^{\ln(\mathrm{ROR})\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$

Information components (IC) = $log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$

$IC_{025} = e^{\ln(IC)-1.96\ (\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})^{*}0.5}$

TABLE 2 Demographic information on patients treated with anti-CGRP mAbs.

	Total		Erenumab		Galcanezumab		Fremanezumab		Eptinezumab	
	(n = 65,792)		(n = 38,515)		(n = 19,485)		(n = 5,332)		(n = 2,460)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	7,646	11.62	4,736	12.30	2,124	10.90	493	9.25	293	11.91
Female	47,431	72.09	26,365	68.45	14,860	76.26	4,362	81.81	1,844	74.96
Unknown	10,715	16.29	7,414	19.25	2,501	12.84	477	8.95	323	13.13
Age (years)										
<18	278	0.38	202	0.52	43	0.22	29	0.54	4	0.16
18–45	12,163	11.91	7,909	20.53	2,597	13.33	1,000	18.75	657	26.71
45–65	15,456	24.58	10,689	27.75	2,643	13.56	1,112	20.86	1,012	41.14
>65	5,343	6.52	4,067	10.56	632	2.25	383	7.18	261	9.44
Unknown	32,552	56.61	15,648	40.63	13,570	69.64	2,808	52.66	526	21.38
Mean (SD)	48.66 (14.96)		49.84 (15.18)		46.32 (14.42)		48.19 (15.04)		49.59 (13.83)	
Reporting year										
2018	7,427	11.29	7,088	18.40	218	1.12	121	2.27	0	0
2019	16,444	24.99	10,716	27.82	4,499	23.09	1,229	23.05	0	0
2020	15,783	23.99	8,439	21.91	6,351	32.59	869	16.30	124	5.04
2021	12,131	18.44	5,629	14.62	4,408	22.62	1,359	25.49	735	29.88
2022	11,240	17.08	5,335	13.85	3,305	16.96	1,387	26.01	1,213	49.31
2023	2,767	4.21	1,308	3.40	704	3.61	367	6.88	388	15.77
Serious outcomes										
Hospitalization	1,264	2.86	1,271	3.30	456	2.34	289	5.42	67	2.72
Disability	348	0.79	515	1.34	160	0.82	98	1.84	7	0.28
Life-threatening	175	0.40	209	0.54	42	0.22	32	0.60	6	0.24
Death	252	0.57	296	0.77	40	0.21	35	0.66	9	0.37
Reported from the United States	62,721	95.33	36,436	94.60	19,151	98.29	4,703	88.20	2,431	98.82

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TABLE 3 Signal detection of four anti-CGRP mAbs at the SOC level.

Erenumab				Galcanezumab				Fremanezumab				Eptinezumab			
SOC	PT	n	%	SOC	PT	n	%	SOC	PT	n	%	SOC	PT	n	%
General disorders and administration site conditions	30	6,918	42.97	General disorders and administration site conditions	35	10,539	62.97	General disorders and administration site conditions	35	3,465	58.87	Respiratory, thoracic and mediastinal disorders	11	323	29.74
Gastrointestinal disorders	17	3,434	21.33	Skin and subcutaneous tissue disorders	6	1,701	10.16	Skin and subcutaneous tissue disorders	12	885	15.04	General disorders and administration site conditions	11	305	28.08
Skin and subcutaneous tissue disorders	5	1,459	9.06	Psychiatric disorders	13	1,160	6.93	Psychiatric disorders	11	336	5.71	Infections and infestations	2	92	8.47
Psychiatric disorders	8	1,444	8.97	Gastrointestinal disorders	6	683	4.08	Gastrointestinal disorders	6	247	4.20	Skin and subcutaneous tissue disorders	1	89	8.20
Musculoskeletal and connective tissue disorders	7	1,091	6.78	Nervous system disorders	10	597	3.57	Musculoskeletal and connective tissue disorders	3	223	3.79	Immune system disorders	3	82	7.55
Nervous system disorders	10	616	3.83	Musculoskeletal and connective tissue disorders	6	567	3.39	Nervous system disorders	8	203	3.45	Gastrointestinal disorders	4	59	5.43
Investigations	3	425	2.64	Investigations	3	547	3.27	Investigations	2	144	2.45	Vascular disorders	2	34	3.13
Cardiac disorders	3	267	1.66	Immune system disorders	3	329	1.97	Immune system disorders	1	112	1.90	Nervous system disorders	2	29	2.67
Reproductive system and breast disorders	8	182	1.13	Eye disorders	1	194	1.16	Cardiac disorders	1	85	1.44	Injury, poisoning and procedural complications	3	29	2.67
Injury, poisoning and procedural complications	6	91	0.57	Reproductive system and breast disorders	8	131	0.78	Injury, poisoning and procedural complications	5	63	1.07	Investigations	1	17	1.57
Vascular disorders	2	54	0.34	Cardiac disorders	2	124	0.74	Respiratory, thoracic and mediastinal disorders	4	53	0.90	Eye disorders	2	12	1.10
Respiratory, thoracic and mediastinal disorders	1	46	0.29	Respiratory, thoracic and mediastinal disorders	2	54	0.32	Reproductive system and breast disorders	4	32	0.54	Musculoskeletal and connective tissue disorders	1	9	0.83
Eye disorders	2	34	0.21	Injury, poisoning and procedural complications	3	42	0.25	Vascular disorders	1	14	0.24	Metabolism and nutrition disorders	1	6	0.55
Immune system disorders	1	21	0.13	Vascular disorders	1	35	0.21	Infections and infestations	2	12	0.20				
Endocrine disorders	1	11	0.07	Infections and infestations	3	19	0.11	Eye disorders	2	12	0.20				
Renal and urinary disorders	1	6	0.04	Ear and labyrinth disorders	1	14	0.08								
Total	105	16,099	100.00		103	16,736	100.00		97	5,886	100.00		44	1,086	100.00

Notes:SOC: system organ class; PT: preferred term.

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TABLE 4 Top 30 AEs for four anti-CGRP mAbs.

	Erenmab			Galcanezumab			Fremanezumab			Eptinezumab		
	AE	n	%	AE	n	%	AE	n	%	AE	n	%
1	Constipation	2,887	17.93	Injection site pain	4,079	24.37	Injection site pain	771	13.10	Fatigue	147	13.54
2	Injection site pain	2,267	14.08	Injection site erythema	896	5.35	Injection site erythema	413	7.02	Throat irritation	98	9.02
3	Alopecia	1,164	7.23	Injection site haemorrhage	831	4.97	Injection site pruritus	322	5.47	Pruritus	89	8.20
4	Injection site haemorrhage	926	5.75	Injection site pruritus	676	4.04	Injection site swelling	262	4.45	Nasal congestion	81	7.46
5	Muscle spasms	625	3.88	Injection site swelling	663	3.96	Pruritus	216	3.67	Feeling abnormal	61	5.62
6	Feeling abnormal	542	3.37	Injection site reaction	595	3.56	Injection site reaction	193	3.28	COVID-19	61	5.62
7	Injection site bruising	535	3.32	Alopecia	582	3.48	Rash	190	3.23	Hypersensitivity	56	5.16
8	Anxiety	444	2.76	Weight increased	528	3.15	Alopecia	182	3.09	Oropharyngeal pain	45	4.14
9	Injection site erythema	437	2.71	Constipation	495	2.96	Injection site rash	170	2.89	Rhinorrhoea	40	3.68
10	Injection site swelling	418	2.60	Injection site bruising	434	2.59	Injection site extravasation	167	2.84	Nasopharyngitis	31	2.85
11	Weight increased	407	2.53	Pruritus	389	2.32	Constipation	159	2.70	Constipation	31	2.85
12	Insomnia	386	2.40	Rash	381	2.28	Arthralgia	146	2.48	Memory impairment	25	2.30
13	Depression	338	2.10	Injection site urticaria	378	2.26	Weight increased	139	2.36	Chest discomfort	24	2.21
14	Myalgia	317	1.97	Anxiety	378	2.26	Urticaria	132	2.24	Infusion site pain	23	2.12
15	Influenza like illness	274	1.70	Feeling abnormal	355	2.12	Injection site mass	131	2.23	Flushing	22	2.03
16	Injection site reaction	257	1.60	Injection site mass	346	2.07	Feeling abnormal	128	2.17	Anaphylactic reaction	21	1.93
17	Urticaria	253	1.57	Arthralgia	335	2.00	Anxiety	122	2.07	Sneezing	20	1.84
18	Hypoaesthesia	253	1.57	Urticaria	296	1.77	Hypersensitivity	112	1.90	Infusion related reaction	19	1.75
19	Paraesthesia	252	1.57	Injection site rash	270	1.61	Injection site urticaria	109	1.85	Heart rate increased	17	1.57
20	Palpitations	245	1.52	Hypersensitivity	261	1.56	Injection site bruising	94	1.60	Throat tightness	13	1.20
21	Injection site pruritus	215	1.34	Insomnia	203	1.21	Insomnia	93	1.58	Dry mouth	13	1.20
22	Abdominal distension	181	1.12	Visual impairment	194	1.16	Injection site haemorrhage	91	1.55	Hot flush	12	1.10
23	Injection site urticaria	158	0.98	Depression	187	1.12	Erythema	85	1.44	Infusion site bruising	11	1.01
24	Injection site rash	134	0.83	Injection site warmth	177	1.06	Palpitations	85	1.44	Infusion site extravasation	9	0.83
25	Injection site mass	120	0.75	Myalgia	148	0.88	Injection site warmth	76	1.29	Paraesthesia oral	9	0.83
26	Injection site extravasation	109	0.68	Paraesthesia	135	0.81	Myalgia	66	1.12	Fibromyalgia	9	0.83

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TABLE 4 (*Continued*) Top 30 AEs for four anti-CGRP mAbs.

	Erenmab			Galcanezumab			Fremanezumab			Eptinezumab		
	AE	n	%	AE	n	%	AE	n	%	AE	n	%
27	Injection site indentation	107	0.66	Hypoaesthesia	125	0.75	Paraesthesia	58	0.99	Pharyngeal swelling	8	0.74
28	Panic attack	85	0.53	Memory impairment	125	0.75	Hypoaesthesia	56	0.95	Sinus congestion	8	0.74
29	Injection site discomfort	70	0.43	Stress	120	0.72	Chest pain	53	0.90	Eye pruritus	8	0.74
30	Irritable bowel syndrome	70	0.43	Palpitations	120	0.72	Injection site discharge	52	0.88	Feeling cold	7	0.64

Notes: AE, adverse event.

2.2 Data mining and analysis

Disproportionality analysis was performed in our study to indicate the proportion of AEs occurring between a specific drug and all other drugs. Two disproportional signal detection methods used in this study were reporting odd ratio (ROR) and Bayesian confidence propagation neural network (BCPNN). These methods were based on the two-by-two contingency table, if the ratio exceeds the specified threshold, i.e., the ratio is out of proportion, it indicates signal generation (Huang et al., 2014). The corresponding ROR, information components (IC), and 95% confidence interval (CI) were calculated accordingly to determine the signal intensity of each adverse event for each drug. The calculation formulas are shown in Table 1.

To generate a valid signal in screening, the number of reports should be at least 3, the lower limit of ROR 95% CI should be greater than one, and IC_{025} must be above 0. An association between the AE and the target drug was demonstrated by valid signal generation. A larger signal value (i.e., ROR) indicated a stronger association between the target drug and the suspected AE. However, it does not necessarily mean that there was a causal relationship between the two biologically according to FDA instruction, and reports do not have enough detail to evaluate an event properly. In our study, we excluded AEs associated with product problems, medication errors, off-label or unlicensed use, indication-related, and disease states.

3 Results

3.1 Characteristic of the patients

A total of 65,792 reports for CGRP mAbs have been entered into the FAERS from the Q1 of 2018 to the Q1 of 2023, including 38,515 for erenumab, 19,485 for galcanezumab, 5,332 for fremanezumab, and 2,460 for eptinezumab. Most patients were between 45 and 65 years old, and the average age was 48.66 (14.96). There were more women than men in these reports and the percentages of females in the reports for erenumab, galcanezumab, fremanezumab, and eptinezumab were 68.45%, 76.26%, 81.81%, and 74.96%, respectively. The highest rates of AE reporting were concentrated in the second to third years after the launch of the drugs. The country with the most reported data was the United States (95.33%). The demographic information of the patients treated with the four anti-CGRP mAbs is shown in Table 2.

3.2 Signal detection at the SOC for four anti-CGRP mAbs

Based on the disproportionality analysis, the final positive signals for the 4 CGRP antibodies, erenumab, galcanezumab, fremanezumab, and eptinezumab, used for analysis were 105, 103, 97, and 44, respectively, and the numbers of reports were 16,099, 16,736, 5,886, and 1,086, respectively (Table 3). For erenumab, the top three SOCs are general disorders and administration site conditions (n = 6,918, 42.97%), gastrointestinal disorders (n = 3,434, 21.33%), and skin and

TABLE 5 AEs co-reported for the four anti-CGRP mAbs.

	AE	Erenumab			Galcanezumab			Fremanezumab			Eptinezumab		
		n	%	ROR (95% CI)	n	%	ROR (95% CI)	n	%	ROR (95% CI)	n	%	ROR (95% CI)
1	Constipation	2,887	17.93	10.32 (9.94,10.72)	495	2.96	3.60 (3.30,3.94)	159	2.70	2.86 (2.45,3.35)	31	2.85	1.77 (1.24,2.52)
2	Feeling abnormal	542	3.37	1.64 (1.51,1.79)	355	2.12	2.31 (2.08,2.57)	128	2.17	2.07 (1.74,2.46)	61	5.62	3.16 (2.45,4.06)
3	Throat tightness	46	0.29	1.36 (1.02,1.81)	32	0.19	2.02 (1.43,2.86)	29	0.49	4.57 (3.17,6.59)	13	1.20	6.53 (3.79,11.26)
4	Paraesthesia oral	38	0.24	2.08 (1.51,2.86)	16	0.10	1.87 (1.14,3.05)	11	0.19	3.19 (1.77,5.77)	9	0.83	8.34 (4.34,16.05)
5	Alopecia	1,164	7.23	3.31 (3.12,3.51)	582	3.48	3.53 (3.25,3.83)	182	3.09	2.73 (2.36,3.16)			
6	Anxiety	444	2.76%	1.12 (1.02,1.23)	378	2.26%	2.05 (1.86,2.27)	122	2.07%	1.64 (1.38,1.97)			
7	Weight increased	407	2.53	1.37 (1.24,1.51)	528	3.15	3.86 (3.54,4.20)	139	2.36	2.51 (2.12,2.96)			
8	Insomnia	386	2.40	1.19 (1.07,1.31)	203	1.21	1.34 (1.16,1.53)	93	1.58	1.52 (1.24,1.87)			
9	Myalgia	317	1.97	1.50 (1.34,1.68)	148	0.88	1.50 (1.27,1.76)	66	1.12	1.66 (1.31,2.12)			
10	Influenza like illness	274	1.70	2.96 (2.63,3.33)	75	0.45	1.72 (1.37,2.16)	34	0.58	1.94 (1.39,2.72)			
11	Hypoaesthesia	253	1.57	1.34 (1.19,1.52)	125	0.75	1.42 (1.19,1.69)	56	0.95	1.58 (1.22,2.06)			
12	Urticaria	253	1.57	1.14 (1.01,1.29)	296	1.77	2.88 (2.57,3.23)	132	2.24	3.19 (2.69,3.79)			
13	Paraesthesia	252	1.57	1.25 (1.11,1.42)	135	0.81	1.44 (1.21,1.70)	58	0.99	1.54 (1.19,1.99)			
14	Palpitations	245	1.52	1.67 (1.47,1.89)	120	0.72	1.75 (1.46,2.09)	85	1.44	3.09 (2.50,3.83)			
15	Abdominal distension	181	1.12	1.38 (1.19,1.59)	104	0.62	1.69 (1.40,2.05)	37	0.63	1.50 (1.08,2.07)			
16	Panic attack	85	0.53	1.99 (1.61,2.46)	57	0.34	2.85 (2.20,3.70)	34	0.58	4.23 (3.02,5.93)			
17	Fear of injection	66	0.41	6.07 (4.76,7.75)	56	0.33	11.02 (8.45,14.35)	12	0.20	5.79 (3.28,10.21)			
18	Menstruation irregular	53	0.33	3.32 (2.53,4.35)	29	0.17	3.87 (2.69,5.58)	9	0.15	2.98 (1.55,5.73)			
19	Abnormal dreams	52	0.32	2.32 (1.77,3.05)	29	0.17	2.77 (1.92,3.98)	10	0.17	2.37 (1.27,4.41)			
20	Raynaud's phenomenon	50	0.31	8.28 (6.24,10.97)	35	0.21	12.31 (8.81,17.21)	14	0.24	12.12 (7.16,20.51)			
21	Muscle tightness	42	0.26	2.10 (1.55,2.84)	16	0.10	1.71 (1.04,2.79)	11	0.19	2.92 (1.62,5.28)			
22	Menstrual disorder	40	0.25	3.97 (2.90,5.42)	20	0.12	4.22 (2.72,6.56)	14	0.24	7.35 (4.35,12.43)			
23	Trichorrhexis	22	0.14	6.10 (3.99,9.30)	9	0.05	5.28 (2.74,10.17)	6	0.10	8.74 (3.92,19.51)			
24	Hormone level abnormal	15	0.09	2.20 (1.32,3.65)	13	0.08	4.08 (2.36,7.04)	5	0.08	3.89 (1.62,9.37)			
25	Oligomenorrhoea	7	0.04	3.73 (1.77,7.87)	4	0.02	4.55 (1.7,12.16)	3	0.05	8.48 (2.73,26.40)			
26	Concussion	36	0.22	3.32 (2.39,4.61)	12	0.07	2.35 (1.33,4.15)				6	0.55	9.34 (4.19,20.82)
27	Fibromyalgia	43	0.27	1.38 (1.02,1.86)	24	0.14	1.65 (1.10,2.46)				9	0.83	4.90 (2.55,9.43)
28	Blepharospasm	31	0.19	4.90 (3.44,6.99)				6	0.10	5.00 (2.24,11.14)	4	0.37	10.62 (3.98,28.33)
29	Pruritus				389	2.32	1.58 (1.43,1.74)	216	3.67	2.19 (1.91,2.50)	89	8.20	2.88 (2.34,3.55)
30	Pharyngeal swelling				22	0.13	2.20 (1.45,3.35)	12	0.20	2.99 (1.70,5.26)	8	0.74	6.35 (3.17,12.72)
31	Swollen tongue				34	0.20	2.02 (1.44,2.83)	26	0.44	3.84 (2.62,5.65)	6	0.55	2.82 (1.27,6.29)

Notes: AE: adverse event; ROR: reporting odd ratio; CI: confidence interval.

subcutaneous tissue disorders (n = 1,459, 9.06%). For galcanezumab, AEs are mainly focused on the three SOCs of general disorders and administration site conditions (n = 10,539, 62.97%), skin and subcutaneous tissue disorders (n = 1,701, 10.16%), and psychiatric disorders (n = 1,160, 6.93%). General disorders and administration site conditions (n = 3,456, 58.87%), skin and subcutaneous tissue disorders (n = 885, 15.04%), and psychiatric disorders (n = 336, 5.71%) are the top three SOCs for fremanezumab. Respiratory, thoracic, and mediastinal disorders (n = 323, 29.74%), general disorders and administration site conditions (n = 305, 28.08%), and infections and infestations (n = 92, 8.47%) are the common SOC for eptinezumab. AEs signal detection under each SOC for four anti-CGRP mAbs were shown in Supplementary Table S1–S4.

3.3 The common AEs for four anti-CGRP mAbs

AEs were ranked according to frequency of occurrence, and the top 30 AEs were listed for each drug in Table 4. The five most common AEs to erenumab included constipation (n = 2,287, 17.93%), injection site pain (n = 2,267,14.08%), alopecia (n = 1,164,7.23%), injection site haemorrhage (n = 926, 5.75%), and muscle spasms (n = 625,3.88%). The AEs that occurred more frequently with galcanezumab included injection site pain (n = 4,079, 24.37%), injection site erythema (n = 896, 5.35%), injection site haemorrhage (n = 831, 4.97%), injection site pruritus (n = 676, 4.04%), injection site swelling (n = 663, 3.96%). Common AEs related to fremanezumab were injection site pain (n = 771, 13.10%), injection site erythema (n = 413, 7.02%), injection site pruritus (n = 322, 5.47%), injection site swelling (n = 262, 4.45%), and pruritus (n = 216, 3.67%). There were fewer signals mined for eptinezumab since it launched later than the three other anti-CGRP mAbs. AEs with an incidence of more than 5% were fatigue (n = 147, 13.54%), throat irritation (n = 98, 9.02%), pruritus (n = 89, 8.20%), nasal congestion (n = 81, 7.46%), feeling abnormal (n = 61, 5.62%), COVID-19 (n = 61, 5.62%), and hypersensitivity (n = 56, 5.16%).

3.4 AEs co-reported for the four anti-CGRP mAbs

We conducted a comparison of the AEs with the four drugs (Table 5). In addition to injection-related adverse events, 31 AEs were reported in more than three anti-CGRP mAbs. Four AEs have been reported to all four anti-CGRP mAbs, including constipation, feeling abnormal, throat tightness, and paraesthesia oral. There are 21 AEs co-reported in all three subcutaneously administered drugs, including alopecia, anxiety, weight increase, insomnia, myalgia, influenza-like illness, hypoaesthesia, urticaria, paraesthesia, palpitations, abdominal distension, panic attack, fear of injection, menstruation irregular, abnormal dreams, Raynaud's phenomenon, muscle tightness, menstrual disorder, trichorrhexis, hormone level abnormal, and oligomenorrhoea. Some of the AEs have been reported with eptinezumab, which are also reported in galcanezumab, fremanezumab, and erenumab, including concussion, fibromyalgia, blepharospasm, pruritus, pharyngeal swelling, and swollen tongue.

3.5 Injection-related AEs for the four anti-CGRP mAbs

Erenumab, fremanezumab, and galcanezumab are administered subcutaneously, so injection-related AEs were common. In contrast, eptinezumab is the only anti-CGRP mAb administered by intravenous infusion, so the corresponding adverse reaction is an infusion site reaction. Aggregating the AEs related to injection or infusion (Supplementary Table S5), 37 AEs related to injection and 8 AEs related to infusion were found. Specifically, the largest number of injection-site AEs associated with galcanezumab, amounting to 10,012 cases and accounting for 59.82% of all mined AEs; 6,099 cases of injection-site reactions associated with erenumab, accounting for 37.88%; 3,086 cases related to fremanezumab, accounting for 52.43%. 85 cases of infusion-related reactions have been reported with eptinezumab, which represents 7.83% of all AEs. Common injection site AEs included injection site pain, injection site erythema, injection site pruritus, and injection site haemorrhage.

4 Discussion

This study mined the AE signals of four anti-CGRP mAbs from the FAERS database using ROR and BCPNN. The ROR method has the advantages of simplicity of calculation, reduction of bias due to control group selection, and high sensitivity. However, the specificity is relatively low and prone to false positives. The BCPNN method, on the other hand, combines Bayesian logic and neural network structure for more stable results and higher specificity. Those two methods were combined in this study to reduce the results bias caused by a single algorithm. It is the first retrospective study to analyze and compare all post-marketing AEs related to the four drugs to date, intending to provide a reference for predicting AEs of anti-CGRP drugs and clinical drug selection.

The signal mining revealed that the primary SOC for the four antibodies was general disorders and administration site conditions, with injection site reactions being the most frequently reported AE, which was similar to the main AE described in the instruction. Nevertheless, the injection-related AEs observed in this study were more diverse, manifesting as injection site depression, swelling, bruising, urticaria, rash, warmth, induration, irritation, and extravasation, etc. The incidence of injection site reactions is high among FDA-approved self-injectable biologics, with up to 40% reported (Thomaidou and Ramot, 2019), which can directly reduce patient compliance and, thus, the drug's efficacy. Nevertheless, the symptoms of injection-related reactions in this study were mild, and no medication discontinuation due to injection reactions has been reported. However, long-term subcutaneous drug administration may lead to fear of injection in patients. In this study, strong signals of fear of injection were mined for all three subcutaneously injected drugs, with erenumab (ROR = 6.07; 95% CI, 4.76–7.75), galcanezumab (ROR = 11.02; 95% CI, 8.45–14.35), fremanezumab (ROR = 5.79; 95% CI, 3.28–10.21). It is noteworthy

that since eptinezumab is administered intravenously and at long intervals between doses, it has a low incidence of injection-induced AEs. Compared to the other three drugs, it may provide patients with a better treatment experience.

It can be seen from the reported AEs related to anti-CGRP mAbs that a large proportion of the cases were female patients, consistent with the epidemiological profile of migraine (Broner et al., 2017; Charles, 2017). Females are more likely to suffer migraine attacks than males, with hormonal fluctuations, particularly changes in estrogen levels, playing an important role (Broner et al., 2017). Migraine attacks in women are more frequent, severe, and prolonged and are accompanied by many symptoms, such as photophobia, phonophobia, and nausea (Boardman et al., 2003; Pavlovic et al., 2017). The AEs of hormone level abnormal, menstrual disorder, menstruation irregular, and oligomenorrhoea were mined in the three subcutaneously injected drugs in this study, which had not been reported previously in previous studies. A decrease in estrogen during the luteal phase of the menstrual cycle is an important trigger for migraine attacks during menstruation, and 70% of women with migraine can develop menstrual migraines (Calhoun, 2018). This might be due to the change of CGRP levels during the menstrual cycle (Raffaelli et al., 2021), while CGRP can promote neurogenic inflammation of the endometrial tissues (Yan et al., 2019). Therefore, blocking CGRP could induce changes in menstruation. However, there were no relevant signals of menstrual disorder have been mined in the novel drug for eptinezumab.

Constipation was the most reported post-marketing AE of erenumab. It had been reported in previous clinical trials of erenumab (Sun et al., 2016; Tepper et al., 2017; Takeshima et al., 2021) and mentioned in real-world studies (Ornello et al., 2020; Deligianni et al., 2021). Compared with other drugs, erenumab showed a stronger signal of constipation (ROR = 10.32, 95% CI, 9.94–10.72) and was reported most frequently. However, there was no mention of constipation in any of the clinical trials of galcanezumab, fremanezumab, or eptinezumab (Dodick et al., 2018; Skljarevski et al., 2018; Ferrari et al., 2019; Lipton et al., 2020; Mulleners et al., 2020), but the signal was strong in our study. According to another study based on the FAERS database of three drugs administered subcutaneously 6 months after marketing, only erenumab was reported to cause constipation (Silberstein et al., 2023). This discrepancy between the present study and the previous one may be because short-term constipation may not be easily taken seriously by patients, and only chronic constipation caused by long-term medication may attract their attention. CGRP, as an endogenous neuropeptide, is also distributed in the primary afferent nerve cells of the submucosal plexus of the enteric nervous system; it transmits signals from various physical and chemical stimuli in the intestinal lumen or intestinal wall and is involved in regulating the functions and activities of the gastrointestinal tract (Clifton et al., 2007; Holzer and Holzer-Petsche, 2021). Hence, constipation during treatment with anti-CGRP mAb treatment has a biological basis. There has been a warning included in the instructions for erenumab that the drug may cause constipation companied serious complications. It is the first time that eptinezumab has been reported to cause constipation, and the signal strength is (ROR = 1.77, 95% CI, 1.24–2.52) with 31 cases.

Alopecia was another most common AE, observed in three subcutaneous injections, which was only reported post-marketing (Ruiz et al., 2023) and not found in the clinical trial phase. Initially, the reports did not attract clinical attention and were not sufficient for meaningful analysis due to the small number of cases at the time. Nevertheless, a more recent study has observed an association between CGRP inhibitor use and alopecia in migraine sufferers (Woods, 2022). Likewise, erenumab, fremanezumab, and galcanezumab all had strong signals of alopecia in our study, with signal intensities of 3.31 (95% CI, 3.12–3.51), 2.73 (95% CI, 2.36–3.16), and 3.53 (95% CI, 3.25–3.83), respectively. Thus, it is essential to focus on the long-term AE of alopecia in clinical practice, since alopecia may affect patients' quality of life (Tzur et al., 2022). Moreover, the AE of trichorrhexis which may be associated with alopecia was tapped in those three drugs. CGRP plays an important role in maintaining the immune privilege of hair follicles (Pi et al., 2013). In addition, reduced levels of CGRP result in reduced blood supply to the hair follicle (Rossi et al., 1997). The repetitive activation of C fibers in migraine can also result in the depletion of substance P and CGRP, leading to the loss of hair growth promotion and reduction of microvascular blood flow to the hair follicle (Bedrin and Dougherty, 2020). Therefore, drugs inhibiting CGRP can lead to alopecia. In the reports of eptinezumab, we temporarily did not observe a signal related to alopecia.

A new signal that was not mentioned in the instructions of any anti-CGRP mAbs but had a strong signal was found in the present study. Raynaud phenomenon is an exaggerated physiological response to cold exposure or emotional stress characterized by a triphasic color change in extremities due to impaired blood circulation that can lead to ulceration, scarring, or gangrene (Goundry et al., 2012). There have been some previous case reports reported that fremanezumab, galcanezumab, and erenumab could induce Raynaud's phenomenon (Evans, 2019; Manickam et al., 2021), but the number was less. In this study, the cases were reported more frequently and with a strong signal for all three drugs: ROR = 8.26 (95% CI, 6.24–10.97) for erenumab, ROR = 12.31 (95% CI, 8.81–17.21) for galcanezumab, and ROR = 12.12 (95% CI, 7.16–20.51) for fremanezumab. CGRP is stored in vesicles on sensory nerve endings, and activation of its receptors contributes to blood vessel dilation. One study showed that CGRP immunoreactive fibers were significantly reduced in the epidermis and subepidermis of skin in patients with the Raynaud phenomenon compared to controls (Terenghi et al., 1991), suggested that blocking CGRP could cause the Raynaud phenomenon. Therefore, while anti-CGRP drugs can reduce the release of CGRP and relieve migraine attacks, they also can induce Raynaud's phenomenon in some cases. A real-world study showed that anti-CGRP drugs could induce or aggravate Raynaud's phenomenon with a significantly stronger signal than triphenylamine, which is a migraine drug that can induce the Raynaud phenomenon (Gerard et al., 2022). Although the Raynaud phenomenon was rare and the use of anti-CGRP mAbs in patients with the Raynaud phenomenon had a low incidence of microvascular complications, this was still considered worthy of attention in clinical practice (Breen et al., 2021).

The AE of weight increased have been reported frequently for all three drugs administered subcutaneously, with the number of 407, 528, and 139 for erenumab, galcanezumab, and fremanezumab, respectively. To date, there have been no case reports of anti-CGRP

mAbs causing weight increase. CGRP and amylin are both members of the same peptide family and have been investigated as potential treatments for metabolic diseases (Sonne et al., 2021). The release of CGRP may play an important role in adipocyte lipid metabolism and thus in systemic metabolism (Nogueiras et al., 2010). Anti-CGRP mAbs may inhibit the release of CGRP thereby affecting metabolism and leading to weight increase. An explorative, prospective, questionnaire-based study showed that 18.8% reported an increase in body weight 3 months after treatment with anti-CGRP mAbs (Iannone et al., 2022). The severity of the weight increase caused by anti-CGRP drugs is unknown based on current reports, but for patients who need or are undergoing weight control, the three subcutaneously administered drugs can induces the risk of weight control failure.

Migraine is the second most common neurological disorder in which the patient has prodromal or concomitant symptoms during the attack. In our study, we have discovered signals that may be associated with co-morbidities or concomitant symptoms and presented in at least three drugs, including feeling abnormal, anxiety, insomnia, hypoaesthesia, paraesthesia, palpitations, panic attack, etc. In addition, this study also uncovered musculoskeletal and connective tissue disorders, such as muscle tightness, muscle spasm, myalgia, and fibromyalgia, which were reported in the erenumab but not in the instruction of other drugs. However, in this study there was no detection of hypertension-related signals. Since CGRP is a microvessel dilator, vascular-related adverse effects have been monitored since the beginning of the clinical trials. This study detected cardiovascular signals, including palpitations, postural tachycardia syndromes, and coronary artery spasms, while no hypertension signals were found. Recently, Sessa et al. showed no significant association between CGRP receptor antagonists and increased risks of hypertension events, consistent with the present study (Sessa and Andersen, 2021). Further data will be required at a later stage to continue to detect the relevant AEs.

Eptinezumab is a newly marketed anti-CGRP mAb that is administered intravenously once every 3 months, which greatly improves patient compliance, especially with patients who fear injections. Previous studies have demonstrated a favorable safety and tolerability for eptinezumab in adult patients with migraine. According to this study, the AEs of post-marketing with high incidence observed in the three subcutaneous anti-CGRP mAbs, including alopecia, weight gain, urticaria, and Raynaud's phenomenon, were not observed in eptinezumab. It may be more beneficial to choose eptinezumab for patients suffering from previous allergic conditions, afraid of alopecia, with a history of Raynaud's phenomenon, and worried about obesity. Furthermore, no reports of menstrual disorders, menstruation irregular, and oligomenorrhoea were reported with eptinezumab, and this drug may be more suitable for women of childbearing age. The common AEs to eptinezumab are fatigue, throat irritation, and pruritus. It is possible that fatigue is a concomitant symptom of migraine, which is relieved during the course of the drug therapy (usually 4 weeks after the second dose) (Lipton et al., 2021). Pruritus is a common allergic skin reaction and is labeled in the instructions, which was observed in fremanezumab and galcanezumab. Throat irritation (ROR = 29.51; 95% CI, 24.15–36.06) was a new and stronger signal AE that should receive attention. There are also several signals associated with throat irritation, including oropharyngeal pain, throat tightness, and swelling of the pharynx. An early study suggested autonomic and peptidergic innervation in the human larynx (Hauser-Kronberger et al., 1993) and that the concentration of pharyngeal sensory CGRP positively correlated with pharyngeal function (Tomsen et al., 2022). Therefore, peptinezumab should be avoided in patients with laryngeal disorders. Of note, due to the late launch of eptinezumab, certain adverse effects may not have yet been reported. Consequently, it is imperative to maintain ongoing surveillance of the AEs linked to anti-GCRP mAbs.

There are several limitations to this study. First, spontaneous reporting is prone to reporting bias, such as incomplete data, duplicate data, unstandardized completion, and high variability in data quality. Second, FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. The reports in FAERS submitted may not fully reflect the causal relationship between exposure and the outcome, and it is impossible to use such data to determine the incidence of a particular reaction in a population. Therefore, additional studies are needed to determine causality. Third, the AE reporting of new drugs can suffer from the Weber effect, in which higher rates of AEs are reported in the early period of drug approval (Arora et al., 2017). Nevertheless, the Weber effect has not been observed in FAERS (Hoffman et al., 2014; Arora et al., 2017). Fourth, in this study, many signals related to the indication of migraine were mined, such as migraine with aura, tension migraine, vestibular migraine, migraine from drug overuse, headache, and post-traumatic headache. And concomitant symptoms associated with migraine attack such as fatigue, poor concentration, anxiety, irritability, irritability, tearing, photophobia, phonophobia, vertigo, dizziness, neck pain, etc. Since these mined signals are associated with the indication of the anti-CGRP mAbs or symptoms accompanied by migraine, it is impossible to determine whether the drugs caused them or whether the drugs exacerbated the symptoms. Fifth, considering the relatively brief duration that these drugs, particularly eptinezumab, have been available on the market, it is essential to maintain continuous monitoring of their safety.

5 Conclusion

This study conducted a thorough analysis and comparison of post-marketing AE signals associated with four anti-CGRP mAbs which contribute to understanding the safety profile of anti-CGRP mAbs in clinical practice, providing valuable insights for clinical drug selection.

Data availability statement

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

Author contributions

WS: Data curation, Writing–original draft. YlL: Data curation, Writing–original draft. BX: Writing–review and editing, Supervision. JC: Methodology, Writing–review and editing. YL: Methodology, Writing–review and editing. JP: Data curation,

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Supplementary material

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Identifying new safety risk of human serum albumin: a retrospective study of real-world data

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Objective: To mine and analyze the adverse reaction signals of human serum albumin (HSA) using the FDA adverse event reporting system (FAERS) database for the safe clinical use of this drug.

Methods: Data cleaning and analysis of adverse event reports in the FAERS database for a total of 76 quarters from Q1 2004 to Q4 2022 were performed using the reporting odds ratio (ROR), Medicines and Healthcare Products Regulatory Agency (MHRA), and Bayesian confidence propagation neural network (BCPNN). Gender-differentiated signal detection was used to investigate the gender differences in the occurrence of HSA adverse events.

Results: Through a combination of three methods, a total of 535 adverse event reports were identified. These reports involved 1,885 cases of adverse reactions, with respiratory, thoracic, and mediastinal disorders, as well as general disorders and administration site conditions, as the most common. One noteworthy new signal was the occurrence of transfusion-related acute lung injury. Additionally, gender-differentiated signals were present, with females experiencing paraesthesia, hypertension, pulmonary oedema, loss of consciousness, and vomiting.

Conclusion: This study has revealed that HSA poses a risk of causing transfusion-related acute lung injury. It has also been observed that adverse reactions, including paraesthesia, hypertension, pulmonary oedema, loss of consciousness, and vomiting, are more prevalent in females. These findings should be taken into account when using HSA in a clinical setting.

KEYWORDS

real-world data, human serum albumin, adverse reactions, safety, FAERS database

1 Introduction

Human serum albumin (HSA) is a biological product derived from plasma collected from hepatitis B vaccine-immunized healthy individuals by low-temperature ethanol protein isolation and heat-inactivated virus at 60°C for 10 h (Basu and Kulkarni, 2014) which can maintain plasma colloid osmolality, inhibit apoptosis and regulate trauma-induced inflammatory response, and has antioxidant activity (Chalidis et al., 2007). As an ideal natural colloid, HSA is now widely used clinically to increase blood volume, replenish plasma albumin, diagnose oedema or ascites of unknown etiology, aid in the treatment of cardiovascular diseases such as ischemic heart disease, heart failure, atrial fibrillation,

stroke, etc. (Arques, 2018); chronic liver diseases such as renal insufficiency, decompensated cirrhosis, circulation in patients with ascites, and spontaneous bacterial peritonitis (Spinella et al., 2016; Jagdish et al., 2021); acute diseases such as hemorrhagic shock, burns, organ transplantation, therapeutic plasmapheresis; and chronic conditions of hypoalbuminemia such as malnutrition syndromes, nephrotic syndromes, and large-volume puncture procedures (Liumbruno et al., 2009).

Since its introduction in 1942, there has been significant interest in studying the safety of HSA due to its widespread use and high clinical dose as an injectable. Based on clinical experience over the past 35 years, it has been generally accepted that HSA is highly safe, to the point where its safety is rarely discussed (Tullis, 1977). This conclusion has been supported by large-scale pharmacovigilance studies (Haase et al., 2013; Tseng et al., 2020). Adverse reactions to HSA have been reported in the literature as isolated incidents (Facciorusso et al., 2011), with most clinical studies focusing on allergy-like reactions such as erythema, immediate hypersensitivity reactions, and anaphylaxis (Fujita et al., 2007; Wang et al., 2019; Daniel et al., 2020).

Over the past few years, the summary of product characteristics for HSA has been updated with additional information on adverse reactions. These reactions include cardiopulmonary issues such as dyspnea, arrhythmia, heart failure, blurred vision, and joint pain (U.S., 2023; FDA, 2023). Post-marketing safety studies on HSA have primarily been conducted between the 1990s and early 2000s (Vincent et al., 2003; Zhou et al., 2013). To better understand the safety of HSA, this study aims to analyze adverse event (AE) signals in the existing real-world big data and conduct a subgroup analysis based on gender. The results will provide a basis for the rational use of HSA in clinical practice, as well as warning revisions to the instructions.

2 Methods

2.1 Data sources and processing

This study was conducted using data from the FDA's adverse event reporting system (FAERS), one of the largest adverse event databases in the world currently available to the public free of charge. It contains all mandatory and spontaneous reports of adverse events related to drug use since 2004 and provides open access to real-world raw data from the FDA on safety reports related to drugs, therapeutic biologics, and case-specific safety reports that can help researchers dig deeper into pharmacovigilance information (FDA., 2023).

The data for this study were obtained from the FAERS database, which has been publicly available since 2004 and is updated quarterly. Data from all ASCII data packages spanning 76 quarters, from Q1 2004 to Q4 2022, were extracted and imported into SAS 9.4 (Statistics Analysis System Institute Inc.) for data cleaning and analysis. According to the FDA's recommended method for removing duplicate reports, reports with missing values for key information such as age and gender are excluded. After Q1 2019, a list of deleted reports exists in each quarterly packet, and after the data are de-weighted, reports are excluded based on the CASEID in the list of deleted reports.

After data cleaning and processing, we used "ALBUMIN HUMAN" to screen the PROD_AI and DRUG_NAME fields to obtain the adverse reaction reports of HSA as the "Primary suspicion" drug, and all other adverse reaction reports in the database were used as the reference group for categorical statistical analysis and signal detection analysis using SAS 9.4 for categorical statistical analysis and signal detection analysis.

Medical Dictionary for Regulatory Activity (MedDRA) has been used by drug regulatory authorities and the regulated pharmaceutical industry for the entry, retrieval, evaluation, and presentation of data throughout the regulatory process from pre-market to post-market application of human products. MedDRA ® 26.0 was used in this study to standardize all preferred terms (PTs), which were then mapped to system organ classification (SOC) for further analysis.

2.2 Descriptive statistics

Descriptive statistics refers to the organization, overview, and calculation of a large amount of data information contained in a survey sample and is a method of summarizing and expressing quantitative data in a way that reveals the characteristics of the data distribution. This study categorized and statistically analyzed HSA-related adverse event reports for patient characteristics such as age, sex, and country.

2.3 Disproportionality analysis

The disproportionality analysis is a commonly used signal detection method based on the concept that a signal is considered to have been generated if a combination of drug-specific events in a database is significantly higher than the background frequency of the entire database and meets certain criteria. The calculation of the ratio imbalance measure is based on the construction of a 2 × 2 matrix table of behavioral target drugs and all other drugs, listed as target adverse events and all other adverse events, as shown in Table 1. Where A is the number of target adverse events for the target drug in the database, B is the number of other adverse events for the target drug in the database, C is the number of target adverse events for other drugs in the database, and D is the number of other adverse events for other drugs in the database.

To avoid generating signals with high false positives, this study used the reporting odds ratio (ROR), medicines and healthcare products regulatory agency (MHRA), and Bayesian confidence propagation neural network (BCPNN) methods for signal detection (Evans et al., 2001; van Puijenbroek et al., 2002; Sakaeda et al., 2013). A positive signal is generated if all three methods yield positive results. If ROR, PRR, and IC-2SD signal values are larger, the signal is stronger. The specific algorithms and thresholds are shown in Supplementary Table S1.

After the disproportionality analysis, we compared the obtained signal results one by one with the description in the specification, and defined those that were not in the specification or whose descriptions were inconsistent as new signals.

TABLE 1 Two-by-two contingency table for Measure of Disproportion.

	Number of target AE reports	Number of other AE reports
Target drug	A	B
Other drugs	C	D

TABLE 2 Characteristics of AE reports associated with HSA.

Characteristics		N	Proportion (%)
Total		535	100.00
Gender	Male	276	51.59
	Female	247	46.17
	Unknown	12	2.25
Age	<1 month	2	0.37
	1 month–2 year	6	1.12
	2 years–12 years	13	2.43
	12 years–22 years	13	2.43
	22 years–65 years	145	27.10
	65 years–120 years	147	27.48
	Unknown	209	39.07
Outcome	Death	96	13.79
	Life-threatening	104	14.94
	Disability	10	1.44
	Hospitalization	128	18.39
	Congenital anomaly	2	0.29
	Other	307	44.11
	Required intervention	13	1.87
	Unknown	36	5.17
Occurrence country (n>10)	CN	87	16.26
	US	80	14.95
	JP	59	11.03
	CA	13	2.43
	GB	12	2.24

2.4 Gender differential signal detection

In this study, gender differential signal detection (Tan, 2021) was used to investigate the presence of gender variability in the occurrence of adverse drug events. Its calculation is also based on the 2 × 2 matrix table, and the algorithm is based on the ROR. Where A is the number of target adverse events for the female patient group, B is the number of other adverse events for the female patient group, C is the number of target adverse events for the male patient group, and D is the number of other adverse events for the male patient group. The ratio of A to B (A/B) was divided by the ratio of C to D (C/D) to obtain the ROR, which was used to assess the relative risk of each drug-related adverse event by gender.

If A>5, C>5, A+C>50, and $\log_2$ROR>1, this indicates a higher risk of this side effect in females; if A>5, C>5, A+C>50, and $\log_2$ROR<-1, this indicates a higher risk of this side effect in males.

3 Results

3.1 Characteristics of the report

After data mining and pre-cleaning, a total of 535 HSA adverse event reports were reviewed in this study, involving 1,885 adverse events.

In terms of gender, there were more males (51.59%), in terms of age, the largest number of patients were between 65–120 years old (27.48%), followed by 27.10% of patients between 22–65 years old, in terms of regression, 128 patients (18.39%) progressed to hospitalization, and in terms of countries where they occurred, China (16.26%), United States of America (14.95%), Japan (11.03%) had more cases of adverse events (Table 2).

The 535 reports of adverse reactions to HSA collected in this study were mainly related to SOCs at the site of general disorders and administration site conditions, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, and most commonly manifested as symptoms such as dyspnea, fever, chills, pruritus, hypotension, and pulmonary oedema. Details are provided in Supplementary Table S2.

3.2 Signal detection results

After analysis by the three methods, the signals generated were mainly related to 11 SOCs, which were ranked according to the number of instances of the signals involved, A, and shown in Table 3 for details.

Of all the PTs, with Transfusion-related acute lung injury (IC-2SD: 1.16; ROR: 1109.90; PRR: 1104.61; χ^2:8533.19), signal strength is the strongest and deserves attention (Table 3).

In SOC of respiratory, thoracic and mediastinal disorders, the strongest signals were Tachypnoea (IC-2SD: 0.95; ROR: 24.62; PRR: 24.49; χ^2: 202.34). Signals such as Pulmonary oedema (IC-2SD: 2.28; ROR: 18.73; PRR: 18.46; χ^2: 445.31), and Hypoxia (IC-2SD: 1.51; ROR: 15.29; PRR: 15.17; χ^2: 211.01) also warranted attention (Table 3).

In SOC of general disorders and administration site conditions, the strongest signals were chills (IC-2SD: 2.16; ROR: 11.53; PRR: 11.29; χ^2: 384.44). In SOC of skin and subcutaneous tissue disorders, the strongest signals were urticaria (IC-2SD: 1.48; ROR: 7.44; PRR: 7.33; χ^2: 174.40) (Table 3).

3.3 Gender differential signal analysis

To assess whether there is a gender difference in the occurrence of adverse events of HSA, the corresponding ROR, and $\log_2$ROR

TABLE 3 Overview of statistically significant IC-2SD, RORs, and PRRs (PT).

PT	A	IC-2SD	ROR (95%CI)	PRR	χ^2
Respiratory, thoracic and mediastinal disorders (120)					
Dyspnoea	53	0.59	3.01 (2.29–3.95)	2.95	67.06
Pulmonary oedema	28	2.28	18.73 (12.89–27.20)	18.46	445.31
Hypoxia	17	1.51	15.29 (9.49–24.66)	15.17	211.01
Respiratory distress	12	0.91	13.18 (7.47–23.25)	13.10	122.28
Tachypnoea	10	0.95	24.62 (13.22–45.84)	24.49	202.34
General disorders and administration site conditions (113)					
Pyrexia	44	0.85	3.90 (2.89–5.26)	3.83	89.90
Chills	42	2.16	11.53 (8.49–15.56)	11.29	384.44
Chest discomfort	19	0.78	6.11 (3.89–9.61)	6.06	75.44
No therapeutic response	8	0.40	17.38 (8.68–34.82)	17.31	107.17
Skin and subcutaneous tissue disorders (89)					
Pruritus	35	0.66	3.74 (2.68–5.23)	3.69	66.41
Urticaria	33	1.48	7.44 (5.27–10.50)	7.33	174.40
Erythema	21	0.28	3.69 (2.40–5.67)	3.66	38.05
Vascular disorders (82)					
Hypotension	48	1.8	7.91 (5.94–10.53)	7.73	275.37
Flushing	18	0.64	5.65 (3.55–8.98)	5.60	63.62
Shock	8	0.16	11.08 (5.53–22.20)	11.04	63.35
Circulatory collapse	8	0.28	13.56 (6.77–27.17)	13.51	80.58
Immune system disorders (72)					
Anaphylactic reaction	29	2.41	20.82 (14.43–30.05)	20.52	519.14
Hypersensitivity	24	0.66	4.60 (3.07–6.87)	4.55	63.14
Anaphylactic shock	19	2.03	25.96 (16.52–40.80)	25.71	426.61
Investigations (72)					
Blood pressure decreased	37	2.47	16.97 (12.26–23.50)	16.66	529.31
Oxygen saturation decreased	21	1.65	13.23 (8.60–20.34)	13.09	222.67
Body temperature increased	8	0.16	11.08 (5.53–22.19)	11.04	63.34
hepatitis c antibody positivedecreased	6	0.25	548.4 (244.26–1231.22)	546.66	2695.45
Injury, poisoning and procedural complications (57)					
Infusion related reaction	23	1.75	13.12 (8.69–19.79)	12.97	242.37
Exposure during pregnancy	13	0.63	7.99 (4.63–13.79)	7.94	72.13
Foetal exposure during pregnancy	12	0.45	7.34 (4.16–12.94)	7.3	59.1
Transfusion-related acute lung injury	9	1.16	1109.90 (569.70–2162.31)	1104.61	8533.19
Infections and infestations (32)					
Sepsis	18	0.52	5.07 (3.19–8.06)	5.03	54.23
Hepatitis c	8	0.44	19.02 (9.49–38.09)	18.94	118.55
Suspected transmission of an infectious agent via product	6	0.24	220.98 (98.86–493.98)	220.28	1091.54

(Continued on following page)

TABLE 3 (*Continued*) Overview of statistically significant IC-2SD, RORs, and PRRs (PT).

PT	A	IC-2SD	ROR (95%CI)	PRR	χ^2
Cardiac disorders (28)					
Tachycardia	18	0.80	6.56 (4.12–10.44)	6.51	78.57
Cardio-respiratory arrest	10	0.20	7.33 (3.94–13.64)	7.29	48.22
Pregnancy, puerperium and perinatal conditions (17)					
Premature baby	11	0.86	14.85 (8.21–26.87)	14.77	127.78
Foetal death	6	0.11	46.49 (20.85–103.69)	46.35	222.47
Metabolism and nutrition disorders (14)					
Fluid overload	8	0.29	13.88 (6.93–27.80)	13.83	82.79
Hypervolaemia	6	0.20	95.65 (42.86–213.46)	95.35	468.30

TABLE 4 Disproportionality analysis of signals stratified by case gender.

PT	SOC	A	ROR	log_2ROR
Male				
Drug ineffective	General disorders and administration site conditions	7	0.43	−1.22
Female				
Pulmonary oedema	Respiratory, thoracic and mediastinal disorders	17	2.13	1.09
Maternal exposure during pregnancy	Injury, poisoning and procedural complications	10	11.28	3.50
Hypertension	Vascular disorders	9	2.53	1.34
Vomiting	Gastrointestinal disorders	8	2.24	1.17
Loss of consciousness	Nervous system disorders	6	6.74	2.75
Paraesthesia	Nervous system disorders	6	6.74	2.75

values were calculated for males and females, respectively, in the present study. The results showed that males were more likely to experience drug ineffective (ROR: 0.43; log_2ROR: −1.22), whereas females experienced paraesthesia (ROR: 6.74; log_2ROR: 2.75), hypertension (ROR: 2.53; log_2ROR: 1.34), pulmonary oedema (ROR: 2.13; log_2ROR: 1.09), loss of consciousness (ROR: 6.74; log_2ROR: 2.75), vomiting (ROR: 2.24; log_2ROR: 1.17), and maternal exposure during pregnancy (ROR: 11.28; log_2ROR: 3.50), putting them at a higher risk, as shown in Table 4.

4 Discussion

In this study, we evaluated the post-marketing safety of HSA by disproportionality analysis and gender differential signal detection of the FAERS database. The results of the disproportionality analysis showed that the most common adverse events associated with HSA were dyspnoea, pyrexia, chills, hypotension, and pruritus, and transfusion-related acute lung injury was identified as a potential novel signal. Gender differential signal detection further revealed females are more likely to experience adverse events after HSA including paraesthesia, hypertension, pulmonary oedema, loss of consciousness, vomiting, and maternal exposure during pregnancy. Maternal exposure during pregnancy was not included in the discussion because it is a female-specific adverse reaction.

4.1 Potential new signals- transfusion-related acute lung injury

The results of this study found that Transfusion-related acute lung injury (TRALI) had the strongest signal strength. TRALI is a clinical syndrome with clinical features including acute dyspnea, hypoxemia, fever, hypotension, tachycardia, and leukopenia (Yu and Lian, 2023)]. One of the major causes of transfusion-related death is the occurrence of hypoxia-associated acute noncardiogenic pulmonary oedema. This can happen during or after a blood transfusion and is caused by damage to the pulmonary vasculature. Antibodies to human neutrophil antigens (HNAs) or human leukocyte antigens (HLAs) in the donor's blood can bind to the recipient's antigens and mediate this damage (Yu and Lian, 2023).

TRALI is a condition that is commonly associated with blood products, especially those that have a high plasma content such as plasma and platelets (van Stein et al., 2010). In addition, studies have found that plasma from female donors has a higher incidence of

TRALI due to the presence of HLA antibodies in parturient donors (Toy et al., 2012). A study conducted by Sa K et al. discovered that age and female gender are factors associated with TRALI. Specifically, females who receive transfusions are more likely to develop TRALI than males (Kuldanek et al., 2019). It has been reported that females who give birth often have HLA I, HLA II, and granulocyte antibodies. When these antibodies come into contact with homologous antigens in transfused plasma, they trigger neutrophil activation and the release of oxidizing substances that can damage the lung endothelium (Popovsky and Moore, 1985; Kopko et al., 2001). This suggests that previous pregnancy experience plays a significant role in contributing to TRALI.

Our research indicates that HSA is strongly linked to TRALI, and that there is a higher likelihood of occurrence in females. Notably, all nine cases of TRALI in our retrospective analysis involved female patients. This was due to the absence of male patients, resulting in a sex-specific signal detection that could not be accurately calculated to generate a corresponding signal value. The manual emphasizes the cardiovascular overload caused by the use of HSA without mentioning TRALI, which requires careful identification. Further details can be found in Supplementary Table S3.

It is important to thoroughly understand a patient's medical history, pregnancy, and health status before administering HSA. If a patient experiences shortness of breath or other related symptoms after taking the drug, it could be a sign of TRALI. In such cases, blood transfusion should be stopped immediately and the patient's vital signs closely monitored. It is worth noting that transfusion-related pulmonary complications are often under-reported due to under-diagnosis. Healthcare professionals can use the Uniform Standardized Model Reporting Form and Recommendations for Transfusion-Related Pulmonary Complications (van Wonderen et al., 2023) to improve the collection of data on pulmonary transfusion reactions. This will facilitate better hemovigilance and related research.

4.2 Gender-differentiated signals

4.2.1 Paraesthesia

Paresthesia is a condition where patients feel discomfort in certain body parts without any external stimulation. This discomfort is often described as sensations like ants crawling, electric shocks, numbness, heat or cold, tingling, or pins and needles. It is usually caused by sensory pathway stimulation and is commonly seen in individuals with peripheral neuropathy, spinal cord lesions, and brain disorders (Boulware, 2003).

A study conducted by Jeffrey T. and his team involved a retrospective analysis of patients with myasthenia gravis who underwent intravenous plasma exchange with 5% human albumin solution from 2005 to 2010. The study found that some patients experienced minor complications such as paresthesia (Guptill et al., 2013). It has been reported that abnormal sensation is an important clinical feature of peripheral neuropathy, and its prevalence is higher in females (Savettieri et al., 1993; Baldereschi et al., 2007; Kandil et al., 2012; Kruja et al., 2012). This prevalence does not vary with age (Baldereschi et al., 2007; Kruja et al., 2012), according to various studies. A screening study by Sharon G. Bruce also found that females with peripheral neuropathy have a higher risk of developing abnormal sensations (Bruce and Young, 2008). The present study's findings are consistent with these results, indicating that females are at a higher risk of developing paresthesia after HSA use. It is essential for female patients to immediately notify their healthcare provider and be closely monitored if such symptoms occur.

4.2.2 Hypertension

Hypertension is a medical condition that occurs when there is an increase in arterial blood pressure in the body's systemic circulation. This is characterized by elevated systolic and/or diastolic pressure, with a minimum reading of 140 mmHg and 90 mmHg respectively. It can cause damage to vital organs like the heart, brain, and kidneys (Messerli et al., 2007).

Several studies have indicated that using HSA may lead to hypertension. In a prospective study conducted by C. Pusey (Pusey et al., 2010), data was collected on 154 patients who underwent plasma exchange with human albumin 4.5% solution (Zenalb 4.5). The study recorded possible treatment-related adverse effects, and all six of the patients experienced elevated blood pressure as an adverse effect.

Our study revealed that hypertension is not only associated with HSA, but also with gender, particularly in females. It is worth noting that although hypertension is more prevalent in adult females than in males in America, it becomes even more common in females after the age of 60, and this gap continues to widen with age. Similar studies conducted in Canada and other developing countries have also shown that hypertension is becoming more prevalent among older females (Prince et al., 2012; Robitaille et al., 2012).

During the perimenopausal period, the decrease in estrogen concentration can lead to increased blood pressure levels in hypertensive postmenopausal females. Sex hormones play a crucial role in regulating blood pressure, with both endogenous and exogenous estrogens known to lower it (Reckelhoff, 2001). The World Health Organization reports that most females enter menopause after the age of 45 (World Health Organization, 2023). As estrogen levels decrease in perimenopausal females, vasoconstrictors like endothelin and angiotensinogen are produced, while increased androgen levels alter the plasma ratio of circulating estrogens/androgens (Salpeter et al., 2006). This hormonal interaction leads to increased activation of the renin-angiotensin-aldosterone system, resulting in renal vasoconstriction, sodium reabsorption, and ultimately elevated blood pressure levels (Coylewright et al., 2008).

In our retrospective analysis, 14 patients developed hypertension. Out of these patients, nine were female, and six of them were older than 45 years (Supplementary Table S4). Therefore, middle-aged and elderly females should monitor their blood pressure closely after using HSA. They should pay attention to any increase in blood pressure and consult a doctor promptly.

4.2.3 Pulmonary oedema

Pulmonary oedema is when there is an abnormal buildup of fluid in the lungs, which can lead to difficulty with breathing and respiratory failure (Murray, 2011). The use of HSA can sometimes cause pulmonary oedema, which has been warned against in instructions and highlighted in studies. A position statement on

the use of HSA infusion for cirrhosis-related complications recommends monitoring cirrhotic patients closely for the development of pulmonary oedema (concordance score: 5; degree of consensus: very high) (Bai et al., 2023).

Differential signaling for gender in this study found that pulmonary oedema was associated with HSA use and occurred at higher risk in females. While transfusion-related acute lung injury may be the main cause of pulmonary oedema. This aligns with the research of Sa K et al., who also found that previous pregnancy and being female are potential risk factors for TRALI (Kuldanek et al., 2019).

HSA plays an important role in maintaining plasma colloid osmolality and should be administered slowly, as an infusion of high doses of HSA over a short period can lead to an excessive increase in circulating blood volume and an increased risk of pulmonary oedema (Jagdish et al., 2021). Kugelmas et al. (2023) suggest that attention must also be paid to the sodium content of HSA, as high sodium can lead to pulmonary oedema, and that one must be careful when combining it with vasoconstrictors. Special attention should be paid to the occurrence of lung injury and pulmonary oedema in female patients after the use of HSA.

The HSA is vital for maintaining a proper balance of fluids in the body, but it should be administered slowly to prevent any harmful effects. If given in high doses over a short period, it can lead to an excessive increase in blood volume and an increased risk of pulmonary oedema. It is important to note that the sodium content of HSA needs to be monitored, as high levels can cause pulmonary oedema (Kugelmas et al., 2023). Additionally, combining it with vasoconstrictors requires caution. Extra care should be taken when administering HSA to female patients, as there is a risk of lung injury and pulmonary oedema.

4.2.4 Loss of consciousness

The term "loss of consciousness" is sometimes used to describe states, such as apoplectic seizures and complex partial seizures, in which people appear to be awake but unaware of themselves or their surroundings. Plum and Posner's work on the content-related aspects of consciousness supports this usage. Various factors can cause partial or complete loss of consciousness, such as primary cerebral events, metabolic disorders, intoxication, psychogenic causes, or syncope (Plum and Posner, 1972; van Dijk et al., 2009; Sayk et al., 2019). Additionally, heart failure can also cause loss of consciousness, which can be life-threatening. This can be due to underlying ion channelopathies, cardiac inflammation, myocardial ischemia, congenital heart disease, cardiomyopathy, or pulmonary hypertension. Among non-cardiac causes, the most common one is vasovagal response (VVR), as noted by Juan Villafane (Villafane et al., 2021).

Research has studied various perspectives on risk factors for VVR. Studies have shown a higher risk of vasovagal syncope in certain blood donors, including first-time donors, young adults, and females (Trouern-Trend et al., 1999; Newman, 2002; Tomita et al., 2002; Bravo et al., 2011; Odajima et al., 2016). Takeshi Odajima conducted a gender subgroup analysis on factors contributing to VVR and found that females who donated to a single recipient had a higher risk of VVR. The gender difference may be related to the relationship between blood volume and extravascular space (Odajima et al., 2016). Additionally, lower BMI in females has also been reported as a risk factor for VVR, suggesting an association with interstitial space (Takanashi et al., 2012). Takanashi M (Tomita et al., 2002) suggested a higher risk of vasovagal syncope after a single blood donation in females during the blood donation process, and even a higher risk of VVR in females over 45 years of age (Farquhar et al., 2000).

Based on the results of the study, it seems that women are more likely to experience loss of consciousness after using HSA. This finding should be studied further. Our analysis of six cases of loss of consciousness (excluding one case with missing age information) showed that all the affected individuals were elderly women aged 60 years or older. Additional details regarding the cases can be found in Supplementary Table S5. Therefore, healthcare providers should pay close attention to elderly female patients who have used HSA. It is important to monitor patients' vital signs carefully and take appropriate action promptly if syncope or other symptoms occur.

4.2.5 Vomiting

Our findings indicate that females have a greater likelihood of experiencing vomiting as a result of HSA usage. Vomiting entails the forceful expulsion of stomach contents through the mouth, with chronic nausea and vomiting being persistent symptoms lasting for 4 weeks or more. Acute nausea and vomiting, on the other hand, are typically characterized as symptoms lasting for 7 days or less (Hasler and Chey, 2003).

Research conducted in the general population has revealed that females experience a higher prevalence of gastrointestinal symptoms compared to males (Lacy et al., 2018). A prospective study by Luciana Ferreira Silva (Silva et al., 2012) found that females undergoing continuous hemodialysis for MHD displayed a higher prevalence of nausea, vomiting, and decreased appetite than their male counterparts. It is possible that such differences in symptoms between genders are partially due to females being more likely to report feeling unwell, both physically and psychologically.

Gastroparesis is a medical condition that causes symptoms such as nausea, vomiting, and abdominal swelling. Research has shown that 70%–90% of patients with various types of gastroparesis (including diabetes mellitus, idiopathic, postoperative, and viral infections) are female (Jung et al., 2009; Parkman et al., 2011). The reason for this higher susceptibility in females is not clear, but it may have multiple causes. These include higher levels of sex steroid hormones, decreased expression of neuronal NO synthase, slower colonic transit time, altered serotonergic signaling, decreased sinus contractility, impaired uterine regulation and sensation, and increased visceral hypersensitivity (Gonzalez et al., 2020). These findings support the conclusion of the present study, which shows that females are more likely to experience vomiting after using HSA. Therefore, patients with gastrointestinal issues should use HSA with caution and monitor their health closely.

4.3 Limitations

It is important to note that the FAERS database is a self-reporting database, which means that it does not collect every

single report of an adverse event or medication error related to a particular drug. This may result in incomplete data that does not accurately reflect the incidence of adverse events in all populations.

In addition, the database may not always include important indicators, such as gender, or have other reporting quality issues that could affect the reliability of the results. For example, we reviewed the TRALI reports in this study, which consisted of 9 cases, only 3 of which had a specific route of administration as intravenous drip and lacked data otherwise available for further analysis, which hampered our further analysis of the reports.

In addition, the signals of AEs identified by disproportionality analysis may only suggest a statistical association between the drugs and the AEs. Further research and evaluation are needed to establish their causality. This study analyzed only the reports of HSA use and did not take into account the dosage and combination of drugs. What's more, most of the reported countries are from CN, US and JP, and there may be ethnic differences in the data.

5 Conclusion

This study used signal detection in the FAERS database to assess the safety of HSAs in real-world situations. The focus was on drug safety signals. The results showed that the majority of adverse reactions associated with HSA included chills, pruritus, hypotension, fever, dyspnea, and pulmonary oedema. Most of these were already known signals. However, transfusion-associated acute lung injury requires further attention as a potential new signal.

It is possible that women may experience more negative reactions to HSA, such as tingling sensations, high blood pressure, fluid in the lungs, loss of consciousness, and vomiting. This risk is higher for older women who may experience hypertension and loss of consciousness. These symptoms should not be taken lightly and require close monitoring during HSA treatment. If a patient experiences any of these serious side effects, it is essential to reduce the dosage or stop the treatment immediately. It is important to note that the study's results are solely statistical associations and not a definitive cause-and-effect relationship. Further research is needed to confirm these findings.

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

HL: Writing–original draft, Writing–review and editing. YZ: Writing–original draft, Writing–review and editing. PL: Writing–review and editing.

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Conflict of interest

Author HL is employed by Shanghai RAAS Blood Products Co., Ltd.

The remaining 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

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Disproportional signal of pericarditis with biological diseasemodifying antirheumatic drugs (bDMARDs) in patients with ankylosing spondylitis: a disproportionality analysis in the FAERS database

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Objective: This study aimed to investigate the potential association between biological disease-modifying antirheumatic drugs (bDMARDs) and pericarditis and uncover relevant clinical characteristics in ankylosing spondylitis (AS).

Methods: Reports of pericarditis recorded in the FDA Adverse Event Reporting System (FAERS) (January 2004–December 2022) were identified through the preferred term "pericarditis." Demographic and clinical characteristics were described, and disproportionality signals were assessed through the reporting odds ratio (ROR) and information component (IC). A significant signal was detected if the lower bound of IC (IC_{025}) was more than zero.

Results: We found 1,874 reports of pericarditis with bDMARDs (11.3% of cases with fatal outcomes). Adalimumab (IC_{025} 3.24), infliximab (IC_{025} 4.90), golimumab (IC_{025} 5.40), certolizumab (IC_{025} 5.43), etanercept (IC_{025} 3.24), secukinumab (IC_{025} 3.97), and ustekinumab (IC_{025} 7.61) exhibit significant disproportionality signals compared to other medications in the FAERS database. After excluding pre-existing diseases and co-treated drugs that may increase the susceptibility of pericarditis, the disproportionality signal associated with infliximab, certolizumab, etanercept, secukinumab, and ustekinumab remained strong. Pericarditis cases associated with all bDMARDs were predominantly recorded in women aged 25–65 years.

Conclusion: More reports of pericarditis were detected with AS patients on bDMARDs than with other drugs in the overall database. Further studies are

warranted to investigate the underlying mechanisms and identify patient-related susceptibility factors, thus supporting timely diagnosis and safe(r) prescribing of bDMARDs.

KEYWORDS

tumor necrosis factor inhibitors, interleukin-17 inhibitor, pericarditis, ankylosing spondylitis, pharmacovigilance, FDA Adverse Event Reporting system, disproportionality analysis

1 Introduction

Ankylosing spondylitis (AS) is a rare chronic inflammatory disorder that in its worst form can result in the bony fusion of vertebral joints, ultimately resulting in chronic back pain. In the previous decade, AS has become a recognized subgroup of the more comprehensive and prevalent diagnostic entity referred to as axial spondyloarthritis (Taurog et al., 2016). Non-steroidal anti-inflammatory drugs (NSAIDs) represent the first-line symptomatic treatment for pain and stiffness (Ortolan et al., 2023). The introduction of tumor necrosis factor inhibitors (TNFi), as the first biological disease-modifying antirheumatic drugs (bDMARDs) in axial spondyloarthritis, opened a new era in the management of this disease (Webers et al., 2023). In patients with active AS who failed to respond to conventional NSAID treatment, treatment with TNFi, including adalimumab, infliximab, golimumab, certolizumab, and etanercept, results in an excellent response (Sieper and Poddubnyy, 2017). Interleukin-17 inhibitors (IL-17i), such as secukinumab, ixekizumab, and brodalumab, are another type of bDMARDs for AS. The latest 2022 ASAS-EULAR recommendations (Ramiro et al., 2023) supported the use of TNFi, IL-17i, and targeted synthetic DMARDs (i.e., JAKi), depending on patient's characteristics such as extra-musculoskeletal manifestations. Of note, cardiovascular risk management represents a key priority in patients with AS since various cardiovascular complications may occur (Atzeni et al., 2020). The cardiovascular safety of TNFi is still a matter of debate. While a number of studies have reported a reduction in sub-clinical atherosclerosis in AS as a consequence of their anti-inflammatory effect (Atzeni et al., 2020), a recent review (Hussain et al., 2021) showed that TNFi may increase the risk of adverse cardiovascular events (CVEs) because of stronger inhibition effects on TNFR2 (a cardioprotective receptor) than TNFR1 (an apoptotic receptor).

Pericarditis refers to the inflammation of the pericardial layers and is the most common form of pericardial disease. It may be associated with pericardial effusion that can result in impaired cardiac filling (tamponade) (Chiabrando et al., 2020). Drug-induced pericarditis, though uncommon, is a potentially life-threatening condition since it could result in pericardial tamponade, which could be fatal (Harnett et al., 2014). Previous case reports (Vyas et al., 2020; Lee et al., 2023; Obeidat et al., 2023) showed that pericarditis could be associated with TNFi in psoriatic arthritis. However, there are no reports of pericarditis with bDMARDs in AS. Moreover, pleuro-pericarditis was recently identified as a post-marketing safety signal for TNFi based on 42 well-documented cases reported in the international spontaneous reporting system WHO VigiBase (Zhang and Yue, 2020).

Therefore, large-scale pharmacovigilance archives are particularly suited to detect rare adverse events that may escape detection from clinical trials and may provide a comprehensive overview of unpublished case reports collected so far (Noguchi et al., 2021). This pharmacovigilance study used the FDA Adverse Event Reporting System (FAERS) to investigate the potential association between bDMARDs approved in AS and pericarditis.

2 Materials and methods

2.1 Study design and data source

The study was designed as a retrospective pharmacovigilance analysis of the FAERS database, which contains adverse event reports, reports of medication errors, and complaints about the quality of products that led to adverse events submitted to the FDA by healthcare professionals, consumers, and manufacturers. AERS*Mine* is a multi-cohort analyzing application designed to mine FAERS data across millions of patient reports (2004–2022, currently 19,089,556) (Sarangdhar et al., 2016). We performed a disproportionality analysis of pericarditis cases with bDMARDs in AS using data from the FAERS database. Ethical approval and patient consent were not needed because this study used de-identified data.

2.2 Definition of drugs, exposure, and cases of interest

We included nine bDMARDs: adalimumab, infliximab, golimumab, certolizumab, etanercept and secukinumab, ixekizumab, ustekinumab, and brodalumab. Exposure assessment considered these drugs recorded as suspects ("primary suspect" and "secondary suspect") or concomitants. Only reports where AS was specified as a therapeutic indication were retained.

Adverse events in FAERS were coded through the so-called Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 26.0) in terms of Preferred Terms (PTs), identifying unique signs and symptoms. To obtain a comprehensive understanding, we firstly detected the signals of all PTs within "noninfectious myocarditis/pericarditis" (Standardized MedDRA Query, SMQ) with bDMARDs. Then we focused on the signal of "Pericarditis" with bDMARDs. We only included pericarditis reports with a number more than five. For each pericarditis report, the following data were gathered: report year, reporter type (e.g., healthcare professionals and consumers), demographic information (gender and age), drugs, outcomes (with a focus on serious cases, i.e., those resulting in death,

hospitalization or life-threatening condition, or disability), and co-reported adverse events.

2.3 Disproportionality analysis

To determine if pericarditis was differently reported with bDMARDs compared to other drugs in the FAERS, we performed the so-called case/non-case design. If the proportion of adverse events of interest is higher in patients exposed to a particular drug (cases) than in patients not exposed to this drug (non-cases), a disproportionality signal is generated (Faillie, 2019). Two different disproportionate measures were calculated, namely, the frequentist reporting odds ratios (RORs) and the Bayesian information components (ICs) to decrease the possibility of false-positive results. Significant disproportionality was noted when the lower limit of the 95% confidence interval of ROR (ROR_{025}) >1 (Rothman et al., 2004) or the lower limit of the 95% confidence interval of IC (IC_{025}) >0 (Bate et al., 1998). First, we used other drugs in the FAERS database as a comparator. To reduce the indication bias, we did not include NSAIDs as comparators in this study because a previous paper showed that NSAIDs could be used to treat pericarditis (Imazio et al., 2015). In addition, NSAIDs are usually used to treat stable AS. However, bDMARDs are usually used to treat more active AS. Therefore, NSAIDs are not suitable to be comparators in this study. We checked the website of Spondylitis Association of America (https://spondylitis.org/about-spondylitis/treatment-information/medications/) and the "2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of AS and Nonradiographic Axial Spondyloarthritis" (Ward et al., 2019) and included the following medications as the second comparators: sulfasalazine, mesalazine (the active moiety of sulfasalazine) (Dekker-Saeys et al., 2000), methotrexate, tofacitinib, and upadacitinib. These agents are also utilized to treat more active AS.

A time trend analysis was also performed to explore the stability of the disproportionality signals over time. Moreover, we conducted the following sensitivity analyses to account for potential confounders like underlying comorbidities and bias:

(a) We excluded cases where pre-existing diseases (including "pericarditis," "epstein-barr viral infections," "cytomegalovirus infection," "human herpesvirus 6 infection," "parvovirus b19 infection," "echovirus test positive," "*mycobacterium tuberculosis* complex test positive," "*borrelia burgdorferi* serology positive," "*coxiella* infections," "histoplasma infections," "blastomyces infections," "*candida* infections," "toxoplasma infections," "systemic lupus erythematosus," "sjogren&apos_s syndrome," "rheumatoid arthritis," "scleroderma," "eosinophilic granulomatosis with polyangiitis," "familial Mediterranean fever," "tumor necrosis factor receptor-associated periodic syndrome," "sarcoidosis," "inflammatory bowel disease," "pericardial mesothelioma malignant" "lymphomas nec," "non-small-cell lung cancer," "small cell lung cancer," "breast cancer," "uremia," "anorexia nervosa," "pericardial disorders," "postpericardiotomy syndrome," "coronary artery bypass," "cardiac pacemaker insertion," "radiofrequency ablation," "transcatheter aortic valve implantation," "percutaneous coronary intervention," "hypothyroidism," "tuberculosis," and "noninfectious pericarditis") were recorded as possible alternative causes of pericarditis (Imazio et al., 2015; Chiabrando et al., 2020).

(b) We also excluded cases with co-treated drugs (including "procainamide," "hydralazine," "methyldopa," "isoniazid," "phenytoin," "beta-lactam antibacterials, penicillins," "doxorubicin," "daunorubicin," "fluorouracil," "cyclophosphamide," "minocycline," "sulfasalazine," "enalapril," "clofarabine," "carfilzomib," "bortezomib," "dasatinib," "ceritinib," "clozapine," "nivolumab," "pembrolizumab," and "atezolizumab" ("ipilimumab" AND "nivolumab": "sulfamethoxazole and trimethoprim" "interferon" "minoxidil" "lisinopril" "apixaban" "rivaroxaban" "streptokinase" "bromocriptine" "dantrolene")] that may induce pericarditis (Imazio et al., 2015; Ma et al., 2021; Dababneh and Siddique, 2023) to minimize the so-called competition bias.

(c) We limited the reports from healthcare professionals and role code as "primary or secondary suspect," respectively.

All these analyses were carried out to further test the robustness of disproportionality signals and enhance relevant clinical transferability.

Finally, subgroup analysis was conducted to investigate the influence of age and gender on disproportionate signals. In line with recent research on immune-related adverse events in patients receiving immune checkpoint inhibitors (Yang et al., 2023), we used IC delta to investigate the effect of age and gender. IC delta was calculated based on the observed-to-expected ratio between older adults (or males) and younger adults (or females) and was used to contrast the risk between the two groups. A positive (negative) IC delta was taken to reflect over (under-) reporting in one group if significant at the 5% significance level.

2.4 Drug interaction analysis

Considering that the co-administration of other drugs with bDMARDs may affect the disproportionate signals of pericarditis, we conducted drug interaction analysis using the Ω shrinkage to measure the drug–drug interactions because a previous study (Noguchi et al., 2020) showed that it is the most conservative among multiple algorithms. The detection criterion is the lower limit of the 95% CI of Ω (Ω_{025}) > 0.

3 Results

3.1 Descriptive analysis

We detected that pericarditis was the most frequent PT term with bDMARDs within the noninfectious myocarditis/pericarditis (SMQ) (Table 1). From Q1, 2004 to Q4, 2022, we detected 281, 361, 269, 270, 248, 208, and 237 pericarditis cases with adalimumab,

TABLE 1 Disproportionality signals for noninfectious myocarditis/pericarditis (SMQ) with bDMARDs.

Category	Overall bDMARDs	Full database	ROR_{025}	IC_{025}
Total number of ICSRs available	109,943	19,089,556	—	—
Pericarditis	1,874	13,816	26.22	4.47
Red blood cell sedimentation rate increased	1,329	12,858	19.01	4.07
Pericardial effusion	154	24,144	0.95	−0.12
Extrasystoles	59	7,817	1.02	−0.05
Cardiac failure acute	42	6,414	0.84	−0.33
Myocarditis	45	9,430	0.62	−0.76
Electrocardiogram abnormal	33	9,082	0.45	−1.24
Atrioventricular block	22	8,146	0.31	−1.79
Bundle branch block left	35	5,242	0.83	−0.35
Dilatation ventricular	19	3,479	0.60	−0.85

bDMARDs, biological disease-modifying antirheumatic drugs; FAERS, FDA Adverse Event Report System; IC_{025}, the lower limit of the 95% credibility interval of the information component; ICSR, individual case safety report; ROR_{025}, the lower limit of the 95% credibility interval of the reporting odds ratio. When $IC_{025} > 0$ or $ROR_{025} > 1$, a significant safety signal was detected.

infliximab, golimumab, certolizumab, etanercept, secukinumab, and ustekinumab, respectively (Table 2). Most cases were reported from 2019 to 2022. Almost 34.0% (637/1874 cases) of pericarditis cases were reported by healthcare professionals. In the majority of the cases, bDMARDs were marked as primary suspects (179 cases) and secondary suspects (1584 cases). Except for two pericarditis cases with adalimumab in the elderly (age >65), other cases were recorded in adults (aged 25–65). A total of 11.3% (212/1874 cases) of pericarditis cases had fatal outcomes, while 18.2% (342/1874) cases needed hospitalization. Edema peripheral (930 cases), dizziness (948 cases), rheumatic fever (468 cases), dyspnea (383 cases), peripheral swelling (373 cases), and tachycardia (100 cases) were the most frequently co-reported adverse events.

3.2 Disproportionality analysis

In the primary analysis using all other drugs in the FAERS database as the comparator, all bDMARDs (adalimumab, infliximab, golimumab, certolizumab, etanercept, secukinumab, and ustekinumab) presented disproportionality signals. Although bDMARDs had lower disproportionality signals for pericarditis than tofacitinib, they presented higher signals of disproportionate reporting than other drugs in the FAERS database (Figure 1). The time trend analysis confirmed that six bDMARDs had a stable disproportionality signal of pericarditis from 2019 to 2022 (Figure 2). After accounting for drug-related competition bias, pre-existing disease, and a limited role code and report source in the sensitivity analysis, the pericarditis disproportionate signals with golimumab and adalimumab became weak. However, infliximab, certolizumab, etanercept, secukinumab, and ustekinumab still presented a higher disproportionate signal of pericarditis compared to tofacitinib, upadacitinib, and mesalazine (Table 3). By conducting subgroup analysis, we found that more pericarditis cases were reported in female patients receiving adalimumab, infliximab, golimumab, certolizumab, etanercept, and secukinumab (IC delta $_{975} < 0$, Supplementary File S1).

3.3 Drug interaction analysis

Our data showed that adalimumab ($\Omega_{025} = 5.5$), infliximab ($\Omega_{025} = 6.2$), golimumab ($\Omega_{025} = 7.8$), certolizumab ($\Omega_{025} = 7.9$), and ustekinumab ($\Omega_{025} = 2.0$) had strong signals of drug interactions with tocilizumab (Supplementary File S2). Etanercept ($\Omega_{025} = 0.6$) and secukinumab ($\Omega_{025} = 0.5$) showed weak signals of drug interactions with tocilizumab (Supplementary File S3).

4 Discussion

To the best of our knowledge, this is the first study to investigate the association of pericarditis with bDMARDs for AS in the real-world setting of spontaneous reporting. By conducting a multimodal approach, comprising multiple stepwise disproportionality analyses, these findings contribute to the ongoing discussion on the cardiovascular risk of patients with AS and strengthen the hypothesis that bDMARDs as a class may increase patient's susceptibility to pericarditis.

First, our disproportionality analysis detected that pericarditis was significantly reported with TNFi, IL-17i, and IL-12/23 inhibitors, with other drugs in the FAERS database as the comparators. Ustekinumab presented the highest disproportionate signal of pericarditis among all bDMARDs. There was only one case report (Tominaga et al., 2021) that showed that tuberculous pericarditis occurred with ustekinumab treatment for Crohn's disease. Previous research (Rubin et al., 2022) reported that four cases of pericarditis were associated with tofacitinib, which is consistent with the strong disproportionate signal of pericarditis with tofacitinib in this study. However, our sensitivity analysis found that the disproportionate signal of pericarditis with ustekinumab and tofacitinib became weak, while infliximab, etanercept, and secukinumab still presented strong signals across three sensitivity analyses. Our study showed that the reports of pericarditis with bDMARDs have rapidly increased since 2019. We checked the data from EudraVigilance and found a

TABLE 2 Clinical features of pericarditis with bDMARDs.

Category/ Drug	Adalimumab 281	Infliximab 361	Golimumab 269	Certolizumab 270	Etanercept 248	Secukinumab 208	Ustekinumab 237
Report year							
2004–2008	1 (0.4%)	29 (8.0%)	0 (0.0%)	0 (0.0%)	7 (2.8%)	0 (0.0%)	0 (0.0%)
2009–2013	3 (1.1%)	13 (3.6%)	1 (0.4%)	0 (0.0%)	5 (2.0%)	0 (0.0%)	0 (0.0%)
2014–2018	9 (3.2%)	9 (2.5%)	2 (0.7%)	2 (0.7%)	7 (2.8%)	5 (2.4%)	2 (0.8%)
2019–2022	268 (95.4%)	310 (85.9%)	266 (98.9%)	268 (99.3%)	229 (92.3%)	203 (97.6%)	235 (99.2%)
Reporter							
Healthcare professionals	89 (31.7%)	139 (38.5%)	84 (31.2%)	83 (30.7%)	81 (32.7%)	80 (38.5%)	81 (34.2%)
Consumer	22 (7.8%)	29 (8.0%)	14 (5.2%)	17 (6.3%)	23 (9.3%)	23 (11.1%)	16 (6.8%)
Unspecified	170 (60.5%)	193 (53.5%)	171 (63.6%)	170 (63.0%)	144 (58.1%)	105 (50.5%)	140 (59.1%)
Role code							
Primary suspect drug	22 (7.8%)	78 (21.6%)	12 (4.5%)	13 (4.8%)	17 (6.9%)	37 (17.8%)	0 (0.0%)
Secondary suspect drug	244 (86.8%)	293 (81.2%)	244 (90.7%)	243 (90.0%)	195 (78.6%)	151 (72.6%)	214 (90.3%)
Concomitant	26 (9.3%)	49 (13.6%)	30 (11.2%)	28 (10.4%)	42 (16.9%)	55 (26.4%)	23 (9.7%)
Sex							
Male	8 (2.8%)	33 (9.1%)	1 (0.4%)	1 (0.4%)	7 (2.8%)	7 (3.4%)	0 (0.0%)
Female	238 (84.7%)	283 (78.4%)	232 (86.4%)	234 (86.7%)	215 (86.7%)	178 (85.6%)	206 (86.9%)
Missing	35 (12.5%)	45 (12.5%)	36 (13.4%)	35 (13.0%)	26 (10.5%)	23 (11.1%)	31 (13.1%)
Age							
0–24	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
25–65	154 (54.8%)	208 (57.6%)	146 (54.3%)	148 (54.8%)	130 (52.4%)	167 (80.3%)	147 (62.0%)
>66	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	125 (44.5%)	153 (42.4%)	123 (45.7%)	122 (45.2%)	118 (47.6%)	41 (19.7%)	90 (38.0%)
Outcome							
Congenital anomaly	5 (1.8%)	5 (1.4%)	5 (1.9%)	5 (1.9%)	5 (2.0%)	5 (2.4%)	5 (2.1%)
Death	32 (11.4%)	30 (8.3%)	30 (11.2%)	30 (11.1%)	29 (11.7%)	31 (14.9%)	30 (12.7%)
Disability	104 (37.0%)	104 (28.8%)	103 (38.3%)	103 (38.1%)	102 (41.1%)	49 (23.6%)	102 (43.0%)
Hospitalization	49 (17.4%)	96 (26.6%)	35 (13.0%)	37 (13.7%)	48 (19.4%)	40 (19.2%)	37 (15.6%)
Life-threatening	49 (17.4%)	54 (15.0%)	47 (17.5%)	47 (17.4%)	52 (21.0%)	34 (16.3%)	47 (19.8%)
Other serious illnesses	271 (96.4%)	317 (87.8%)	262 (97.4%)	265 (98.1%)	234 (94.4%)	203 (97.6%)	232 (97.9%)
Co-reported adverse events							
Cardiac disorders							
Edema peripheral	141 (17.9%)	141 (17.9%)	142 (18.0%)	141 (17.9%)	83 (10.5%)	141 (17.9%)	141 (59.5%)
Dizziness	143 (17.8%)	148 (18.4%)	143 (17.8%)	143 (17.8%)	85 (10.6%)	143 (17.8%)	143 (60.3%)
Rheumatic fever	83 (17.7%)	84 (17.9%)	84 (17.9%)	84 (17.9%)	84 (17.9%)	49 (10.5%)	0 (0.0%)

(Continued on following page)

TABLE 2 (*Continued*) Clinical features of pericarditis with bDMARDs.

Category/ Drug	Adalimumab 281	Infliximab 361	Golimumab 269	Certolizumab 270	Etanercept 248	Secukinumab 208	Ustekinumab 237
Dyspnea	70 (18.3%)	71 (18.5%)	70 (18.3%)	69 (18.0%)	73 (19.1%)	30 (7.8%)	0 (0.0%)
Peripheral swelling	61 (16.4%)	78 (20.9%)	62 (16.6%)	61 (16.4%)	74 (19.8%)	37 (9.9%)	0 (0.0%)
Tachycardia	17 (17.0%)	18 (18.0%)	16 (16.0%)	17 (17.0%)	16 (16.0%)	16 (16.0%)	0 (0.0%)
Vascular disorders							
Hypertension	89 (17.7%)	90 (17.9%)	90 (17.9%)	90 (17.9%)	90 (17.9%)	55 (10.9%)	0 (0.0%)
Contusion	68 (18.7%)	69 (19.0%)	69 (19.0%)	69 (19.0%)	69 (19.0%)	20 (5.5%)	68 (28.7%)
Hemorrhage	5 (6.2%)	25 (30.9%)	0 (0.0%)	5 (6.2%)	21 (25.9%)	25 (30.9%)	0 (0.0%)

bDMARDs, biological disease-modifying antirheumatic drugs.

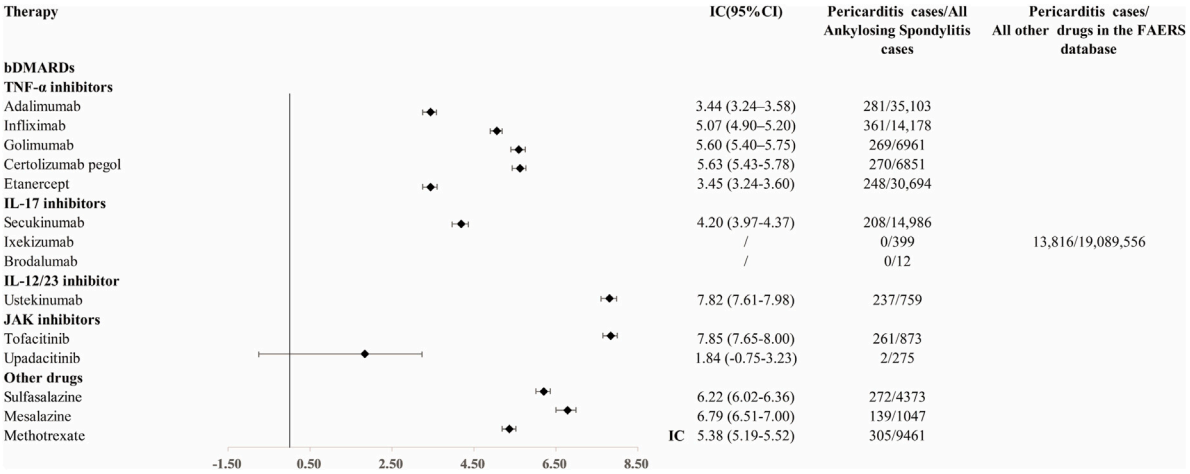

FIGURE 1
Disproportionality signal for pericarditis with TNFi, IL-17i, and IL-12/23 inhibitors and other medications for AS. IC, information component; 95% CI, 95% of credibility interval.

similar tendency (Supplementary File S4). Previous research (Patone et al., 2022) showed that COVID-19 vaccination or SARS-CoV-2 infection may increase the risk of pericarditis in patients. Considering the similar timeline of a huge increase in pericarditis reports in bDMARDs and an outbreak of COVID-19, we investigated the influence of COVID-19 on the reports of pericarditis in our analysis. We combined tocilizumab, remdesivir, baricitinib, and other FDA-approved COVID-19 vaccines with bDMARDs and searched for pericarditis reports (limit the indication as AS) in the FAERS database. There is only one report of pericarditis with the combination of adalimumab and COVID-19 vaccines. No reports of pericarditis were detected for the co-administration with bDMARDs and remdesivir or baricitinib. However, we detected hundreds of pericarditis reports with the combination of tocilizumab and bDMARDs. We further limited COVID-19 as the indication and tocilizumab as the drug of interest, and no reports of pericarditis were detected in the FAERS database. This indicated a weak influence of COVID-19 itself on the signals of pericarditis with bDMARDs. Previous literature (Shikama et al., 2001; Imai et al., 2022) showed that pericarditis may be associated with IL-6 receptor antagonists in POEMS syndrome and eosinophilic granulomatosis with polyangiitis. We further investigated if the co-administration of bDMARDs and tocilizumab would increase the reports of pericarditis in AS. Our data showed that the co-administration of tocilizumab with bDMARDs may synergistically increase the reports of pericarditis in patients with AS. Tocilizumab is an FDA-approved agent for COVID-19. Its utilization during COVID-19 may contribute to the increased reports of bDMARDs in AS. More research is warranted to further investigate the mechanisms of drug interactions.

Second, this study depicted the clinical characteristics of pericarditis with bDMARDs. Pericarditis was found to predominantly occur in women compared to men. This is consistent with previous research (Zhang and Yue, 2020). Moreover, another review (Stovall et al., 2022) indicated that axial spondyloarthritis has equal prevalence in women and men. This study indicated that women may be more susceptible to pericarditis than men when they receive DMARDs. Previous

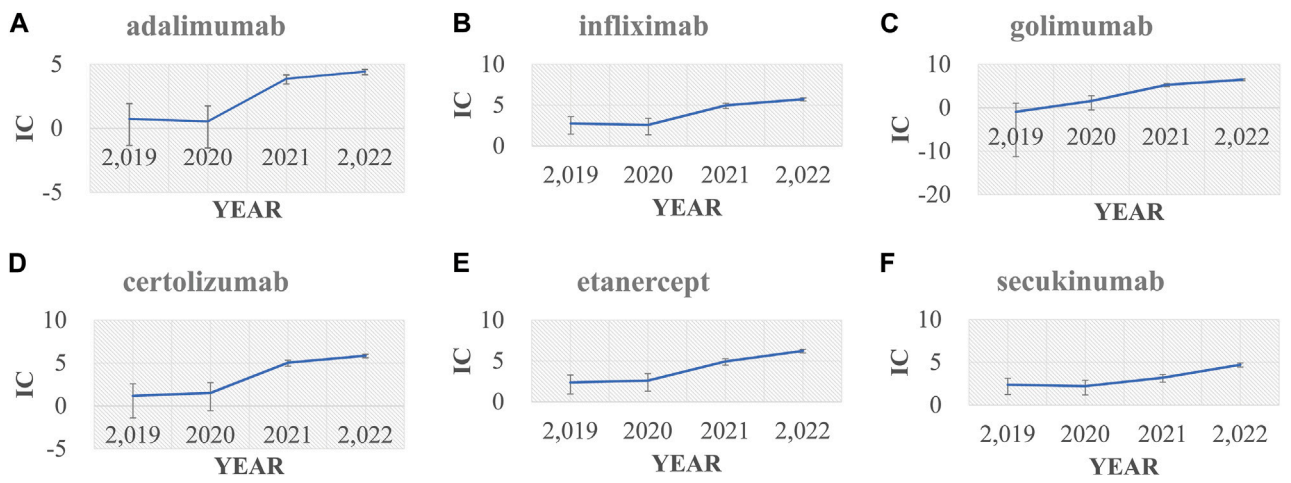

FIGURE 2
Information component (IC) and its 95% credibility interval over time for **(A)** adalimumab, **(B)** infliximab, **(C)** golimumab, **(D)** certolizumab, **(E)** etanercept, and **(F)** secukinumab. IC, information component.

TABLE 3 Sensitivity analysis of pericarditis associated with drugs in AS compared with all other drugs in the FAERS database.

Drug	Corrected for drug-related competition bias, N, IC_{025}	Corrected for suspect drugs and reports from healthcare professionals, N, IC_{025}	Corrected for pre-existing disease, N, IC_{025}	Signal consistency
Adalimumab	82/6499, 3.72	12/31655, −0.83	19/32436, −0.17	Weak (1/3)
Infliximab	130/7333, 4.30	85/12304, 3.83	96/13268, 3.78	Strong (3/3)
Golimumab	79/2674, 4.74	5/6012, −0.45	4/6392, −1.15	Weak (1/3)
Certolizumab	77/2090, 4.97	2/6050, −2.62	7/6097, 0.11	Intermediate (2/3)
Etanercept	71/17116, 2.18	37/28774, 1.32	44/28922, 1.45	Strong (3/3)
Secukinumab	62/3556, 4.01	40/13437, 2.47	46/14573, 2.45	Strong (3/3)
Ustekinumab	75/231, 6.47	0/355	5/461, 1.46	Intermediate (2/3)
Tofacitinib	70/206, 6.39	2/488, −0.68	2/387, −0.64	Weak (1/3)
Upadacitinib	1/55, −2.30	0/264	0/238	No signal (0/3)
Sulfasalazine	76/523, 6.11	97/3823, 5.42	9/3738, 1.17	Strong (3/3)
Mesalazine	53/108, 6.09	0/720	0/817	Weak (1/3)
Methotrexate	83/1460, 5.45	39/7181, 3.22	43/8237, 3.07	Strong (3/3)
Comparator	4773/7100723	4961/14603848	6170/16200491	—

Comparator in the sensitivity analysis is all other drugs in the FAERS database.

pharmacovigilance studies also showed that pleuro-pericarditis was more commonly reported in women (Zhang and Yue, 2020). Another research (Rusman et al., 2018) showed that women seemed to be more prone to infections during TNFi treatment than men. Infection may further induce pericarditis (Imazio et al., 2010). Increased infection risk in women receiving TNFi may contribute to the increased pericarditis reports. Moreover, Vermeire et al. (2003) showed that antinuclear antibodies were associated with the female sex (odds ratio, 3.166; 95% confidence interval, 1.167–8.585; $p = 0.024$) in patients on anti-tumor necrosis factor treatment for Crohn's disease. Previous research (Goswami et al., 2018) showed that pericarditis was diagnosed in women, with 25.4% (104/409) of 409 patients with systemic lupus erythematosus. A higher risk of pericarditis in women was found for cutaneous lupus erythematosus (Olbrich et al., 2023). Those literature works indicated that anti-tumor necrosis factor treatment may increase the risk of lupus in women. In addition, pericarditis is a common cardiac manifestation of lupus. Further research is warranted to provide more evidence regarding this issue.

Third, our study supports the reporting association of pericarditis with TNFi and IL-17i in AS. A recent high impact review (Braun et al., 2017) summarized cardiovascular comorbidity in inflammatory

rheumatological conditions. In this review, we found no evidence of pericarditis as an AS comorbidity. By the way, we found that there were only four pericarditis reports with an event date early compared to the start date of bDMARDs (one for etanercept, one for adalimumab, and two for infliximab), which was a very small percentage among all pericarditis reports with bDMARDs. The time-to-onset data further supported that pericarditis occurred after the administration of bDMARDs for AS (Supplementary File S5). These sources of evidence support that pericarditis may not be a complication of AS. This study only focuses on investigating the potential association of pericarditis with bDMARDs in AS but not in rheumatoid arthritis or psoriatic arthritis because previous studies (Ogdie et al., 2015; Sparks et al., 2019) reported an increased incidence of major adverse cardiovascular events in rheumatoid arthritis, psoriatic arthritis, or psoriasis. This was confirmed by a recent pooled genome-wide association study (Wang et al., 2023), which showed that rheumatoid arthritis itself increases the risk of heart failure. However, previous research (Fang et al., 2022) showed that JAKi and TNFi in rheumatoid arthritis have comparable safety issues and mortality rates. Another meta-analysis (Cai et al., 2023) showed that targeted therapies did not show a higher occurrence of all CVEs in PsO/PsA (RR = 1.03; 95% CI 0.74–1.43l; p = .85) compared to the placebo. Our findings showed that bDMARDs, especially infliximab, etanercept, and secukinumab, significantly presented a disproportionate signal of pericarditis compared to other medications for AS after accounting for confounding factors. Regarding the possible mechanism of pericarditis with bDMARDs, we believe that there are three possible aspects (direct cardiotoxicity, infection induced pericarditis, lupus-induced pericarditis). To begin with, TNFi may directly induce cardiotoxicity and increase the risk of pericarditis. A previous review (Hussain et al., 2021) showed that greater inhibition of TNFR2 (a cardioprotective receptor) than TNFR1(an apoptotic receptor) results in cardiovascular morbidity associated with TNFi. In addition, previous research showed that patients with inflammatory joint diseases initiating bDMARDs treatment had four times increased risk of serious infection compared with the general population (Krabbe et al., 2021). In addition, infection may further induce pericarditis. Lastly, recent research (De Bandt et al., 2005; Costa et al., 2008; Moulis et al., 2014) showed that TNFi had a higher potential to induce lupus than other drugs. As previously discussed, pericarditis may be a manifestation of systemic lupus erythematosus, cutaneous lupus erythematosus, and drug-induced lupus. This showed that pericarditis could be caused by bDMARD-related systemic lupus erythematosus. Much research is warranted to unveil the mechanism of pericarditis with bDMARDs.

This study has some limitations. First, the incidence of pericarditis following TNFi or IL-17i cannot be determined because the number of patients exposed to the drugs is unknown. Second, the source of reports in the FAERS database is heterogeneous, including non-health professionals, such as consumers and lawyers. However, we corrected this in our sensitivity analysis. Third, the detailed diagnosis information including radiography, biochemistry test, disease activity and duration, and the level of antinuclear antibodies is absent in the FAERS database, which may introduce confounding factors in our analysis. Fourth, this study does not allow us to infer causality (ROR and IC are not risk measures). Moreover, the contribution of additional drugs and AS itself to the underlying risk of pericarditis cannot be excluded. A recent study (Micallef et al., 2023) showed that a high number of adverse drug reaction reports for COVID-19 vaccines in EudraVigilance have the potential to affect routine statistical signal detection activities, which may also have an influence on the signal detection of this study.

Nonetheless, our study has some important strengths (Bihan et al., 2020). By using one of the largest publicly accessible pharmacovigilance databases, FAERS, this study contributed to the cumulative knowledge about the potential reporting association of pericarditis with bDMARDs for AS in an unselected real-world population, an evolving clinical issue. Moreover, we conducted stepwise sensitivity analyses to evaluate the robustness of results, accounting for potential co-reporting biases and using sulfasalazine, mesalazine (the active moiety of sulfasalazine), methotrexate, tofacitinib, and upadacitinib as comparators, which could provide a clinical perspective. More studies are warranted to validate this finding.

5 Conclusion

In patients with active AS, we found an increased reporting of pericarditis with bDMARDs, including TNFi and IL-17i, notably when compared with other medications in the FAERS database. Pericarditis could be potentially considered among the spectrum of major adverse cardiovascular events with bDMARDs in patients with AS. Further investigations are needed to better elucidate patients' susceptibility (e.g., female sex) and the potential underlying autoimmune mechanism. The remarkable proportion of serious cases further calls clinicians to increase awareness of this life-threatening safety issue; this will finally support early detection and safe(r) prescribing of bDMARDs in AS 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 author.

Ethics statement

Anonymized data were collected from a publicly available database and do not require approval from the ethics committee.

Author contributions

SX: writing–review and editing, data curation, formal analysis, visualization, and writing–original draft. Y-FL: writing–original draft, writing–review and editing, data curation, formal analysis, and visualization. ER: writing–review and editing. B-KZ: writing–review and editing and resources. YN: writing–review and editing. MS: writing–review and editing and software. MY: writing–review and editing and resources. J-AM: writing–review and editing and conceptualization.

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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

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Clinical characteristics and risk factors analysis of 505 cases of infusion reactions in a tertiary hospital

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Background: The clinical characteristics and risk factors of infusion reactions (IRs) are inadequately described in clinical practice due to underreported cases. In the present study, we reported the current status of IRs based on an in-hospital pharmacovigilance database of a tertiary care hospital.

Methods: Our study conducted a retrospective analysis of drug-induced IRs recorded at an in-hospital pharmacovigilance center between January 2015 to December 2019. The descriptive statistical analysis encompassed main causative agents, clinical manifestations, organ/system involvement and outcome. The severity of IRs was assessed with reference to the CTCAE version 5.0 criteria and we investigated risk factors associated with severe IRs.

Results: During the study period, a total of 505 cases of inpatient drug-induced IRs were detected, of which 79.2% (400 cases) were classified as general IRs and 20.8% (105 cases) were categorized as severe IRs. The primary drugs responsible for these reactions were antibiotics (23%, 116 cases), with piperacillin sodium—sulbactam sodium being the most prevalent, followed by antineoplastic agents (18.4%, 93 cases) and traditional Chinese medicine injections (TCMIs) (12.9%, 65 cases). The administration of cefoperazone - sulbactam, mannatide, Shenqi Fuzheng, elemene, and diterpene ginkgolides meglumine resulted in a higher incidence of critical IRs. Among all cases of IRs, 43.2%, 41.2%, and 23.4% showed signs and symptoms of circulation, skin mucosa, and respiratory organs/systems, respectively. 9.1% of cases experienced systemic damage, while 7.1% and 5.9% of cases reported neurological and gastrointestinal related adverse reactions, respectively. The multivariate analysis revealed that alcohol consumption (OR = 2.389%, 95% CI 1.141–5.002, p = 0.021), age over 65 (OR = 1.814%, 95% CI 1.052–3.127, p = 0.032) and the utilization of contrast media (OR = 4.072%, 95% CI 1.903–8.713, $p < 0.001$) were identified as risk factors for the development of severe IRs.

Conclusion: Understanding the clinical characteristics of IRs helps to implement effective pharmaceutical monitoring and appropriate preventive measures for susceptible populations with risk factors.

KEYWORDS

infusion reactions, clinical characteristics, risk factors, pharmacovigilance, tertiary hospital

1 Introduction

Intravenous infusion is a prevalent therapeutic modality in medical practice. Infusion reactions (IRs) encompass a spectrum of adverse events that occur during or following the administration of pharmacologically active substances or biologically active agents. These reactions may manifest either immediately during the infusion process or within a few hours to days post-administration. (Roselló et al., 2017). IRs were previously defined as unpredictable, also unrelated to dose and pharmacological activity of the drug, generally, they would be relieved or reversed when the treatment is terminated (Edwards and Aronson, 2000; Baldo, 2013). The two types of IRs can be classified as anaphylaxis, which is mediated by immunoglobulin E (IgE) antibody responses, and IgE non-dependent reactions (Joerger, 2012). Both types exhibit similar clinical symptoms that commonly affect the skin mucosa, respiratory system, circulatory system, gastrointestinal organs, and may pose life-threatening risks (Roselló et al., 2017).

A survey conducted by the Portuguese Pharmacovigilance System revealed that drug-induced anaphylaxis accounted for approximately 6% of all adverse drug reactions (ADRs), with antibiotics being reported as the most common causative agents, followed by acetaminophen and antineoplastics. Furthermore, contrast medium emerged as a significant contributor to allergic events (Ribeiro-Vaz et al., 2013). According to the latest research from the US Food and Drug Administration Adverse Event Reporting System, major agents associated with anaphylaxis include antibiotics, monoclonal antibodies, and non-steroidal anti-inflammatory drugs, while antibiotics, radiocontrast agents, and intraoperative drugs were linked to fatal allergic reactions (Yu et al., 2021). Additionally, the field of allergic reactions focuses on recognizing and exploring risk factors. Numerous studies have demonstrated a significant association between advanced age, coexisting asthma, and underlying cardiovascular disease with the occurrence of severe or fatal anaphylaxis (Turner et al., 2017; Kim et al., 2018; Worm et al., 2018; Pflipsen and Vega Colon, 2020). The evaluation of an in-hospital pharmacovigilance database from a tertiary care hospital in Korea shown that the use of iodine-containing contrast agents and neuromuscular blocking agents were regarded as potential risk factors for the development of anaphylactic shock (Park et al., 2017). Given that allergic reactions are a subset of IRs, it is plausible to postulate the presence of similar drug triggers and risk factors in IRs, thereby necessitating an exploration for reliable causative drugs and risk factors.

Successive reports have documented the occurrence of pegloticase, vancomycin, and intravenous iron-related IRs (Baraf et al., 2014; Alvarez-Arango et al., 2021; Stojanovic et al., 2021). The clinical features description and risk causes cognition of IRs, however, have received limited attention. The objective of this retrospective analysis of real-world data is to provide a comprehensive report on the current status of IRs, including the main culprit agents, clinical symptoms, organ/system involvement, outcome and regression. Additionally, it aims to evaluate the risk factors related to severe IRs. Understanding the clinical characteristics of IRs can help with active drug monitoring and adequate preventive measures for vulnerable groups with risk factors.

2 Methods

2.1 Clinical data

This retrospective study was based on the in-hospital pharmacovigilance system, setting triggers for infusion-related reactions/events triggers, and spanned the period from January 2015 to December 2019, with a total of 924 cases reviewed by pharmacists eligible for inclusion. Repeat reports and non-drug-induced adverse reactions, such as events related to blood transfusions and transfusion ports, were excluded. In addition, cases aged <18 years, suspected unknown drugs, and incomplete disease course were excluded (Figure 1). The patient's demographic and clinical data, including age, gender, history of drug-related allergies, smoking status, alcohol consumption history, co-morbidities, initial suspected medication, anti-allergic pretreatment regimen, eosinophil count, clinical presentations, outcome and regression of IRs were systematically recorded. The study was reviewed and approved by the First Affiliated Hospital of Guangzhou Medical University ethics committee (No. ES-2023-146-01).

2.2 Assessment of IRs

The assessment was conducted in accordance with the National Cancer Institute common terminology criteria for adverse events (CTCAE, version 5.0). Our study protocol defines the classification of IRs as follows: Grade 1 refers to transient and mild reactions that do not necessitate interruption of the infusion, such as reducing the infusion dose or slowing down the infusion rate, and do not require any specific treatment. Grade 2 requires therapy or suspension of infusion, but can be rapidly alleviated with symptomatic treatment (e.g., antihistamines, glucocorticoids, intravenous fluids, supportive care) and prophylactic medication for less than 24 h. Grade 3 represents serious or medically important, yet not immediately life-threatening, characterized by prolonged symptom duration, poor response to symptomatic treatment, and/or relapse after

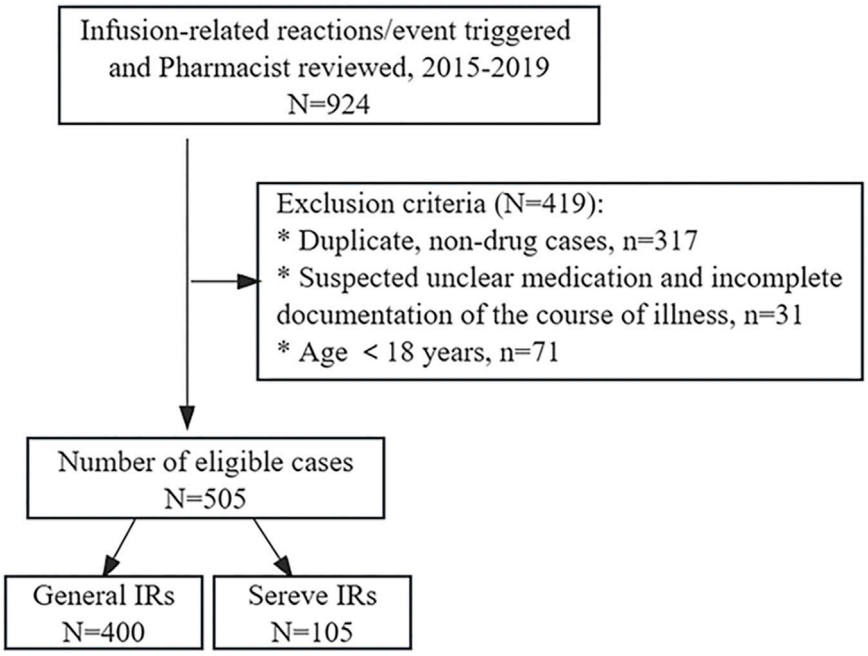

FIGURE 1
Flowchart of case selection.

initial improvement. Grade 4 indicates life-threatening and deserving urgent treatment. Grade 5 denotes death connected with an adverse event. Of these, grades 1 and 2 are categorized as general IRs, while grades 3, 4, and 5 are recognized as severe IRs.

2.3 Statistical analysis

The count data were statistically described by frequency and compared using Pearson's chi-square test and Fisher's exact test for univariate analysis. Variables with *p*-values <0.2 were screened, and logistic regression analysis was performed to determine risk factors relevant to severe IRs, with severity of IRs as the dependent variable. One-way ANOVA was employed to compare the difference in eosinophil count between groups. Statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA, RRID: SCR_016479), considering *p*-values <0.05 as statistically significant.

3 Results

3.1 Demographic and clinical characteristics of drug-induced IRs

A total of 505 cases of IRs were retrieved. The severity of IRs was evaluated based on CTCAE version 5.0, of which 400 cases (79.2%) classified as mild and 105 cases (20.8%) categorized as severe. Of these patients, 151 cases (29.9%) were aged between 18 and 50 years, while 188 cases (37.2%) fell within the age range of 50–65 years. Additionally, 166 patients (32.9%) were aged over 65. Adverse reactions resulting from intravenous drug infusion were predominantly observed in patients aged 50 and above. The gender composition of male and female patients was similar, with a history of drug-induced allergies reported in 110 cases (21.8%). The majority of combined diseases were hypertensive in nature. Anti-allergic premedication was administered to 106 cases (21%), comprising 92 cases of general IRs and 14 cases of severe IRs (Table 1).

3.2 The main causative agents of IRs

Antibiotics (116/23%) were the primary causative agents for in-hospital IRs. Among the antibiotics, piperacillin sodium-sulbactam sodium was the most frequently implicated, while cefoperazone sodium-sulbactam sodium exhibited the highest propensity for severe IRs. The second most often reported antineoplastic agents (93/18.4%) were predominantly characterized by the high prevalence of platinum compounds and mannatide, with mannatide displaying the highest number of instances resulting in severe IRs. Subsequently, Traditional Chinese Medicine Injections (TCMIs) were observed in 65 cases (12.9%), of which Sulfotanshinone sodium was the principal trigger for IRs. However, severe IRs were mainly caused by Shenqi Fuzheng, elemene and diterpene ginkgolides meglumine. Furthermore, more than half of the severe IRs were attributed to intravenous infusion of contrast media. The main causative agents of IRs may be associated with the overall frequency of utilization. However, there does not appear to exist a correlation between the frequency of utilization and the severity of IRs (Table 2).

TABLE 1 Demographic and clinical characteristics.

	Total number N = 505	IRs		P-value[ξ]
		General	Severe	
		N = 400 (79.2)	N = 105 (20.8)	
Age(y)				0.075
18≤age≤50	151 (29.9)	123 (30.8)	28 (26.7)	
50<age≤65	188 (37.2)	139 (34.8)	49 (46.7)	
>65	166 (32.9)	138 (34.5)	28 (26.7)	
Sex				0.408
Male	256 (50.7)	199 (49.8)	57 (54.3)	
Female	249 (49.3)	201 (50.3)	48 (45.7)	
History of drug-derived allergy				0.273
Have	110 (21.8)	83 (20.8)	27 (25.7)	
None	395 (78.2)	317 (79.3)	78 (74.3)	
Smoking status				0.426
Have	143 (28.3)	110 (27.5)	33 (31.4)	
None	362 (71.7)	290 (72.5)	72 (68.6)	
History of drinking				0.008
Have	37 (7.3)	23 (5.8)	14 (13.3)	
None	468 (92.7)	377 (94.3)	91 (86.7)	
Pretreatment medication				0.03
Have	106 (21)	92 (23)	14 (13.3)	
None	399 (79)	308 (77)	91 (86.7)	
Co-morbidities				
Airway diseases[δ]	56 (11.1)	45 (11.3)	11 (10.5)	0.822
Ischemic heart disease	81 (16)	60 (15)	21 (20)	0.214
Hypertension	148 (29.3)	116 (29)	32 (30.5)	0.767
Diabetes	61 (12.1)	50 (12.5)	11 ((10.5))	0.571
Culprit drugs				
Antibiotics	149 (29.5)	128 (32)	21 (20)	0.16
Antineoplastics	93 (18.4)	73 (18.3)	20 (19)	0.851
Contrast medium	35 (6.9)	17 (4.3)	18 (17.1)	<0.001
Nutrients	22 (4.4)	19 (4.8)	3 (2.9)	0.564
Biological preparations	36 (7.1)	30 (7.5)	6 (5.7)	0.527
TCMIs	65 (12.9)	46 (11.5)	19 (18.1)	0.072

δ, Asthma or Chronic obstructive pulmonary disease (COPD). ξ, Pearson's chi-square test and Fisher's exact test. TCMIs, Traditional Chinese Medicine Injections.

3.3 Organ/system involvement and major clinical signs of IRs

Among the 505 cases included in this retrospective analysis, 43.2%, 41.2%, and 23.4% experienced signs and symptoms of circulatory, cutaneous mucosal, and respiratory, respectively. In addition, systemic damage was reported in 9.1% of cases. While neurological and gastrointestinal adverse reactions occurred in 7.1% and 5.9% of cases, respectively. Detailed clinical manifestations are provided in Table 3.

The details of both overall and severe IRs involving various organ systems are presented in Figure 2, revealing a notable predominance of severe IRs affecting the respiratory system and significantly heightened systemic damage compared to the overall incidence of IRs.

The administration of antibiotics was predominantly associated with skin and mucosal adverse reactions, while being less correlated with circulatory events. Conversely, the use of antineoplastic agents primarily exhibited relevance to respiratory events. Moreover, the application of contrast agents often accompanied by systemic damage and less related to respiratory and circulatory events. In contrast, the side effects linked to the administration of nutritional drugs and herbal injections showed the opposite pattern to that of antibiotics (Figure 3).

3.4 Outcome and regression

General IRs are typically transient and mild, and do not necessitate treatment discontinuation or complete resolution of signs and symptoms in all cases following interruption of infusion or management. Conversely, severe IRs often manifest as life-threatening events subsequent to intravenous drug administration, demanding immediate therapeutic

TABLE 2 Details of the distribution of the main causative drugs.

Drug name	Total patients of drug use (N)	Number of IRs (with severe)
Antibiotics		149 (21)
Piperacillin-Sulbactam/ Tazobactam	29876	46 (6)
Cefoperazone-Sulbactam	14266	15 (5)
Cefmetazole	18005	9 (1)
Cefuroxime	21972	7 (2)
Ceftazidime	3254	5 (0)
Cefazolin	22536	5 (0)
Vancomycin	3584	5 (0)
Cefathiamidine	22944	4 (1)
Meropenem	13199	4 (1)
Teicoplanin	2079	4 (0)
Imipenem And Cilastatin	6630	3 (0)
Azithromycin	3507	3 (0)
Latamoxef	9574	2 (1)
Clindamycin	4268	2 (0)
Cefepime	766	1 (0)
Aztreonam	-	1 (0)
Levofloxacin	40740	16 (2)
Moxifloxacin	19978	14 (1)
Ciprofloxacin	2629	3 (1)
Antineoplastic agents		93 (20)
Platinum compounds	39114	32 (4)
Mannatide	16387	25 (8)
Monoclonal antibodies	2124	14 (4)
Paclitaxel	8086	8 (1)
Doxorubicin	89	5 (1)
Docetaxel	7256	2 (0)
Recombinant Human Tumor Necrosis Factor	3686	2 (1)
Recombinant Human Interleukin-2 (125Ala)	615	1 (0)
Group A *Streptococcus*	1027	1 (0)
Etoposide	5307	1 (0)
Thymalfasin	11098	1 (0)
Cytarabine	782	1 (1)
TCMIs		65 (19)
Sulfotanshinone Sodium	30174	13 (1)
Shenqi Fuzheng	21387	9 (4)
Cervus and Cucumis Polypeptide	10257	6 (3)
Aidi	8005	6 (1)
Elemene	3182	5 (3)
Compound Kushen	6048	5 (0)
Diterpene Ginkgolides Meglumine	2239	3 (2)
Lentinan	14219	3 (1)
Shuxuetong	3882	3 (1)
Xueshuantong	8523	3 (1)
Kangai	8552	3 (1)
Xiyanping	3824	2 (1)
Canfu	1987	2 (0)
Kanglaite	10066	1 (0)
Xingnaojing	7429	1 (0)
Contrast media	4705	35 (18)

Note: Our study counted only the top four major causative drugs.

intervention. Most of these cases were resolved through a series of clinical pathway interventions, including discontinuation of the suspected drug infusion, administration of intravenous fluids, anti-allergy medications (such as corticosteroids/ antihistamines), and adjunctive support. However, a minority of cases exhibited unsatisfactory management outcomes with prolonged symptom duration and even two adverse event-related deaths (Table 4).

3.5 Risk factors for severe IRs

A total of 105 cases of severe IRs were reported. There was a significant association between intravenous administration of contrast media and an elevated risk of systemic damage. In addition, the administration of antineoplastic agents was found to induce severe IRs specifically affecting the respiratory system. Among these cases, cefoperazone-sulbactam, mannatide, Shenqi Fuzheng, elemene, and diterpene ginkgolides meglumine were relatively more serious IRs triggered by antibiotics, antineoplastic drugs, and TCMIs, respectively.

The factors influencing severe IRs were further investigated through logistic regression analysis, aiming to identify the risk factors associated with serious IRs. Univariate analysis was conducted to screen for variables with a significance level of $p < 0.2$, including age, alcohol consumption, use of antibiotics, contrast agents and TCMIs, as well as whether or not premedication was administered. Multivariate analysis confirmed that alcohol consumption (OR = 2.389%, 95% CI 1.141–5.002, $p = 0.021$), age over 65 (OR = 1.814%, 95% CI 1.052–3.127, $p = 0.032$) and contrast media use (OR = 4.072%, 95% CI 1.903–8.713, $p < 0.001$) were substantial risk factors associated with the development of serious IRs (Table 5).

3.6 Changes in eosinophil count

The number of cases that fulfilled the criteria for testing serum eosinophil counts at, before, and after the onset of the IR was 106. Multiple measurements were averaged to compare the differences between these three time points. However, no statistically significant differences were observed (Figure 4).

4 Discussion

Our study retrospectively reported the current status of IRs based on domestic real-world data from hospital pharmacovigilance centre. Studies derived from domestic and foreign pharmacovigilance databases have consistently found the primary causative agents responsible for allergic reactions, which align with the characteristics of drugs that triggered IRs in this investigation (Ribeiro-Vaz et al., 2013; Wang et al., 2017). A majority of previous studies have demonstrated that β-lactam antibiotics were the culprit drugs of anaphylaxis (Renaudin et al., 2013; Ribeiro-Vaz et al., 2013; Turner et al., 2017), and one study suggested that piperacillin, a

TABLE 3 Involving organs/systems and the main clinical manifestations.

Involved organs/ systems	Clinical symptoms	Number (percentage)
Skin mucosa system	Rash, itching, transient skin flushing, congestion and swelling of the mucous membranes of the nose/ eyes/throat	208 (41.2)
Digestive system	Nausea, vomiting, abdominal pain	30 (5.9)
Respiratory system	Chest tightness, shortness of breath, difficulty breathing, cough	118 (23.4)
Circulatory system	Chills, fever, sweating, decreased oxygen/blood pressure, tachycardia, cyanosis, syncope, pallor	218 (43.2)
Nerves system	Dizziness, headache, weakness, convulsions, confusion or restlessness, incontinence	36 (7.1)
Systemic damage	Anaphylactic shock	46 (9.1)

Note: The total number of cases of system-organ involvement is greater than the total number of ADR, reports because more than one type of system-organ damage may occur in a single ADR, report.

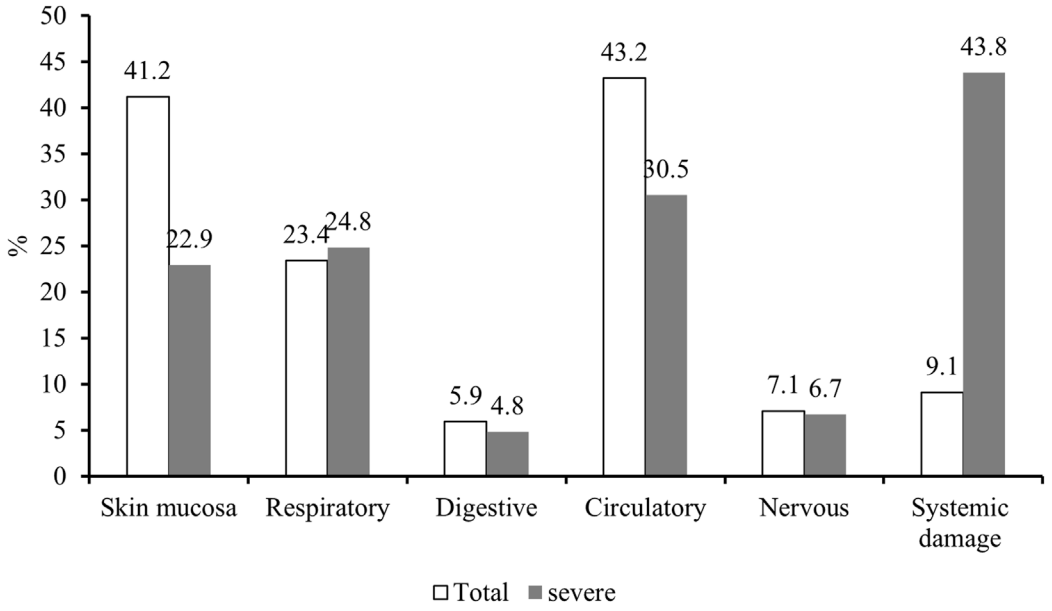

FIGURE 2
Organ/system involvement in IRs.

penicillin derivative, was the most frequently reported drug (Park et al., 2021). The current study indicated that antibiotics were the most common causative agents of IRs, with piperacillin sodium-sulbactam sodium being recorded in the greatest frequency, revealing parallels between the profiles of the drugs triggering IRs and the prevalent drugs formerly described as allergic reactions. Therefore, clinical use of medications should be alert to and prevent the possibility of IRs induced by intravenous infusion of allergy-prone drugs.

The idea that the skin mucosa is the organ/system most significantly affected by ADRs to antibiotics is consistently supported by a large number of studies (Diaz and Ciurea, 2012; Zhao et al., 2019; Jourdan et al., 2020). Therefore, meticulous attention was given to possible skin and mucosal side effects such as rash, pruritus, and flushing during intravenous infusion. Meanwhile, piperacillin, levofloxacin, cefoperazone and moxifloxacin were reported mostly antibiotics in present study. Notably, cefoperazone was the culprit of severe IRs, which need to be strengthened to prevent and monitor the drugs that cause frequent and serious ADRs.

Although platinum compounds were the primary cause of IRs among antineoplastic agents, mannatide induced the highest number of severe IRs. This may be attributed to adherence to clinical dosing principles or institutional policies, where routine administration of classical antineoplastic agents such as platinum compounds, paclitaxel, docetaxel, and monoclonal antibodies significantly mitigated the risk of IRs associated with chemotherapy drugs. The available evidence suggests that a combination of prophylactic strategies, including antihistamines, H2 antagonists, leukotriene receptor antagonists, corticosteroids, and other reasonable interventions, can effectively reduce the incidence and severity of chemotherapy drug-induced IRs while

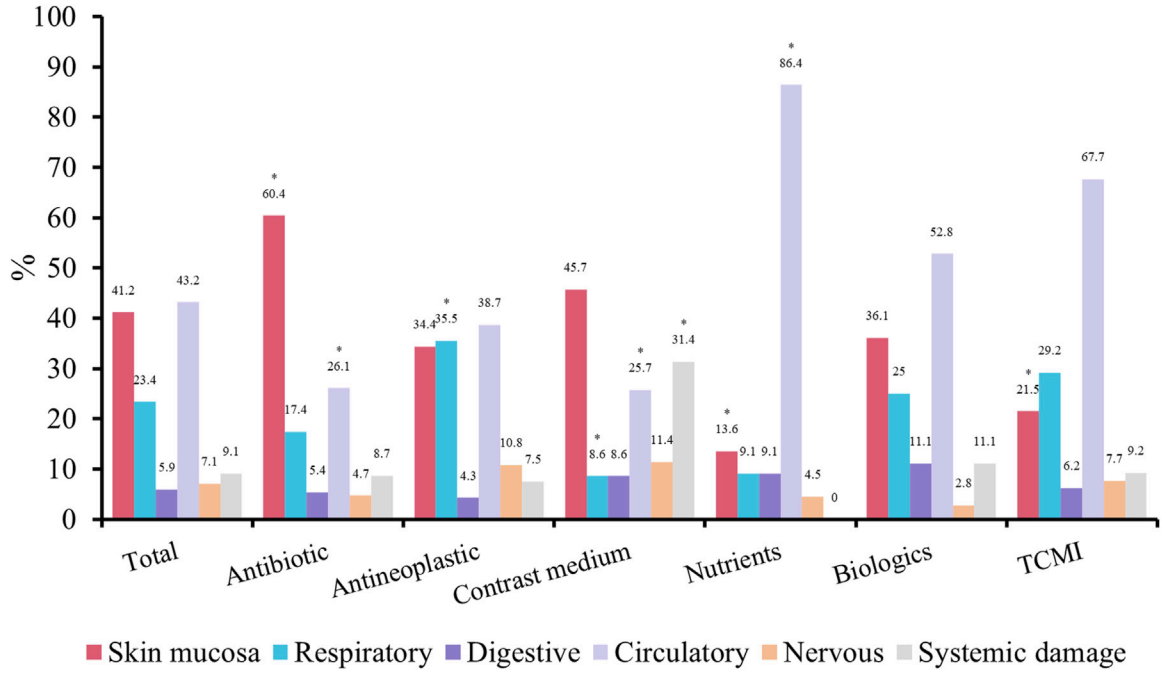

FIGURE 3
Symptoms and signs of IRs. *$p < 0.05$ compare with total patients. TCMI, Traditional Chinese medicine injection.

TABLE 4 Outcome and regression.

Ending transitions	IRs	
	General	Severe
	N = 400	N = 105
Improvement	400 (100)	74 (70.5)
Sustained	0	29 (27.6)
Death	0	2 (1.90)

enhancing safety (ALMuhizi et al., 2022). Mannatide, a glycopeptide compound distinct from conventional anti-tumour drugs. A study on the pro-inflammatory response and chemotaxis of mannatide demonstrated its potential impact on the severity of IgE-mediated diseases, including allergic reactions (Żelechowska et al., 2021). The findings of this study caution that mannatide was susceptible to severe IRs, and this product has been linked to ADRs such as hypersensitivity responses, chest tightness and dyspnea. Therefore, it is recommended to use under close physician supervision and with resuscitative measures.

TABLE 5 Multifactorial logistic regression analysis of severe IRs.

Covariate	B	S.E.	Wald	OR	95% CI		*p*-value
					Lower	Upper	
Age							
18≤age≤50				Reference			
50<age≤65	0.190	0.307	0.382	1.209	0.662	2.206	0.537
>65	0.595	0.278	4.586	1.814	1.052	3.127	0.032
Drink	0.871	0.377	5.337	2.389	1.141	5.002	0.021
Antibiotic	−0.320	0.298	1.156	0.726	0.405	1.302	0.282
Contrast medium	1.404	0.388	13.088	4.072	1.903	8.713	<0.001
TCMI	0.433	0.329	1.732	1.543	0.809	2.942	0.188
Pretreatment	−0.591	0.333	3.150	0.554	0.289	1.064	0.076

Pretreatment refers to the application of antineoplastic drugs for prophylaxis, such as antihistamines, glucocorticoids, anti-inflammatory drugs.

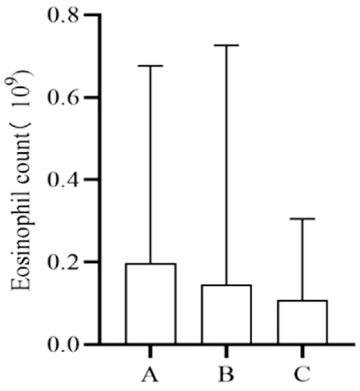

FIGURE 4
Changes in eosinophil count. A, Baseline level before IRs. B, Time level of IRs. C, Level after IRs.

TCMIs are an extension and development of traditional Chinese medicine, boasting a rich history spanning over 70 years. As of 2017, the sale of TCMI products has been authorized for a total of 134 generic names from 224 reputable manufacturers (Li et al., 2018). The utilization of TCMIs, however, has resulted in a growing number of documented IRs (Li et al., 2019). The results of this study demonstrated that TCMIs are important triggers of IRs, often involving the circulatory system. This suggests that TCMIs are becoming more prevalent in clinical use, however, continued attention to ADRs is warranted, common clinical manifestations include chills, fever, sweating, reduced blood oxygen levels/pressure, tachycardia, cyanosis, syncope and pallor.

According to a study conducted between 2014 and 2019 on the safety of TCMIs, Shenmai, Xiangdan, Danshen, Shengmai, Huangqi, and Xuebijing injection exhibited a higher proportion of severe ADRs compared to the average (Huang et al., 2021). The findings are inconsistent with current research, which reported a higher incidence of ADRs associated with Shenqi Fuzheng, Elemene, and diterpene ginkgolides meglumine injection. The variation in culprit drugs was inferred to reflect the diversity in in-hospital drug utilization patterns among tertiary medical centers. Furthermore, there are discrepancies in the drug characteristics summary between individual hospitals and provincial municipalities. Therefore, it is imperative to implement targeted drug monitoring during the clinical application of Shenqi Fuzheng, elemene, and diterpene ginkgolides meglumine herbal injections to mitigate the occurrence of severe IRs.

Previous studies have primarily focused on the risk factors of individual drug-induced IRs, such as infliximab (Duron et al., 2015; Wang et al., 2019) and cetuximab (Touma et al., 2014). The present study investigated the risk factors of severe IRs, and established alcohol consumption, age over 65 and the application of contrast media as risk factors for severe IRs. The reports stated that drinking may interfere with the absorption, distribution, metabolism and excretion of drugs, thereby increase the likelihood of ADR (Weathermon and Crabb, 1999; Castle et al., 2016). To prevent alcohol-drug interactions, it is recommended to avoid consuming alcohol while taking drugs that interact with it. Drug use varies by age. Polypharmacy is very common in the elderly, which may contribute to mainly the growth in the severity of IRs in older individuals (Jerschow et al., 2014). Among pathogenic medications, the use of contrast agents was found to increase the vulnerability to critical IRs, which may be attributed to their inherent properties. The *p*-value for univariate analysis of anti-allergic pretreatment was 0.03, while for multivariate analysis it approached 0.05, suggesting a potential protective effect against drug-induced severe IRs. However, due to limitations in sample size, this difference was not statistically significant. Moreover, several studies have identified comorbidities such as asthma, chronic obstructive pulmonary disease (COPD), and cardiovascular disorders as significant risk factors for severe allergic reactions (Simons et al., 2011; Turner et al., 2017). In this study, airway disease (asthma/COPD), hypertension, diabetes mellitus, and ischemic heart disease were assessed as co-morbidities increasing the risk of severe IRs, however, these differences did not reach statistical significance. Adverse event-related deaths occurred in 2 cases, mainly owning to patients suffering from an underlying disease that did not progress optimistically progressing to cardiac arrest, with the corresponding medication considered as a secondary factor.

Serum eosinophilia can arise from various drug reactions, including but not limited to NSAIDs, antibiotics, and anticonvulsants (Gottlieb et al., 2022; Hama et al., 2022; Awad et al., 2023). We endeavored to assess alterations in eosinophil counts following drug-induced IRs, unfortunately, no statistically significant differences were observed when comparing eosinophil counts before, during, and after the onset of IRs. This analysis may be attributed to the fact that the causative drugs of IRs are not among the primary agents known to induce serum eosinophilia.

This study has several limitations. Firstly, it was a retrospective analysis, which inevitably introduces bias and confounding factors. Additionally, accurately tracking the time interval between drug infusion and onset of adverse reactions posed challenges. Moreover, the rate of infusion may be considered an influential factor in IRs. To overcome these constraints and provide a more precise evaluation of severe IR risk factors, large-scale prospective studies are warranted.

In conclusion, the present study retrospectively reported an update on IRs based on domestic real-world data from hospital pharmacovigilance center and demonstrated antibiotics, antineoplastic agents and TCMIs as the prime culprit drugs in the tertiary care center, with a relatively high number of drugs triggering serious IRs including cefoperazone and sulbactam, mannatide, Shenqi Fuzheng, elemene and diterpene ginkgolides meglumine. The occurrence of IRs may be associated with the total number of medications administered. However, no such correlation seems to exist in terms of severity. In addition, alcohol consumption, age over 65 and the use of contrast media were risk factors of serious IRs. Therefore, reaching a comprehensive understanding of the clinical characteristics of IRs will facilitate active pharmacovigilance and the implementation of appropriate preventive measures for susceptible groups with risk factors.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the First Affiliated Hospital of Guangzhou Medical University ethics committee (No. ES-2023-146-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WY: Conceptualization, Data curation, Writing–original draft, Writing–review and editing. BW: Conceptualization, Investigation, Writing–review and editing. GW: Data curation, Writing–review and editing. ZW: Investigation, Writing–review and editing. XK: Writing–review and editing, Data curation. YW: Data curation, Writing–review and editing. XM: Investigation, Writing–review and editing. XO: Data curation, Writing–review and editing. LW: Supervision, Writing–review and editing, Conceptualization. PY: Conceptualization, Project administration, Supervision, Writing–review and editing.

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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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Risk of immune system and skin and subcutaneous tissue related adverse events associated with oxaliplatin combined with immune checkpoint inhibitors: a pharmacovigilance study

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Background: Few studies have analysed oxaliplatin-induced adverse events (ADEs) in the immune system and skin and subcutaneous tissues through pharmacovigilance. We used this approach to analyse the risk of such ADEs when oxaliplatin combined with immune checkpoint inhibitors (ICIs).

Methods: We evaluated the association between oxaliplatin and ADEs in the immune system and skin and subcutaneous tissues using the reporting odd ratio (ROR) for mining the ADE report signals in the FDA Adverse Event Reporting System database. Risk factors were analyzed using a binary logistic regression analysis using the sex and age of the patients.

Results: There were 40,474 reports of oxaliplatin as primary suspect drug or second suspect drug. The signal intensities of ADEs such as type II hypersensitivity, type I hypersensitivity, type III immune complex–mediated reaction, anaphylactoid shock and cytokine release syndrome were high in PTs classified by SOC as immune system disorders; in the PTs classified as skin and subcutaneous tissue disorders by SOC, the signal intensities of ADEs such as skin toxicity, skin reaction, rash maculo-papular and skin fissures were higher. In the risk assessment between the two groups, rash showed an increased risk in the oxaliplatin-ICI group, with an OR of 1.96. Nivolumab in combination with oxaliplatin had an OR of 2.196 and an adjusted OR of 2.231. Combined with pembrolizumab, OR was 2.762 and the adjusted OR was 2.678.

Conclusion: Type II hypersensitivity shows a stronger pharmacovigilance signal. Oxaliplatin in combination with nivolumab or pembrolizumab has been shown to increase the risk of rash.

KEYWORDS

oxaliplatin, immune checkpoint inhibitors, type II hypersensitivity, rash, pharmacovigilance, signal mining

1 Introduction

Oxaliplatin is a third-generation platinum agent that is used in a wide variety of tumours, including pancreatic, biliary, gastroesophageal, and gynaecologic malignant tumours (Shao et al., 2010; Yu et al., 2021). Immune checkpoint inhibition therapy is a novel treatment regimen that is being progressively applied to treat a variety of solid tumours. Immune checkpoint inhibitors (ICIs) based on this regimen can prevent the immune escape of tumour cells by blocking the programmed cell death protein 1 (PD1)/programmed cell death-ligand 1 (PD-L1) pathway, thereby restoring the role of immune cells (Haanen et al., 2022; Johnson et al., 2020). Combinations of ICIs have emerged in addition to conventional chemotherapy drugs such as oxaliplatin, which have been combined in chemotherapy regimens for specific tumours (Galluzzi et al., 2020) and have achieved good clinical results in clinical practice.

Reports of oxaliplatin-induced hypersensitivity have been increasing yearly. Many patients have to stop treatment because of hypersensitivity reactions, with a discontinuation rate of about 21% (Yanai et al., 2012; Hewitt and Sun, 2006). Some studies have also suggested that the overall incidence of allergic reactions to oxaliplatin is between 2% and 25%, which seems to be independent of the type of tumour (Okayama et al., 2015; Shibata et al., 2009). The most common allergic reactions include pruritus, rash, urticaria, etc. (Rogers et al., 2019), and the median time of occurrence is usually in the first 4 cycles of chemotherapy treatment (Thomas et al., 2003). Meanwhile, immune-related adverse events (irAEs) have occurred during the use of ICIs, and the mechanism of such ADEs is still unclear (Zhu et al., 2021; Apalla et al., 2021). Among which skin tissue-related adverse events (ADEs) are the most common. And it is also reported that they often present within the first 2 cycles of treatment (i.e., within several weeks) (Villadolid and Amin, 2015; De Velasco et al., 2017).

In the real scenario, when patients experience the above-mentioned ADEs during OXA combined with ICIs treatment, it is difficult for clinicians to determine which drug dominates the occurrence of the ADE, thus making it difficult to accurately adjust the treatment plan reasonably. And whether such combination therapy increases oxaliplatin-induced skin allergic reactions or even life-threatening hypersensitivity reactions has not been reported.

The FDA Adverse Event Reporting System (FAERS) is a voluntary reporting system for ADEs. It can be used to evaluate the safety of drugs by collecting real-world ADEs (Takao et al., 2012). In this study, we used oxaliplatin reports in the FAERS database to analyze the oxaliplatin-related ADEs of the immune system, skin, and subcutaneous tissues by using signal data-mining methods and to assess the risk of such ADEs in the chemotherapy regimens of oxaliplatin combined with ICIs.

2 Materials and methods

2.1 Data source

The data used in the study are all from the FAERS database. Initially, data on adverse events recorded from the first quarter of 2013 to the first quarter of 2023 in the FAERS database were downloaded from the FDA website (US Food and Drug Administration, 2022). We built an original database that reintegrated the downloaded records using Oracle Database 11 g software and used SQL queries to retrieve relevant information.

The target drug of this study was oxaliplatin. We took a text-mining approach that searched for the drug in terms of its generic name and brand name (eloxatin). The target drug was set as the primary suspected drug (PS) or the secondary suspected drug (SS).

We followed the FDA's recommendation to use the most recent case number to identify duplicate reports of the same patient that came from different reporting sources. Duplicate reports were also removed by matching age, sex, initial FDA date, and reporter country.

We also retrieved reports of the use of ICIs with oxaliplatin. This text-mining approach searched for the ICIs in terms of their generic and brand names: "nivolumab" and "opdivo," "pembrolizumab" and "keytruda," "atezolizumab" and "tecentriq," "durvalumab" and "imfinzi," "tremelimumab" and "imjudo," "ipilimumab" and "yervoy," "relatlimumab" and "opdualag," "avelumab" and "bavencio," "cemiplimab" and "libtayo," "dostarlimab" and "jemperli."

2.2 Definition of adverse events

ADE is described according to the preferred term (PT) and Systematic Organ Classification (SOC) in the Medical Dictionary for Regulatory Activities (MedDRA) 23.0 (Maintenance and Support Services Organization, 2022).

Immune System and skin and subcutaneous tissue-related ADEs (ISA-ADEs): ISA-ADEs were defined as adverse events related to immune system disorders and skin and subcutaneous tissue disorders. The SOC classification of immune system disorders was 10021428, and the SOC classification of skin and subcutaneous tissue disorders was 10040785.

2.3 Signal detection method

A disproportionality analysis was conducted by computing the reporting odds ratio (ROR) and the corresponding 95% confidence interval (CI) for the association between each ISA-ADE and oxaliplatin. The ROR was calculated as the ratio of the odds of reporting the ISA-ADE versus all other ADRs for a given drug compared to the reporting odds for all other drugs present in the FAERS (Almenoff et al., 2005). See details in Table 1. The following formula was used to calculate the ROR and 95%

TABLE 1 Four-fold table.

Drugs	Target ADE (n)	Other ADEs (n)	Total
Target drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

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TABLE 2 The number of ISA-ADEs reports and the value of reports odds ratios.

SOC = Immune system disorders				SOC = Skin and subcutaneous tissue disorders			
PT	n	N	ROR (95% CI)	PT	n	N	ROR (95% CI)
Hypersensitivity	989	118,091	2.776 (2.606, 2.958)	Rash	956	262,695	1.186 (1.112, 1.265)
Anaphylactic reaction	386	30,258	4.212 (3.808, 4.659)	Pruritus	810	210,962	1.252 (1.168, 1.343)
Cytokine release syndrome	306	7,429	13.998 (12.480, 15.702)	Skin toxicity	377	3,140	44.555 (39.992, 49.639)
Anaphylactic shock	263	13,378	6.524 (5.773, 7.374)	Urticaria*	213	96,187	0.717 (0.626, 0.820)
Drug hypersensitivity*	257	145,033	0.572 (0.506, 0.646)	Skin reaction	148	8,897	5.490 (4.665, 6.460)
Type I hypersensitivity	155	2,142	32.595 (27.670, 38.398)	Rash maculo-papular	105	12,327	2.784 (2.297, 3.375)
Anaphylactoid reaction	59	1,849	10.679 (8.238, 13.843)	Skin exfoliation*	98	53,942	0.588 (0.482, 0.717)
Immune system disorder*	32	8,545	1.216 (0.860, 1.721)	Skin disorder	94	20,986	1.457 (1.189, 1.785)
Type II hypersensitivity	18	46	208.099 (115.101, 376.236)	Rash erythematous	93	24,335	1.242 (1.013, 1.523)
Type IV hypersensitivity reaction	14	1,593	2.870 (1.695, 4.857)	Skin fissures	82	10,178	2.631 (2.117, 3.271)
Type III immune complex mediated reaction	14	259	18.496 (10.793, 31.696)	Rash pruritic*	66	31,123	0.687 (0.540, 0.875)
Anaphylactoid shock	9	201	15.170 (7.774, 29.603)	Pruritus generalised	64	14,652	1.420 (1.111, 1.816)
Cytokine storm	8	384	6.886 (3.418, 13.871)	Skin lesion*	58	16,369	1.151 (0.889, 1.489)
				Rash papular*	48	14,256	1.093 (0.823, 1.452)
				Skin ulcer*	41	16,202	0.821 (0.604, 1.115)
				Rash macular*	38	20,864	0.590 (0.429, 0.811)
				Toxic skin eruption	38	5,605	2.210 (1.606, 3.041)
				Dermatitis allergic*	22	7,257	0.984 (0.647, 1.495)
				Stevens-Johnson syndrome*	21	10,107	0.674 (0.439, 1.034)
				Dermatitis exfoliative generalised	13	2,109	2.007 (1.163, 3.463)
				Pruritus allergic*	4	821	1.584 (0.593, 4.231)

ISA-ADEs, Immune system and skin and subcutaneous tissue related ADE; PT, preferred term; SOC, systematic organ classification; ROR, reports odds ratio *, not defined as a signal.

confidence interval (CI): ROR=$(a/c)/(b/d)$, 95% CI = $e^{\ln(\mathrm{ROR})\pm1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$. An association was considered to be statistically significant if the lower limit of 95% CI was above 1.0 (Bate and Evans, 2009).

2.4 Data analysis

2.4.1 ISA-ADE signal detection

Based on the ISA-ADE reports of oxaliplatin in the FAERS database, signal detection methods were used to mine the ISA-ADE signals.

2.4.2 Risk assessment of ISA-ADE after oxaliplatin combined with ICIs

First, ADE reports of oxaliplatin were included in the ISA-ADE risk assessment study, and the reported patient population was divided into Group OXA, with oxaliplatin, and Group OXA-ICI, with oxaliplatin and ICI, depending on whether oxaliplatin was reported in combination with an ICI. The exclusion criteria were as follows: age, sex, and country (or region) of the report were taken as the judgement conditions; if any of the three items in the report had missing records, then the patients in the report were not included in the grouping study. The study excluded patients younger than 18 years of age.

Second, risk assessment was conducted between the two groups by using the results obtained from the previous signal-mining study on the ISA-ADEs, already defined as signals. The risk factors were analyzed by binary logistic regression analysis using the sex and age of the patients.

Microsoft™ Excel for Mac (16.72) and SPSS (Ver 25.0) were used for data processing and statistical computation.

3 Results

3.1 ISA-ADE signals of oxaliplatin

A total of 13,136,477 reports were included in the FAERS database. There were 40,474 reports of oxaliplatin as PS or SS based on established screening criteria.

All 34 ISA-ADE-related PTs were included in this study, and the reported frequencies and ROR values are detailed in Table 2. Among them, the signal intensity of ADEs such as type II hypersensitivity, type I hypersensitivity, type III immune complex–mediated reaction, anaphylactoid shock and cytokine release syndrome were all high, especially type II hypersensitivity (ROR = 208.099, 95% CI = 115.101, 376.236). In the PTs classified as skin and subcutaneous tissue disorders by SOC, the signal intensities of ADEs such as skin toxicity, skin reaction, rash maculo-papular and skin fissures were higher, especially skin toxicity (ROR = 44.555, 95% CI = 39.992, 49.639).

For oxaliplatin, there were 12 ADEs that were not defined as ISA-ADE signals: drug hypersensitivity, immune system disorder, urticaria, skin exfoliation, rash pruritic, skin lesion, skin ulcer, rash papular, rash macular, dermatitis allergic, Stevens-Johnson syndrome, and pruritus allergic. The other 22 ISA-ADEs were set as target ADEs for risk assessment.

3.2 Risk assessment of ISA-ADE after oxaliplatin combined with ICIs

Of the 40,474 oxaliplatin reports retrieved, 30,524 patients were enrolled in the risk assessment study by applying the exclusion criteria. They were sorted into both Group OXA and Group OXA-ICI. The flowchart is shown in Figure 1. The characteristics of the patients in the two groups are listed in Table 3. There were significant differences in sex and age between the two groups ($p < 0.01$). In terms of the proportion of reports from each country (or region), France, Italy and Deutschland were the main countries in Europe, the United States was the main country in the Americas, and Japan and China were the main countries in Asia.

There were no reports of oxaliplatin in combination with cemiplimab, dostarlimab, or relatlimumab in the OXA-ICI group, so we did not perform a statistical analysis on these three drugs. When studying target ISA-ADEs, we found that 12 ISA-ADEs did not have oxaliplatin combined with ICI in the reports (see details in Supplementary Material S1), so only 10 ISA-ADEs were finally included in the risk assessment. See details in Table 4. We also found that no use of atezolizumab, durvalumab, or tremelimumab was reported in these 10 ISA-ADEs, so no statistical analysis was performed on these three drugs. See details in Supplementary Material S2.

In the risk assessment of each ISA-ADE between the two groups, only rash showed an increased risk in the OXA-ICI group, with an OR_{cr} of 1.96. See details in Table 4. We further adjusted the OR by sex and age, yielding an OR_{adj} of 1.974 (95% CI = 1.472, 2.647). We also conducted a further risk assessment for each ICI in combination with oxaliplatin. In combination of nivolumab with oxaliplatin, the OR_{cr} was 2.196 and the OR_{adj} was 2.231, while in the combination of pembrolizumab with Oxaliplatin, the OR_{cr} was 2.762, and the OR_{adj} was 2.678. See details in Table 5.

4 Discussion

Oxaliplatin is a third-generation platinum compound that differs from cisplatin and carboplatin, there has been a low incidence of hypersensitivity reactions caused by oxaliplatin in early studies (Thomas et al., 2003; Shepherd, 2003). The signs and symptoms of oxaliplatin-induced hypersensitivity reactions are broad, frequently difficult to define, and include all organ systems (Shepherd, 2003). The mechanism of oxaliplatin-induced hypersensitivity is not fully understood, though most studies agree that it is a type I hypersensitivity reaction (Thomas et al., 2003). Oxaliplatin may act as a superantigen to cause cell proliferation and activation and then release cytokines (IL-6 or TNF-α). Another possible mechanism is the combination of oxaliplatin and major histocompatibility complexes to mediate the immune response (Thomas et al., 2003; Newman Taylor et al., 1999).

In this study, we focused on reports of ADEs of hypersensitivity reactions in the immune system and skin tissues. These ADEs are well known, despite the large number of pharmacovigilance signals in the classification of skin and subcutaneous tissue disorders. In contrast, little attention has been paid to pharmacovigilance signals under the classification of immune system disorders. Among them, type II hypersensitivity

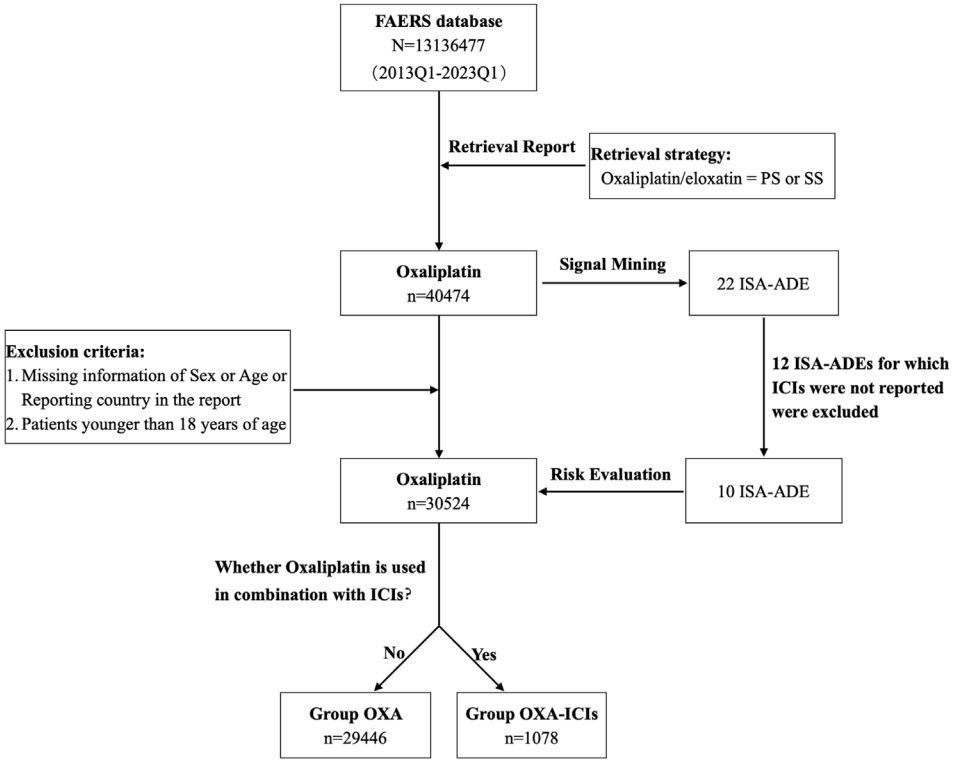

FIGURE 1
The flowchart of risk assessment of ISA-ADE after oxaliplatin combined with ICIs.

was a typical pharmacovigilance signal. Type II hypersensitivity reactions are primarily driven by IgG and IgM antibodies, the most common promotion mechanism being opsonization of antigen-bearing cells with antibodies, followed by phagocytosis or destruction. This can occur via two mechanisms: antibody-dependent cellular cytotoxicity (ADCC) and classical (antibody-mediated) complement activation (Knol and Gilles, 2022). Therefore, our findings contradict the conclusion proposed by some studies that suggest a link between oxaliplatin allergy and type I hypersensitivity reaction (Thomas et al., 2003; Newman Taylor et al., 1999). This finding deserves attention and should be known by both clinicians and patients. Other researchers have studied the occurrence of this ADE, including in patients within a chemotherapy cycle and at a specific time, but our study is limited by not having the report forms themselves and cannot confirm the information mentioned in the above studies.

The conventional chemotherapy drug oxaliplatin in combination with ICIs has been widely used in specific solid tumours, and we therefore performed an additional risk assessment based on previous studies of oxaliplatin signal mining. The major study was to investigate whether the combination of oxaliplatin and ICIs increases the risk of ISA-ADE in patients. The results showed that patients who used ICIs had a roughly two-fold increased risk of developing rash compared with those who did not. Among the ICIs used in combination with oxaliplatin, nivolumab and pembrolizumab also showed an increased risk of rash, at 2.196 and 2.231 times, respectively. These are all new discoveries. Considering that the patient's sex and age may be risk factors for such ADEs (Parel et al., 2014; Kim et al., 2012), we also adjusted for these two factors, but combination therapy still increased the risk of rash. At the same time, there was a negative correlation between age and increased risk (see details in Supplementary Material S3), meaning that the likelihood of such an increase in risk decreased with patient age. This is also an interesting result.

In platinum-based chemotherapy regimens, a preparation of 5-fluorouracil, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) or vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) is commonly used simultaneously, and these drugs can also cause ISA-ADEs (Oyama et al., 2021; Moret et al., 2022). In our study, however, we first qualified the identity of the target drug, that is, explained that it had to be a PS or SS in the report, thus ensuring the role of oxaliplatin in the occurrence of each ISA-ADE while reducing the effect of other drugs on the outcome. ISA-ADEs are among the most common irAEs noted in patients treated with ICIs. However, there is insufficient clinical evidence to suggest an increased risk of ISA-ADEs when ICIs are combined with certain drugs. While the current study found that ICIs in combination with oxaliplatin increased the risk of oxaliplatin-induced rash, there was no statistically significant increase in risk for different ISA-ADEs, which may be related to the fact that oxaliplatin in combination with ICIs has few clinical indications. Moreover, with the exception of nivolumab and pembrolizumab, ICIs were

TABLE 3 Characteristic of 30,524 patients in Group OXA and Group OXA-ICI.

Characteristic	Group OXA (*n* = 29,446)	Group OXA-ICI (*n* = 1,078)	χ2 test *p*-value
Sex, No. (%)			<0.01
Female	12,785 (43.4)	345 (32.0)	
Male	16,661 (56.6)	733 (68.0)	
Age, mean (SD), y	61.5 (12.0)	62.2 (13.0)	<0.01
18–34, No. (%)	864 (2.9)	51 (4.7)	<0.01
35–64, No. (%)	15,225 (51.7)	482 (44.7)	<0.01
>65, No. (%)	13,357 (45.4)	545 (50.6)	<0.01
Country, No. (%)			
France	5,106 (17.3)	124 (11.5)	
Italy	4,095 (13.9)	18 (1.7)	
United States	3,935 (13.4)	165 (15.3)	
Japan	2,248 (7.6)	159 (14.7)	
Deutschland	2,148 (7.3)	199 (18.5)	
United Kingdom	1,769 (6.0)	28 (2.6)	
Netherlands	1,590 (5.4)	17 (1.6)	
China	1,579 (5.4)	78 (7.2)	
Spain	995 (3.8)	51 (4.7)	
Canada	869 (3.0)	28 (2.6)	
Other Countries	5,112 (17.4)	211 (19.6)	

Group OXA, group oxaliplatin; Group OXA-ICI, group oxaliplatin combined with Immune checkpoint inhibitor.

TABLE 4 The number of ISA-ADEs in Group OXA and Group OXA-ICI and the value of odds ratios (10 PTs).

Preferred term (n)	Group OXA (*n* = 29,446)	Group OXA-ICI (*n* = 1,078)	Crude odds ratio point estimate (95% CI)
Hypersensitivity (*n* = 774)	760	14	0.497 (0.292, 0.846)
Anaphylactic reaction (*n* = 302)	295	7	0.646 (0.304, 1.370)
Cytokine release syndrome (*n* = 171)	165	6	0.993 (0.439, 2.248)
Anaphylactic shock (*n* = 244)	239	5	0.569 (0.234, 1.384)
Rash (*n* = 763)	713	50	1.960 (1.462, 2.628)
Pruritus (*n* = 685)	683	2	0.078 (0.020, 0.314)
Skin toxicity (*n* = 270)	269	1	0.101 (0.014, 0.718)
Rash maculo-papular (*n* = 92)	89	3	0.921 (0.291, 2.913)
Skin disorder (*n* = 69)	66	3	1.242 (0.390, 3.957)
Rash erythematous (*n* = 83)	81	2	0.674 (0.165, 2.744)

ISA-ADE, Immune system and skin and subcutaneous tissue related ADE; PT, preferred term; Group OXA, group oxaliplatin; Group OXA-ICI, group oxaliplatin combined with Immune checkpoint inhibitor.

the least common drugs combined with oxaliplatin, which could be related to the late initiation and fewer ADE reports for other drugs.

In any case, as far as the interpretations of this study's results are concerned, certain limitations should be considered: the incompleteness of the contents in the spontaneous reports

TABLE 5 The value of ORs of Rash between Group OXA and Group OXA-ICI.

Group	Total (N = 30,524)	Rash (N = 763)		
		n	Crude odds ratio point estimate (95% CI)	Adjust odds ratio # point estimate (95% CI)
Oxaliplatin	29,446	713	Reference	
Oxaliplatin-ICIs	1,078	50	1.960 (1.462, 2.628)	1.974 (1.472, 2.647)
-Nivolumab	653	33	2.196 (1.543, 3.125)	2.231 (1.567, 3.176)
-Nivolumab + Ipilimumab	70	1	0.565 (0.078, 4.071)	—
-Pembrolizumab	245	16	2.762 (1.655, 4.609)	2.678 (1.604, 4.471)

Group OXA, group oxaliplatin; Group OXA-ICI, group oxaliplatin combined with Immune checkpoint inhibitor #, Adjusted by Sex and Age.

involving missing data, and substantial bias may occur because of the spontaneous and voluntary reporting of ADEs. Although RORs for adverse events can be calculated from the data, they are only an estimate of the actual incidence of adverse events (Stephenson and Hauben, 2007). In addition, this study involved a statistical analysis of data within a certain period, which could not possibly include all reports of adverse events. Therefore, the results may be at a risk of overestimating the occurrence of the adverse events. This study focused on the possible association between the PS or SS drug and ADEs, and there were still confounding factors that may affect the results (such as tumor type, other drugs used in combination, etc.).

5 Conclusion

To our knowledge, there are still a few ADEs associated with immune system disorders induced by oxaliplatin that have not received enough attention, particularly type II hypersensitivity, which showed strong intensity signals as a pharmacovigilance signal. Due to the lack of research comparing the occurrence and related influencing factors of ISA-ADEs when oxaliplatin is used in combination with ICIs, the results of this study are a strong evidence supplement. We observed an approximate 2-fold increase in the risk of rash when oxaliplatin was combined with ICIs. ICIs used in combination with oxaliplatin, nivolumab and pembrolizumab have also been shown to increase the risk of rashes. And there was a negative correlation between age and increased risk. Our research has some inherent limitations due to its research nature, so it is necessary to further observational real-world studies are warranted to understand the occurrence of ISA-ADEs when oxaliplatin and ICIs are used in combination, and to optimize clinical practice.

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

CZ: Writing–original draft, Investigation, Funding acquisition, Conceptualization. FL: Writing–original draft, Validation. YD: Writing–original draft, Validation. YZ: Writing–original draft, Validation, Software. XY: Writing–review and editing, Visualization. DS: Writing–original draft, Project administration, Methodology, Formal Analysis.

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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.2024.1309540/full#supplementary-material

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