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Pharmacovigilance and pharmacoepidemiology: Public health and safety

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Pharmacovigilance and pharmacoepidemiology: Public health and safety

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Variation in adverse drug events of opioids in the United States

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Background: The United States (US) ranks high, nationally, in opioid consumption. The ongoing increase in the misuse and mortality amid the opioid epidemic has been contributing to its rising cost. The worsening health and economic impact of opioid use disorder in the US warrants further attention. We, therefore, assessed commonly prescribed opioids to determine the opioids that were over-represented versus under-represented for adverse drug events (ADEs) to better understand their distribution patterns using the Food and Drug Administration's Adverse Event Reporting System (FAERS) while correcting for distribution using the Drug Enforcement Administration's Automation of Reports and Consolidated Orders System (ARCOS). Comparing the ratio of the percentage of adverse drug events as reported by the FAERS relative to the percentage of distribution as reported by the ARCOS database is a novel approach to evaluate post-marketing safety surveillance and may inform healthcare policies and providers to better regulate the use of these opioids.

Methods: We analyzed the adverse events for 11 prescription opioids, when correcting for distribution, and their ratios for three periods, 2006–2010, 2011–2016, and 2017–2021, in the US. The opioids include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Oral morphine milligram equivalents (MMEs) were calculated by conversions relative to morphine. The relative ADEs of the selected opioids, opioid distributions, and ADEs relative to distribution ratios were analyzed for the 11 opioids.

Results: Oxycodone, fentanyl, and morphine accounted for over half of the total number of ADEs (n = 667,969), while meperidine accounted for less than 1%. Opioid distributions were relatively constant over time, with methadone repeatedly accounting for the largest proportions. Many ADE-to-opioid distribution ratios increased over time, with meperidine (60.6), oxymorphone (11.1), tapentadol (10.3), and hydromorphone (7.9) being the most over-represented for ADEs in the most recent period. Methadone was under-represented (<0.20) in all the three periods.

Conclusion: The use of the FAERS with the ARCOS provides insights into dynamic changes in ADEs of the selected opioids in the US. There is further need to monitor and address the ADEs of these drugs.

KEYWORDS

opiate, oxycodone, hydrocodone, fentanyl, meperidine

Introduction

Opioids have been commonly prescribed to treat moderate to severe pain for various conditions, including cancer and trauma. Fentanyl, methadone, and oxycodone are examples of commonly prescribed opioids. Overuse of these drugs can lead to adverse drug events (ADEs), tolerance, dependence, addiction, overdose, and death. Drug overdose deaths increased four-fold from 1999 to 2017, with opioid-related deaths accounting for about two-thirds of the deaths (Singh et al., 2019). The Centers for Disease Control (CDC) has recently indicated that the number of drug overdose deaths increased by nearly 5% from 2018 to 2019, with over 70% of the 70,630 drug-related deaths in 2019 involving opioids (Centers for Disease Control and Prevention, 2021). Although the volume of opioids prescribed in the US decreased from 2010 to 2015 after peaking in 2011, the amount is still significantly higher relative to 1999 (Guy, 2017; Mack et al., 2018; Piper et al., 2018). An analysis of the International Narcotics Control Board records from 2015 to 2017 revealed that 10% of the world's population consumed 89% of the world's supply of prescription opioids. Furthermore, the US ranked third for the highest opioid consumption *per capita* (Richards et al., 2022). The fatalities and overdoses from the misuse of these analgesics were responsible for $1.02 trillion in costs in the US in 2017 (Florence et al., 2021). The detrimental health and economic impact of both pain and opioid use disorder treatments in the US warrants further attention.

A recent report examining the national patterns in opioid exposure reported to the US poison control centers indicated that the proportion of exposure with adverse drug events (ADEs) increased despite the overall decrease in the frequency and rate of opioid exposure from 2011 to 2018 (Rege et al., 2021). ADEs are reported in the US Food and Drug Administration Adverse Event Reporting System (FAERS), a large government database that consists of ADEs and medication error reports submitted through the MedWatch program primarily from healthcare professionals (Zhou and Hultgren, 2020). In addition to using the FAERS database to quantify the adverse effects, we used the Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Orders System (ARCOS), a comprehensive data collection system, where schedule II and III controlled substances are mandatorily reported when distributed to pharmacies, hospitals, narcotic treatment programs (NTPs), and long-term care facilities (Piper et al., 2018; U.S. Drug Enforcement Administration, 2022). We used both databases to identify the ADEs of several common schedule II and III prescription opioids relative to their distribution in the US for the past one and a half decades. This analysis identifies the opioids that were over- or under-represented for ADEs relative to their use.

Methods

Procedures

FDA FAERS and ARCOS databases were queried from 2006 to 2021 to examine the ADEs and distribution of the 11 opioids. These opioids were selected based on previous studies and their status as being FDA-approved and commonly prescribed. Nine of them are used primarily for pain, namely, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, and tapentadol, and two of them are mainly used for opioid use disorders (OUD), buprenorphine and methadone (Modarai et al., 2013; Mack et al., 2018; Cabrera et al., 2019; Singh et al., 2019; Veronin et al., 2019; Eidbo et al., 2022). We separated the analysis into three time periods based on pre- (2006–2010), intra- (2011–2016), and post-peak (2017–2021) opioid distribution time intervals. Specifically, 2011 was the peak year of opioid count by morphine milligram equivalents (MMEs) (Piper et al., 2018). The search involved both generic and brand opioid names indicated in the FAERS database with ADEs including misuse, overdoses, serious cases, and deaths (U.S. Food and Drug Administration, 2022). Supplementary Table S1 indicates the search terms used for these opioids. Additionally, the DEA ARCOS database is comprehensive and has input from pharmacies, hospitals, distributors, and wholesalers regarding schedule II and III controlled substances in the US. It includes controlled substances for medical use and is, therefore, a very inclusive and valid database (Bokhari et al., 2005). Analyses of oxycodone from the ARCOS showed a high correlation (r = .985) with a state prescription drug monitoring program (Piper et al., 2018). The procedures were approved as exempted by the IRB of Geisinger and the University of New England.

Statistical analyses

The total oral MME was calculated based on the weight of all 11 opioids and expressed in three periods (2006–2010; 2011–2016; 2017–2021) for the US, excluding the US territories. Hereafter, these periods are referred to as the first, second, and third, respectively. The first period showed increases in prescription opioid distribution, 2011 was the peak year, and the third period showed a further decline in the opioids used for pain and an escalation in OUD treatment (Piper et al., 2018; Collins et al., 2019; Azar et al., 2020). The top three reaction groups and reactions were reported for each opioid from 2006–2021 with percentages indicating the amount relative to the total number of adverse events within that period. Three analyses were also completed for each period: (1) the frequency of ADEs of each opioid based on the FAERS, (2) the percentage of total opioid distribution based on the ARCOS, and (3) FAERS to ARCOS ratios. The oral MME was calculated to correct for the relative potency of each opioid relative to morphine. The conversions were as follows: buprenorphine (10), codeine (0.15), fentanyl base (75), hydrocodone (1), hydromorphone (4), meperidine (0.1), methadone (10), morphine (1), oxycodone (1.5), oxymorphone (3), and tapentadol (0.4) (Piper et al., 2018; Eidbo et al., 2022). For buprenorphine, the CDC MME conversion charts ceased to include the opioid in 2016, while at a low dose, buprenorphine can produce significantly greater opioid responses than morphine. Although morphine (a full agonist with low potency) response is dose-related until it reaches 100% maximal response, buprenorphine (partial agonist) effects reach the peak, at which point, further increases in doses within the clinical range do not increase the magnitude of the response. This concept of potency is important for understanding why buprenorphine should not be converted to MMEs for purposes of assessing the overdose risk based

TABLE 1 Adverse event reports by the count and percentage in the US Food and Drug Administration's Adverse Effect Reporting System for 11 prescription opioids for the 2006–2021 period. The three most common reaction groups and reactions are shown.

Opioid	Reaction group	Reaction
Oxycodone (159,441); 23.9%	1. Psychiatric disorders; *n* = 99,132 (62.2%)	1. Drug dependence; *n* = 74,721 (46.9%)
	2. General disorders and administration site conditions; *n* = 79,824 (50.1%)	2. Overdose; *n* = 38,543 (24.2%)
	3. Injury, poisoning, and procedural complications; *n* = 75,491 (47.3%)	3. Pain; *n* = 27,545 (17.3%)
Fentanyl (106,644); 16.0%	1. Injury, poisoning, and procedural complications; *n* = 56,480 (53.0%)	1. Death; *n* = 16,309 (15.3%)
	2. General disorders and administration site conditions; *n* = 51,784 (48.6%)	2. Toxicity to various agents; *n* = 15,225 (14.3%)
	3. Psychiatric disorders; *n* = 23,740 (22.2%)	3. Overdose; *n* = 11,200 (10.5%)
Morphine (102,411); 15.3%	1. General disorders and administration site conditions; *n* = 47,624 (46.5%)	1. Drug dependence; *n* = 28,830 (28.2%)
	2. Injury, poisoning, and procedural complications; *n* = 47,310 (46.2%)	2. Overdose; *n* = 20,224 (19.7%)
	3. Psychiatric disorders; *n* = 43,773 (42.7%)	3. Death; *n* = 17,088 (16.7%)
Buprenorphine (80,685); 12.1%	1. General disorders and administration site conditions; *n* = 47,311 (58.6%)	1. Drug dependence; *n* = 13,011 (16.1%)
	2. Injury, poisoning, and procedural complications; *n* = 34,058 (42.2%)	2. Death; *n* = 12,634 (15.7%)
	3. Psychiatric disorders; *n* = 20,589 (24.5%)	3. Overdose; *n* = 10,981 (13.6%)
Hydromorphone (64,454); 9.6%	1. Injury, poisoning, and procedural complications; *n* = 37,081 (57.5%)	1. Drug dependence; *n* = 25,321 (39.3%)
	2. General disorders and administration site conditions; *n* = 35,763 (55.5%)	2. Overdose; *n* = 18,430 (28.6%)
	3. Psychiatric disorders; *n* = 31,762 (49.3%)	3. Death; *n* = 15,064; (23.4%)
Hydrocodone (44,204); 6.6%	1. Injury, poisoning, and procedural complications; *n* = 24,986 (56.5%)	1. Death; *n* = 12,990 (29.4%)
	2. General disorders and administration site conditions; *n* = 24,626 (55.7%)	2. Drug dependence; *n* = 10,894 (24.6%)
	3. Psychiatric disorders; *n* = 15,673 (35.5%)	3. Toxicity to various agents; *n* = 10,829 (24.5%)
Oxymorphone (31,154); 4.7%	1. Injury, poisoning, and procedural complications; *n* = 20,013 (64.2%)	1. Death; *n* = 12,654 (40.6%)
	2. General disorders and administration site conditions; *n* = 17,132 (55.0%)	2. Toxicity to various agents; *n* = 9,757 (31.3%)
	3. Psychiatric disorders; *n* = 6,396 (20.5%)	3. Overdose; *n* = 7,160 (23.0%)
Tapentadol (29,290); 4.4%	1. Injury, poisoning, and procedural complications; *n* = 17,678 (60.4%)	1. Death; *n* = 11,579 (39.5%)
	2. General disorders and administration site conditions; *n* = 15,316 (52.3%)	2. Toxicity to various agents; *n* = 9,411 (32.1%)
	3. Psychiatric disorders; *n* = 4,188 (14.3%)	3. Overdose; *n* = 5,815 (19.9%)
Methadone (27,454); 4.1%	1. Injury, poisoning, and procedural complications; *n* = 14,405 (52.5%)	1. Toxicity to various agents; *n* = 5,226 (19.0%)
	2. Psychiatric disorders; *n* = 12,229 (51.9%)	2. Drug dependence; *n* = 4,339 (15.8%)
	3. General disorders and administration site conditions; *n* = 11,155 (40.6%	3. Drug abuse; *n* = 3,937 (14.3%)
Codeine (16,731); 2.5%	1. Immune system disorders; *n* = 7,075 (42.3%)	1. Drug hypersensitivity; *n* = 6,576 (39.3%)
	2. Injury, poisoning, and procedural complications; *n* = 5,702 (34.1%)	2. Toxicity to various agents; *n* = 2,538 (15.2%)
	3. General disorders; *n* = 4,611 (27.6%)	3. Drug ineffective; *n* = 1,210 (7.2%)
Meperidine (5,501); 0.82%	1. Immune system disorders; *n* = 3,143 (57.1%)	1. Drug hypersensitivity; *n* = 2,920 (53.1%)
	2. General disorders and administration site conditions; *n* = 1,598 (29.0%)	2. Drug ineffective; *n* = 433 (7.9%)
	3. Injury, poisoning, and procedural complications; *n* = 1,096 (19.9%)	3. Pain; *n* = 350 (6.4%)

on the daily opioid dose; according to the American Society of Addiction Medicine, "Opioid dosing guidelines developed for chronic pain, expressed in morphine milligram equivalents (MMEs), are not applicable to medications for the treatment of opioid use disorders." Therefore, the authors selected a conversion factor, for buprenorphine to morphine, of 10 from a range of values documented in potency studies for the purpose of this pharmacoepidemiologic study (ASAM, 2020). Methadone's MME was calculated based on the dose (Centers for Disease Control and Prevention, 2023). We decided to conduct an average of narcotic treatment programs (12) and other sources (8) for an MME of 10. Additionally, there is a range of the equianalgesic dose ratio of

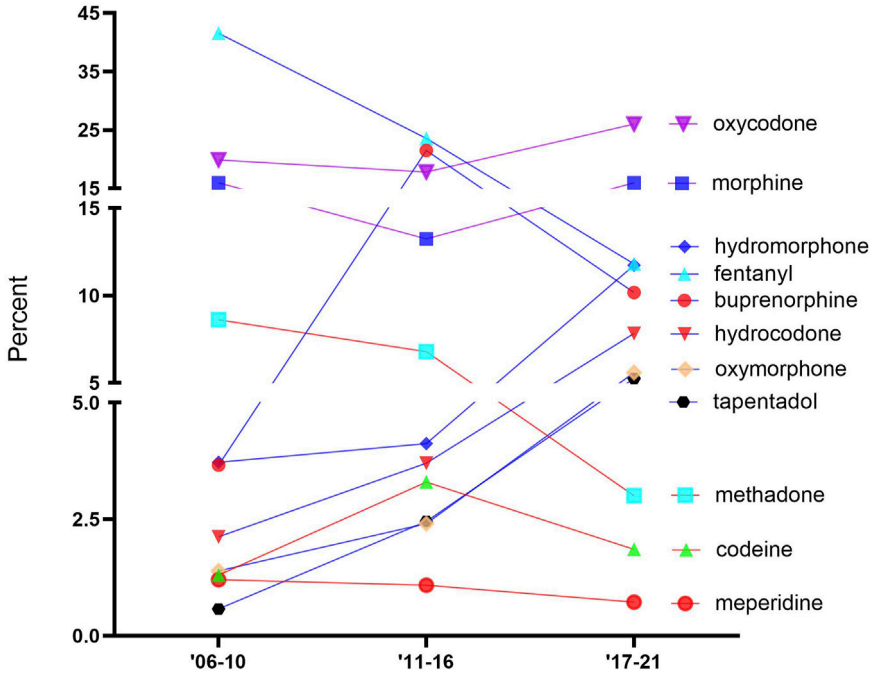

FIGURE 1
Percentage of adverse drugs events (ADEs) of the 11 prescription opioids obtained from the FDA Adverse Event Reporting System over time.

methadone established from previous studies with a median dose ratio ranging 5.98–16.27 (Lawlor et al., 1998) relative to morphine and 0.81–2.47 for hydromorphone (Ripamonti, et al., 1998). As for fentanyl, 75 was selected as it is 50–100 times more potent than morphine (Higashikawa and Suzuki, 2008; Volpe et al., 2011).

We identified any ratio >1.0 as an over-representation and <1.0 as under-representation of the ADEs of the opioid when correcting for distribution, for example, an opioid which accounted for 10% of ADEs but 5% of the distribution would have a ratio of 2.0 (i.e., over-represented). We extracted the top three reaction groups and reactions to outline the common adverse drug effects associated with the selected opioids, indicating which adverse effects may have been contributing to the reports. We chose the top three reports as they made up >60–75% of the ADEs. It is important to note that the death report percentages are overestimated as large public databases involve individuals who can submit more than one report (Stephenson and Hauben, 2007; United States Drug Enforcement Administration, 2016). We also prepared a Supplementary Table S1 that differentiated the death reports either by "outcome" or "reaction" for the opioids, meaning that not all reports are associated with direct deaths from the drugs. Data analysis and figure preparation were completed with GraphPad Prism, version 9.3.1.

Results

We queried data from FAERS and ARCOS databases for the 11 opioids from 2006 to 2021. Supplementary Figure S1 indicates the percentage of ADE reports submitted by healthcare professionals to the FAERS for the 11 opioids from 2006 to 2021. Almost one-third (31.2%) of the reports were from providers. Codeine (72.9%), meperidine (70.5%), and methadone (68.1%) had the most submissions from healthcare workers, while the remaining eight opioid ADEs were submitted mainly from patients. Table 1 indicates the ADE reports from 2006 to 2021 obtained from the FAERS. Oxycodone, fentanyl, and morphine were responsible for over half (55.2%) of the total number of ADEs (n = 667,969), while meperidine accounted for less than 1% of them. The top three most common reaction groups included injury, poisoning, and procedural complications; general disorders and administration site conditions; and psychiatric disorders. The common specific reactions consisted of abnormal drug effects (e.g., dependence, hypersensitivity, and ineffectiveness), overdose, and death. The death rates varied among the opioids, with oxymorphone having the largest proportion of death as the "reaction" (40.6%) and death as an "outcome" (70.6%), while meperidine had the least with 1.4% and 7.4% as the reaction and outcome, respectively (Supplementary Table S2).

Figure 1 shows the percentage of ADEs for each opioid. The opioids were classified into three groups in 2017–2021, namely, high (>15%): oxycodone and morphine; intermediate (5%–15%): hydromorphone, fentanyl, buprenorphine, hydrocodone, oxymorphone, and tapentadol; and low (<5%): methadone, codeine, and meperidine. Oxycodone was consistently high across all periods: 2006–2010 (19.9%), 2011–2016 (17.8%), and 2017–2021 (26.0%). Fentanyl accounted for the largest portion of ADEs in the first two periods (2006–2010 (41.6%) and 2011–2016 (23.6%)) but decreased greatly since the second period (−49.9%). Methadone showed a noticeable decrease (−55.8%) from the second to the third period, while oxymorphone indicated a marginal (+114.5%) increase. Codeine and meperidine accounted for less than 5% of the total ADE reports in all periods.

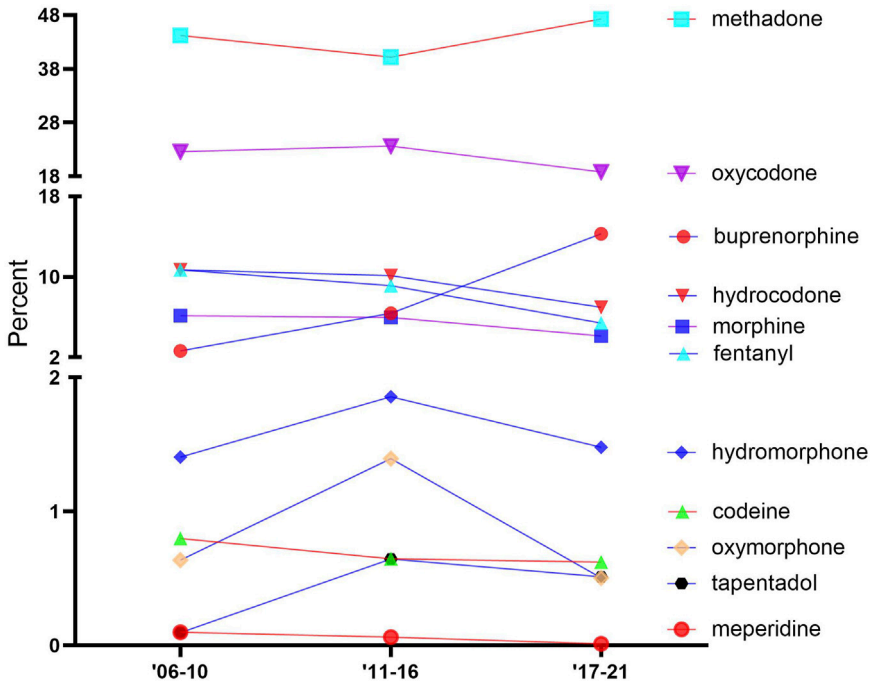

FIGURE 2
Percentage of the total morphine mg equivalent (MME) of the distribution of 11 prescription opioids, as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS) over time.

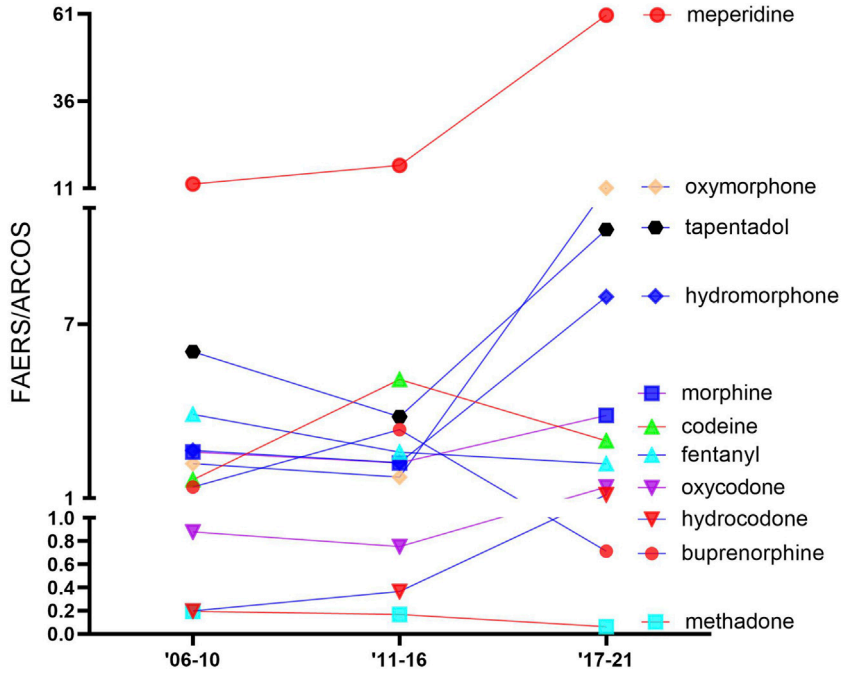

FIGURE 3
Ratio of the percentage of adverse drug events, as reported by the US Food and Drug Administration's Adverse Events Reporting System relative to the percent of distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System database for the 11 prescription opioids over time. Values greater than 1.0 are over-represented, and values less than 1.0 are under-represented.

Figure 2 shows the percentage of the total MMEs due to each opioid over time. The opioids were classified into three groups, which were generally stable over time, namely, high: methadone and oxycodone; intermediate: buprenorphine, hydrocodone, morphine, and fentanyl; and low: hydromorphone, codeine, oxymorphone, tapentadol, and meperidine. Methadone accounted for over two-fifths of the total distribution: 2006–2010 (44.2%), 2011–2016 (40.2%), and 2017–2021 (47.3%). Codeine, tapentadol, and meperidine consistently made up less than 1% of the distribution.

Figure 3 shows the ADE-to-distribution ratio for each opioid for each period. Most opioids showed an over-representation in the FAERS-to-ARCOS ratio. The general pattern was of increases over time, with the most over-represented opioid in the third period being meperidine (60.6), followed by oxymorphone (11.1), tapentadol (10.3), and hydromorphone (7.9). Oxymorphone showed the largest increase (+542.2%) in its ratio from the second to the third period, followed by hydromorphone (+257.7%) and meperidine (+245.2%). Buprenorphine had the greatest decrease (−371.3%), followed by codeine (−71.0%) and fentanyl (−18.2%). Methadone was under-represented (<.20) in the three periods.

Discussion

Our study identified the varied ADEs for 11 commonly used opioids. This is also the first report to describe the ADEs while correcting for the prevalence of each opioid's US distribution.

Stronger opioids, like fentanyl (MME = 75), were associated with more frequent adverse events, while other opioids, like hydromorphone (MME = 4) and oxymorphone (MME = 3), had low adverse events relative to their distribution. Oxycodone, fentanyl, and morphine accounted for over half (55.2%) of the total number of ADEs (n = 667,969) with meperidine comprising less than 1% of it. Oxycodone shows high potential for misuse due to its high reinforcing characteristics and its administration methods, including pill crushing for immediate release and through IV injections, leading to high dependence (Kibaly et al., 2021; Table 1). Fentanyl with its high potency and abuse potential, as well as the tendency to be mixed with other drugs, may contribute to high ADEs across all three periods (United States Drug Enforcement Administration, 2018; Comer and Cahill, 2019; National Institute on Drug Abuse, 2021). Like other opioids, morphine tolerance can develop secondary to its continuous usage due to the changes in the receptor density and G-protein-coupled receptors and its signal transduction pathway (Listos et al., 2019). Although meperidine had a consistently low (<1%) distribution, its elevated ADE-to-distribution ratio may be because of its ability to cause lethal ADEs, including serotonin syndrome and psychological or physical dependence (Boyle et al., 2021). The distribution of this ubiquitous agent has continued to decline (Harrison et al., 2022).

Methadone and buprenorphine both showed increases in distribution in the past decade mostly due to their use for OUD, with buprenorphine also showing a 122.5% increase in hospital distribution in the past decade (Bishop-Freeman et al., 2021; Cicero et al., 2014; Eidbo et al., 2022; Furst et al., 2022; Mattick et al., 2014; Pashmineh Azar et al., 2020). These opioids have been commonly used to treat opioid dependence, and with an expanded Medicaid coverage, their prevalence has been rising (Mattick et al., 2014; Burns et al., 2016). The high distribution of oxycodone may be attributed to its common use and effectiveness for treating moderate-to-severe acute pain (Moradi et al., 2012; Davis and Liberman, 2021).

Given that meperidine demonstrated the lowest frequency of ADEs, it was surprising to find that its adverse effects were the most overly represented compared to its distribution (60.6), particularly in the third period (60.6). In contrast to Veronin et al. (2019), who found that oxycodone had high death-to-count percentages compared to other opioids, our report indicated oxycodone's percentages hovered around 1% of the ratios throughout the study, as seen in Figure 3. The decline in oxycodone overdoses might be attributed to the reduction in abuse since the development of its extended release in late 2010 (Johnson et al., 2014).

Oxymorphone's notable increase in adverse effects (+542.2%) relative to its distribution was unsurprising as it constantly had low counts throughout the three periods relative to other opioids. Oxymorphone as a schedule II drug has a high potency and misuse potential related to its euphoric effects explaining the huge increase in proportion, which might also explain its high proportion of deaths from ADEs (United States Drug Enforcement Administration, 2019). Tapentadol, with its dual mechanism of action acting as both a μ-opioid receptor agonist and noradrenaline reuptake inhibitor, has better tolerability than other commonly prescribed opioids due to its low μ-load (Romualdi et al., 2019). It was, therefore, unexpected to see its over-representation (10.3) in the third period. Furthermore, hydromorphone's pronounced decrease in distribution in the past decade, in addition to its high potential for fatality and overdose rates, may contribute to its over-representation since the second period (+257.7%) (Lowe et al., 2017; Eidbo, et al., 2022). Methadone's potential for overdose death (Kaufman et al., 2023) was overridden by its substantial distribution, explaining the under-representation (Furst et al., 2022). There has been some prior confusion regarding the safety of methadone relative to its role as the most distributed opioid by MMEs in the US (Piper et al., 2018). A prior report claimed that methadone accounted for less than 5% of opioid prescriptions dispensed but accounted for a third of opioid-related deaths (Webster et al., 2011). The data source (IMS Health, now known as IQVIA), however, did not include methadone from predominant sources of distribution from narcotic treatment programs and other federal programs (United States Drug Enforcement Administration, 2022).

The Drug Abuse Warning Network (DAWN), a nationwide public health surveillance system administered by the Substance Abuse and Mental Health Services Administration to monitor drug-related visits to hospital emergency departments, reported in its preliminary findings from its drug-related ED visits in 2021 that opioids were one of the top five substances for ED visits, with most reports being heroin-related, other opioids (oxycodone, buprenorphine, codeine, etc.), and fentanyl-related opioids (Substance Abuse and Mental Health Services Administration, 2022). Our findings indicate that, in the most recent period (2017–21), fentanyl's relative distribution in adverse events and counts has decreased compared to some of the other opioids, highlighting that opioids like oxycodone, morphine, and hydromorphone might be contributing more to opioid adverse events compared to fentanyl. Combined with the reduced distribution based on the ARCOS reports regarding fentanyl counts in recent periods relative to other opioids, the adverse event-to-distribution ratio has decreased throughout the three periods. Like

the FAERS database, it is important to note that the DAWN reports of opioids come from both mono and combo products (i.e., acetaminophen/oxycodone).

The main strengths of our novel study include the analysis of 11 commonly prescribed opioids, separated into uses for pain and OUD, with a new approach using both the FAERS and ARCOS database to quantify adverse events relative to the distribution of the opioids. The limitations to our study involve ARCOS and FAERS databases. A main limitation is that the ARCOS and FAERS do not provide formulation-specific information. There are no available data that break down the formulations of buprenorphine (i.e., by the route of administration). Additionally, the ARCOS does not filter out veterinary uses, although they were modest (Piper et al., 2020). The FAERS database might have over-represented the selected opioids because of duplicates, incomplete results, non-verifiable data, and uncertainty in adverse effect causalities (Veronin et al., 2019). In this case, most of the opioid ADE reports were from patients, with one-third being from medical professionals, which may contribute to the heterogenous quality of reports because of differing report behaviors between healthcare professionals and customers (Toki and Ono, 2020). The FAERS database is specifically populated by both mandatory (manufacturers of drugs) and voluntary (healthcare professionals, consumers, family members, etc.) adverse event reports. The FDA also raises cautions against making true conclusions from an analysis of the FAERS data (U.S. Food and Drug Administration, 2021). However, the FAERS database is a unique resource and has been used extensively by researchers for exploratory analyses and to identify hypotheses for further investigation (Sakaeda et al., 2013; Fang et al., 2014). The database has also been the primary surveillance database used to identify safety issues and adverse events or post-marketed drugs for decades as there is no other database that provides data on the relation of the drugs and ADEs (Wykowski and Swartz, 2005).

We assume that it is justified that individual opioids are equally likely to be reported to the FAERS and that it is the best database to date to analyze adverse events of prescription drugs, although future studies are needed to evaluate these hypotheses. However, as over three-quarters of FAERS submissions were completed by non-healthcare providers for oxycodone, hydrocodone, oxymorphone, and tapentadol, it is also possible that the US public is increasingly aware of the adverse effects of opioids (Macy, 2018) and is increasingly willing to utilize the FAERS to play their role in combatting the opioid epidemic. Further investigations with the FAERS and other similar databases will be necessary to determine if Figures 1, 3 are more informative.

Although the FAERS database has known limitations (US Food and Drug Administration, 2022), our exploratory analysis of the individual opioids provides novel findings that may guide further research in databases like the DAWN as the system only reports fentanyl-related and heroin-related products as separate groups while grouping other known opioids (Substance Abuse and Mental Health Services Administration, 2022). Another key limitation is that to date, there is no known database that consistently and accurately reports adverse events, abuse, and deaths. The CDC reporting of overdoses, for instance, has and continues to lack transparency with errors in counting overdose deaths (Peppin and Coleman, 2021). Another study reports that the death determination process is not uniform across the states (Kaufman et al., 2021).

Our analysis on FAERS and ARCOS databases demonstrated general increases in adverse events relative to opioid counts for the selected opioids, with varied relative individual adverse events when accounting for their distribution. It also provides a novel finding on individual opioids using both databases, further promoting research with other public databases like the Drug Abuse Warning Network. Emergency room visits in 2021 involving fentanyl (presumably predominantly illicit) were only one-fourth as common as other opioids (i.e., prescription), like oxycodone and hydrocodone (SAMHSA, 2022). Overall, the distribution pattern informs us of the need for continuous efforts to address the ADEs of specific opioids to inform healthcare policies and change the perspectives of healthcare providers on these drugs and their prescription practices.

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

BP was responsible for the design of the project with contributions from EL and KM. EL was responsible for the data collection, analysis, and writing of the first version of the manuscript.

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Conflict of interest

BP was part of an osteoarthritis research team (2019-2021) supported by Pfizer and Eli Lilly. His research was supported by the Pennsylvania Academic Clinical Research Center and the Health Resources Services Administration (D34HP31025).

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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Geriatrician-led multidisciplinary team management improving polypharmacy among older inpatients in China

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Background/Aim: Polypharmacy is prevalent among older inpatients and associated with adverse outcomes. To determine whether a geriatrician-led multidisciplinary team (MDT) management mode could reduce medications use among older inpatients.

Methods: A retrospective cohort study was conducted in a geriatric department of a tertiary hospital in China with 369 older inpatients, including 190 patients received MDT management (MDT cohort), and 179 patients received usual treatment (non-MDT cohort). The primary outcome was to compare the changes of the amount of medications before and after hospitalization in two cohorts.

Results: We reported that MDT management significantly reduced the number of medications used in older inpatients at discharge (at home: n = 7 [IQR: 4, 11] vs at discharge: n = 6 [IQR: 4, 8], $p < 0.05$). Hospitalization with the MDT management had a significant effect on the change in the amount of medications (F = 7.813, partial-η^2 = 0.011, p = 0.005). The discontinuance of medications was associated with polypharmacy at home (OR: 96.52 [95% CI: 12.53-743.48], $p < 0.001$), and the addition of medications was associated with a diagnosis of chronic obstructive pulmonary disease (COPD) (OR: 2.36 [95% CI: 1.02-5.49], p = 0.046).

Conclusion: The results indicated that the geriatrician-led MDT mode during hospitalization could reduce the number of medications used by older patients. The patients with polypharmacy were more likely to "deprescription" after MDT management, while the patients with COPD were more likely to be under-prescription at home, polypharmacy which could be made up for after MDT management.

KEYWORDS

polypharmacy, medication therapy management, multidisciplinary communication, aged, inpatients

Introduction

The number of older adults has been continually growing around the world. With their extended lifespan, older adults are more likely to experience comorbidities and geriatric syndromes (American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity, 2012). The prevalence of older people aged ≥65 years old with comorbidities was 64.9% in Scotland (Barnett et al., 2012), which was 91.5% in the United States of America (Bahler et al., 2015). In China, 61.7%–86.3% of older adults suffer from different chronic diseases (Wang et al., 2021). They usually received long-term treatments with multiple medications (Marengoni et al., 2011).

Polypharmacy is most commonly defined in the literature as the concurrent use of five and more medications, including prescription drugs, over-the-counter (OTC) drugs, traditional Chinese medicine (TCM) and complementary medicines used by a patient (World Health Organization, 2022). Polypharmacy and potentially inappropriate medications (PIMs) are prevalent among older patients and are associated with adverse drug events (ADEs), drug interactions, hospitalizations, mortality and medical costs, especially in frail older patients (Mo et al., 2014; Poudel et al., 2016). Furthermore, inappropriate prescription not only refers to overprescribing but also includes misprescribing and underprescribing (San-José et al., 2014). Under such circumstances, older adults are frequently hospitalized due to acute exacerbated chronic diseases or accidents (Australian Institute of Health and Welfare, 2014). Previous studies found that the incidence of drug–drug interactions in the older population was 28.1% (Weng et al., 2020), and 5%–10% of hospital admissions among older people were attributable to undesired side effects of drugs (Kratz and Diefenbacher, 2019).

The optimization of drug treatment is challenging, as both overtreatment and undertreatment issues may exist simultaneously in older people (Kaminaga et al., 2021). Therefore, some medication screening strategies have been created to help physicians optimize prescribing for older adults (Jansen et al., 2016). However, the impact of a single medication screening strategy may be limited, as it only addresses particular areas of the complex process of drug prescribing, such as providing drug names only, not reflecting the need for dose adjustments, interactions and so on (Pazan et al., 2019). Therefore, the objective of this study was to determine whether geriatrician-led MDT management could reduce the amount of medication used among older inpatients.

Materials and methods

Study design and sample size

This retrospective cohort study was conducted in the Geriatric Department of West China Hospital after approval of the Biomedical Ethics Sub-Committee of Sichuan University (2017–405) and was registered on the website of the Chinese Clinical Trial Registry (ChiCTR2000038003).

Older patients aged 65 years old and older admitted to the geriatric department from 1 September 2016, to 31 May 2017, were sampled for the study and were divided into the MDT cohort and the non-MDT cohort. We assumed that compared with the number of medications used at home, the average reduction in the number of medications used by older inpatients at discharge in the MDT cohort was about 1, with a total standard deviation of 3.4, assuming that the reduction in the number of medications use at discharge in the non-MDT cohort was 0 was an acceptable result, two independent sample T-tests ($\alpha = 0.05$, $1\text{-}\beta = 0.8$) were performed using PASS software to estimate the sample size, considering the sample shedding rate of 10%–20%, and finally concluded that at least 175 sample sizes were required for each cohort in this study.

To avoid physician-to-physician contamination, patients in the MDT cohort were recruited from the Acute Care for the Elderly Unit (ACE unit) of the Geriatrics Department, which was managed by the geriatrician-led MDT. Patients in the non-MDT cohort were recruited from other units of the Geriatrics Department except for the ACE unit, which was managed by the usual medical mode. Healthcare facilities, information insufficient and finally included 190 patients in the MDT cohort. Then, to achieve a 1:1 match with samples in the MDT cohort in terms of age, sex and primary diagnosis, STATA software were used for propensity score matching with a caliper of 0.01 to select samples in the non-MDT cohort. However, eleven patients in the non-MDT cohort were excluded due to incomplete data, so the final sample in the non-MDT cohort was 179 patients (Figure 1).

Participants

Patients who met the following criteria were included in this study: 1) aged ≥65 years old and admitted to the Geriatrics Department of West China Hospital for an acute illness, and 2) agreed to receive comprehensive geriatric assessment and MDT management for patients in the MDT cohort. We excluded patients who 1) withdrew from MDT management for any reason, 2) were admitted to hospice care because of end-of-life care, 3) did not have a specific discharge plan, 4) lacked clear medication information, or 5) died or were transferred to another health institution without completing the entire management process.

Management mode

Compared to the patients in the non-MDT cohort who received usual medical care, all the patients who matched the inclusion criteria in the MDT cohort received integrated medical management by a geriatrician-led multidisciplinary team. Each member in the MDT, including geriatricians, geriatric registered nurses, pharmacists, rehabilitation specialists, and nutritionists, would see the patients and evaluate related medical information on the admission day. In addition to these consultations, a geriatrician-led MDT meeting consisting of all the team members mentioned above was set up every 2 days, from day 2 of patient admission until discharge or withdrawal from the management. The goal of the meeting was to share patients' information with all team members, provide a medication review, and discuss the comprehensive advanced care plan. All patients in the MDT cohort were evaluated every 2 days.

Specifically, the pharmacists evaluated and recorded patients' medication use, including scheduled medications at home before admission, medication use and adjustment during hospitalization, and medication use on discharge. The pharmacists provided some patients' information for

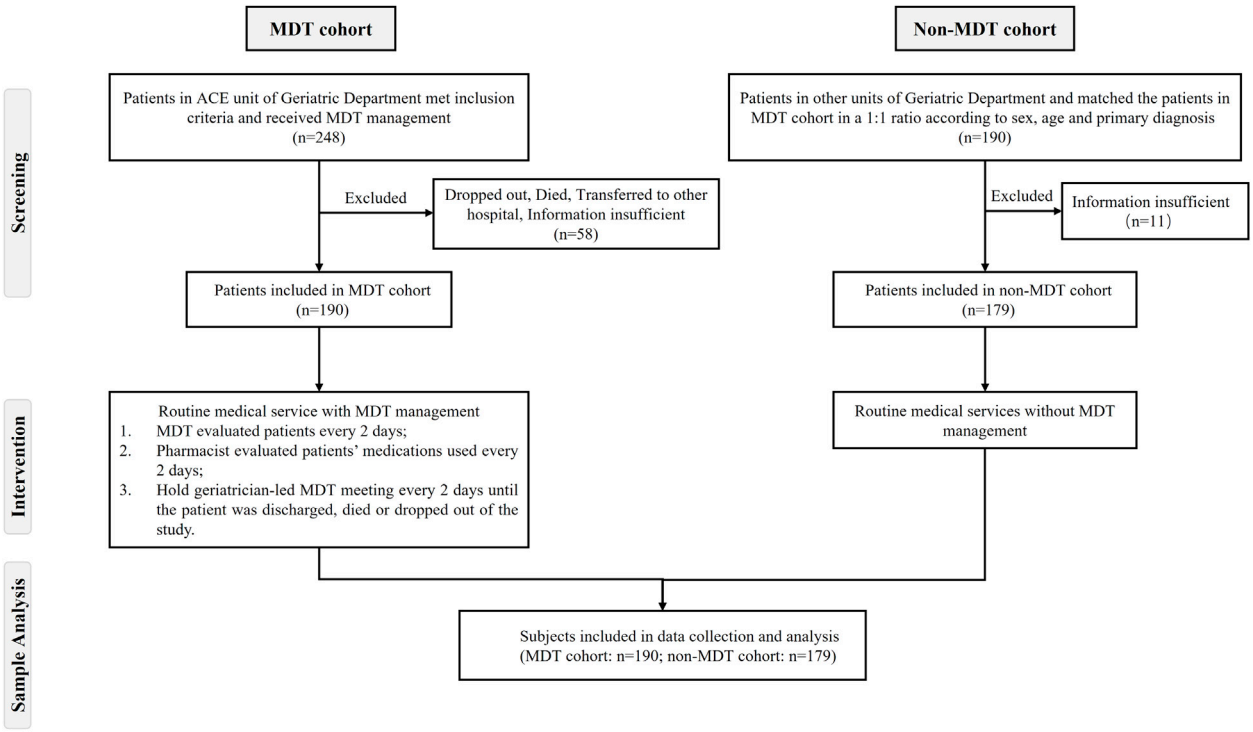

FIGURE 1
Flowchart of patient eligibility for the study.

medications to help geriatricians optimize prescribing, such as PIMs, potentially drug–drug interaction, potentially drug–disease interaction, wrong drug dosage, wrong frequency or route of administration, repeated medication use, possibly missed medication, unreasonable medication duration.

Data collection

We collected data on patient demographics, including age, sex, medical record number, diagnostic diseases, date of admission and discharge, total hospitalization costs and medication costs, from the electronic medical records in West China Hospital. We also collected information on the medication profile from the electronic medical records, mediation administration records and MDT evaluation record sheets (for the MDT cohort) 1) at home before admission, 2) during hospitalization, and 3) at discharge. Polypharmacy was defined as the concurrent use of five and more medications, including OTC drugs, prescription and/or traditional and complementary medicines used by a patient.[6]

Statistical analysis

The baseline characteristics of the patients were described with descriptive statistics, and the data were summarized as the median (interquartile range [IQR]) or number (percentage) according to the distribution of the variables. The changes in the number of medications used before and after hospitalization between the MDT cohort and the non-MDT cohort were compared by the Mann-Whiney *U* test. The amount of medications used among the time points of at home, during hospitalization, and at discharge in each group were compared by the Friedman test. The 2 × 2 factorial design was conducted to verify the effect of the MDT mode on the amount of medication used by participants. To determine the relative factors associated with the discontinuation or addition of medications after MDT management, a multivariate analysis for the factors associated with a change in medication before and after hospitalization was conducted by binary logistic regression analysis (represented by estimating odds ratios [OR] and 95% confidence intervals [CI]). $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 26.0 (IBM Corp, Chicago, IL, U.S. A) and STATA 15.0 (STATA Corp, College Station, TX).

Results

Patient characteristics

In total, 248 inpatients aged 65 years old and above received MDT management from 1 September 2016 to 31 May 2017. A total of 190 patients (male: n = 140, 74%) aged 86 years old

(IQR: 82, 89) were included in the MDT cohort. Meanwhile, the non-MDT cohort included 190 patients who matched the MDT cohort 1:1 in age, sex and primary diagnosis. Finally, a total of 179 patients (male: n = 135, 75%) aged 85 years old (IQR: 80, 89) were included in the non-MDT cohort (Table 1). The prevalence of comorbidities among older inpatients is shown in Table 2.

Geriatrician-led MDT management shortened the hospital stays of older inpatients

Although there were no significant differences between the total costs of hospitalization or medication costs between the two groups, the MDT mode significantly shortened the length of hospital stay of patients compared to the non-MDT cohort (MDT cohort: n = 14 days [IQR: 10, 19] vs non-MDT cohort: n = 19 days [IQR: 12, 28], $p < 0.05$) (Table 1).

The MDT management mode improved medication profile changes among older inpatients

In this study, 68.02% (n = 251) of older patients had polypharmacy at home, and there was no significant difference between the MDT cohort and the non-MDT cohort. During hospitalization, the prevalence of polypharmacy increased both in the MDT cohort and the non-MDT cohort. Although 139 patients (78%) in the non-MDT cohort were still prescribed five and more medications at discharge (compared to at home: n = 114 (64%), $p < 0.001$), the number of patients with polypharmacy in the MDT cohort did not change significantly at discharge (at discharge: n = 131 (69%) vs at home: n = 137 (72%), $p > 0.05$) (Table 1).

Interestingly, we found that the geriatrician-led MDT mode reduced the amount of medications used by one in older patients at discharge compared to the amount of medications used at home (at home: n = 7 [IQR: 4, 11] vs at discharge: n = 6 [IQR: 4, 8], $p < 0.001$).

TABLE 1 Comparison of older inpatients' characteristics and medication change between the MDT cohort and the non-MDT cohort.

	Non-MDT cohort (n = 179)	MDT cohort (n = 190)	*P*
Sex			
Male (n, %)	135 (75)	140 (74)	0.702
Female (n, %)	44 (25)	50 (26)	
Age (years)	85 (80.89)	86 (82.89)	0.495
Length of stay (days)	19 (12.28)	14 (10.19)	<0.05
HE ($)	2,723 (1755,4,717)	2,628 (1916,3,833)	0.595
ME ($)	701 (385,1367)	776 (496,1179)	0.435
ME/HE (%)	26 (18.37)	29 (21.36)	0.068
Diagnostic diseases n)	9 (7.13)	8 (6.11)	0.001
Number of patients with Polypharmacy (n, %)			
At home	114 (64)	137 (72)	0.083
During hospitalization	165 (92)	186 (98)	0.011
At discharge	139 (78)*	131 (69)	0.059
Number of Medication used			
AT home	6 (3.1)	7 (4.11)	0.362
During hospitalization	12 (9.17)	13 (9.17)	0.508
At discharge	7 (5.10)	6 (4.8)**	<0.05
Number of medications changes***	0 (-2.3)	-1 (-4.2)	0.001
Number of patients with medication changes at discharge (n, %)			
Increase	151 (84)	163 (86)	0.699
Decrease	140 (78)	167 (88)	0.013

Abbreviations: HE, Hospitalization expenditure; ME, medicine expenditure.
Data are the median (interquartile range) or number (percentage) unless indicated.
*: $p < 0.001$, compared with the number of patients with polypharmacy at home in the same cohort.
**: $p < 0.05$, compared with the number of medications used at home in the same cohort.
***The difference between the number of medications used by patients at the time of discharge and at home.

TABLE 2 Top ten diagnostic diseases in the MDT cohort and non-MDT cohort.

Non-MDT cohort (n = 179)		MDT cohort (n = 190)	
Diagnostic disease	Number of patients (n, %)	Diagnostic disease	Number of patients (n, %)
Hypertension	121 (68)	Pneumonia*	129 (68)
ICVD	104 (58)	COPD*	123 (65)
COPD	90 (50)	Hypertension	119 (63)
BPH	77 (43)	BPH	73 (38)
CHD	74 (41)	CHD	70 (37)
AS	74 (41)	Cardiac insufficiency	60 (32)
Pneumonia	70 (39)	ICVD*	59 (31)
DM	63 (35)	DM	49 (26)
Arrhythmia	47 (26)	Arrhythmia	47 (25)
Cardiac insufficiency	45 (25)	Mental disorder	42 (22)

Abbreviations: ICVD, ischemic cerebrovascular disease; COPD, chronic obstructive pulmonary disease; BPH, benign prostate hyperplasia; CHD, coronary heart disease; AS, atherosclerosis; DM, diabetes mellitus.
*: $p < 0.05$, Compared with the non-MDT, cohort, the prevalence of patients with the diagnostic disease was significantly different.

TABLE 3 Top five types of medications added/stopped at discharge in the MDT cohort and non-MDT cohort compared with at home.

	Frequency of stopped medications (n=1360), n (%)		Frequency of added medications (n=1177), n (%)	
MDT cohort	Total frequency	811 (100)	Total frequency	574 (100)
	TCM for others [a] *	98 (12)	OTC drugs	38 (7)
	TCM for CCD [b] *	90 (11)	GC	37 (6)
	OTC drugs	86 (11)	β receptor agonists [c]	32 (6)
	Antiplatelet drugs	32 (4)	Mucus relief agents	26 (5)
	ACEI/ARB	31 (4)	Montelukast	25 (4)
non-MDT cohort	Total frequency	549 (100)	Total frequency	606 (100)
	OTC drugs	49 (9)	OTC drugs	39 (6)
	TCM for others	46 (8)	Statins	36 (6)
	TCM for CCD	31 (6)	Antiplatelet drugs	32 (5)
	Externally applied agent	30 (5)	Mucus relief agents	27 (4)
	β receptor agonists [c]	15 (3)	ACEI/ARB	20 (3)
	Mucus relief agents	15 (3)	PPI	20 (3)
			Externally applied agent	20 (3)

Abbreviations: TCM, traditional Chinese medicine; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; OTC, drugs, overthe-counter drugs; PPI, proton-pump inhibitor; GC, glucocorticoids.
*TCM, for others; TCM, for non-cardiovascular and non-cerebrovascular disease.
**TCM, for CCD: TCM, for cardiovascular and cerebrovascular disease.
***β receptor agonists for respiratory disease.
****$p < 0.05$, Compared with the non-MDT, cohort, the amount of medication stopped or added at discharge was significantly different.

In contrast, the number of medications used at discharge did not decrease among patients in the non-MDT cohort (at home: n = 6 [IQR: 3, 11] vs at discharge: n = 7 [IQR: 5, 10], $p > 0.05$) (Table 1).

Overall, approximately 85% of older patients added new medications, and more than 78% of older patients stopped some medications used at home upon discharge in both cohorts (Table 1). Some medications used at home were discontinued 1,360 times upon discharge, of which approximately 60% (n = 811) occurred in the MDT cohort. Meanwhile, the frequency of new medications added at discharge was 1,177 times, and there was almost no

TABLE 4 Factors associated with the discontinuation or addition of medication at discharge

	Medication discontinuation				
	Chi-square test		Binary logistic regression		
	$\chi2$	*P*	OR	95%CI	*P*
Polypharmacy	59.730	<0.001	96.516	12.53-743.48	<0.001
More than 8 coexisting diseases	3.390	0.066	-	-	0.428
Hypertension	4.102	0.043	-	-	0.092
CHD	4.255	0.039	-	-	0.692
COPD	3.278	0.070	-	-	0.624
	Medication addition				
	Chi-square test		Multivariate analysis		
	$\chi2$	*P*	OR	95%CI	*P*
COPD	3.794	0.051	2.36	1.02-5.49	0.046
More than 8 coexisting diseases	2.869	0.090	-	-	0.307
Cardiac insufficiency	4.094	0.043	-	-	0.245
Arrhythmia	7.504	0.022	-	-	0.105
BPH	3.491	0.062	-	-	0.129
Mental disorder	4.626	0.094	-	-	0.074

Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; BPH, benign prostatic hyperplasia.
Factors with $p < 0.1$ in the chi-square test were included in the binary logistic regression analysis.

difference between the two cohorts (MDT cohort: $n = 574$ (49%) vs non-MDT cohort: $n = 606$ (51%), $p > 0.05$) (Table 3).

Compared to at home, approximately 10% of medications discontinued at discharge belonged to OTC drugs both in the MDT cohort and the non-MDT cohort. Twelve percent ($n = 98$) of medications stopped at discharge in the MDT cohort, and 8% ($n = 46$) in the non-MDT cohort were TCM for non-cardiovascular and non-cerebrovascular disease treatment ($p < 0.05$). In the MDT cohort, TCMs for cardiovascular and cerebrovascular disease treatment were discontinued 90 times (11%) at discharge, while only 31 times (6%) were discontinued in the non-MDT cohort ($p < 0.05$). The medicine category with the most added frequency at discharge was OTC drugs in both cohorts. Other drugs stopped or added at discharge are shown in Table 3.

Related factors associated with the discontinuation or addition of medication in older patients

This study illuminated that hospitalization with the MDT management mode had a significant effect on the change in the number of medications at the time of discharge and at home in older inpatients ($F = 7.813$, partial-$\eta^2 = 0.011$, $p = 0.005$), while routine hospitalization without the MDT management mode had no significant effect on it ($F = 0.431$, partial-$\eta^2 = 0.001$, $p = 0.512$).

Our study intended to explore the factors related to discontinuation or addition of medications in older patients after MDT management and incorporated patients' age, gender, the number of comorbidities, polypharmacy at home and types of diseases into the analysis of related factors. The binary logistic regression model showed that the probability of medication discontinuation at discharge was associated with polypharmacy at home (OR: 96.52 [95% CI: 12.53–743.48], $p < 0.001$), and the probability of medication addition was associated with COPD (OR: 2.36 [95% CI: 1.02–5.49], $p = 0.046$) after adjusting for patient age, sex, and the number of comorbidities (Table 4).

Discussion

Geriatrician-led MDT management optimizing prescription for older inpatients

Polypharmacy and prescription omission often coexist in older adults. Polypharmacy was common among older adults, and the prevalence increased with age (Page et al., 2019; Pazan and Wehling, 2021). Our study demonstrated that 68.02% of older patients had polypharmacy at home, which worsened after hospitalization. Polypharmacy is well known to be associated with an increased risk of PIMs and adverse drug reactions (ADRs). It was also an important risk factor that resulted in 90% of older adults being

hospitalized due to ADRs (Pedros et al., 2016). Other adverse health outcomes, such as subsequent fractures, acute renal failure, disability, physical and cognitive function impairment, readmissions and mortality, were also significantly associated with polypharmacy (Gómez et al., 2014; Wastesson et al., 2018).

Our study found that the effect of a geriatrician-led MDT in prescription was not only to reduce the number of medications used by older patients but also to optimize the overall medication plans. Although there was not a reduction in the number of patients with polypharmacy at discharge, geriatrician-led MDT management reduced the number of medications by one in older patients at discharge compared to the number of medications used at home. The World Health Organization (WHO) estimated that approximately 30%–50% of patients could not take medications as prescribed by doctors (Ulley et al., 2019), and older patients who suffered from multiple chronic diseases, hypofunction, cognitive and sensory disorders often had poor adherence to complex and excessive drugs for a long time (de Araujo et al., 2020). Thus, avoiding polypharmacy and optimizing prescribing are increasing challenges in clinical practice, and effective interventions to further improve drug therapy in older adults are strongly recommended.

Our study showed that a geriatrician-led MDT mode was more effective in reducing unnecessary TCM prescribing than conventional medical services. It is well known that TCMs are widely used in China and other East Asian countries and are increasingly used in Europe (Wang et al., 2018). Although most TCMs lack clear indications and clinical benefits, they are still an important part of long-term family medication regimens (Lau et al., 2001; Xiong et al., 2015). Due to cultural causes and national regulations, it is easy to obtain TCMs in China without a physician's prescription. However, the interactions between components of TCMs may lead to potential ADRs, such as drug-induced liver injury, serotonin syndrome, renal impairment, rhabdomyolysis, and acute delirium (Wang et al., 2018).

Furthermore, our study proved that a geriatrician-led MDT mode could significantly reduce the inappropriate use of OTC drugs in older patients. OTC drugs usually contain prescription drug ingredients with an active effect. Taking OTC drugs and prescription medications at the same time may lead to repeated medications and increase the potential risk of overdose (Yang et al., 2021). In China, OTC drugs accounted for 12.6% of ADEs, among which people over 60 years old accounted for 24.4% (Yang et al., 2021). However, only 45% of Chinese residents had a certain understanding of OTC drugs (Yang et al., 2021). In China, clinical pharmacists and doctors rarely intervened in the use of OTC drugs in older adults during non-hospitalization.

Geriatrician-led MDT management improves prescription omissions for older patients with COPD

In this study, older patients with COPD who added new medications at discharge were 2.4 times more likely than older patients without COPD after MDT management, suggesting that the patients with COPD were more likely to be at risk of inadequate medication use at home.

It has been proven that more than 80% of patients with COPD suffer from one or more other chronic diseases (Divo and Celli, 2020). Therefore, patients with COPD were more likely to experience polypharmacy (Hanlon et al., 2018). Many studies have shown that medication adherence rates in patients with COPD were only 10%–40% (Abdulsalim et al., 2018). Approximately 15% of patients with respiratory diseases were unwilling to accept new prescription drugs and stopped taking medications that controlled respiratory symptoms after approximately 6 months (Abdulsalim et al., 2018). Thus, patients were vulnerable to potential prescription omissions (PPOs) during the non-acute onset of COPD. Our study also showed that the management mode of MDT could effectively optimize long-term drug therapy in patients with COPD and reduce PPOs.

Drug prescription is a complex process for older adults with comorbidities. Relying on the geriatrician alone, it is difficult to fully grasp the patient's information of medications, illness, functional status, medication adherence and other issues. The geriatrician-led MDT management mode is a novel clinical practice to improve quality of life for older patients. Our study also illuminated that geriatrician-led MDT management had practical significance in optimizing prescribing for older inpatients.

Limitations

This study had several limitations. First, this study was a single-center retrospective study conducted in the Geriatric Center of West China Hospital of Sichuan University, with a relatively small clinical sample, and its generality in other parts of the country was unclear. Second, the research object of this study was only older patients in hospitals, and there was no relevant research in outpatients, communities or nursing homes. Thirdly, "Drug handover" is very important when patients switch healthcare settings. However few patients have their own family physician in China, which makes it difficult for patients to hand over medications after they are discharged. Therefore, we usually detail the patient's medications at discharge in the discharge paperwork, and the patient and his or her caregiver are instructed on the use of the medications by the nurse practitioners. We also hope that in the future, more family physicians in China will be involved in the medication management of older patients with comorbidities. Therefore, a multicenter prospective randomized controlled trial should be carried out in the future to further confirm the effectiveness of geriatrician-led MDT intervention in medication management.

Conclusion

This study found that implementing the geriatrician-led MDT mode during hospitalization had a significant effect on the management of medications, which could reduce the number of medications used and optimize prescription for older inpatients. Patients with polypharmacy were more likely to "description" after MDT management, while patients with COPD were more likely to be underprescription at home, which could be made up for after MDT management.

This study provides an important reference for the development of MDT modes in geriatric medicine in China. It also provided a feasibility strategy for the drug safety of older people. Since the implementation of the MDT model requires more healthcare providers to participate and increases medical costs, the promotion of the MDT management mode is challenging in China.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by This study was conducted in the Geriatric Department of West China Hospital after approval of the Biomedical Ethics Sub-Committee of Sichuan University (2017-405) and was registered on the website of the Chinese Clinical Trial Registry (ChiCTR2000038003). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study concept and design: LM, YS, LC, JW. Acquisition of data: LM, YS, LC, YL, LC. Analysis and interpretation: LM, YS, LC, XX, LH. Drafting of the manuscript: LM, YS, LC. Critical revision of the manuscript for important intellectual content: All authors.

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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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Detection of potential drug-drug interactions for risk of acute kidney injury: a population-based case-control study using interpretable machine-learning models

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Background: Acute kidney injury (AKI), with an increase in serum creatinine, is a common adverse drug event. Although various clinical studies have investigated whether a combination of two nephrotoxic drugs has an increased risk of AKI using traditional statistical models such as multivariable logistic regression (MLR), the evaluation metrics have not been evaluated despite the fact that traditional statistical models may over-fit the data. The aim of the present study was to detect drug-drug interactions with an increased risk of AKI by interpreting machine-learning models to avoid overfitting.

Methods: We developed six machine-learning models trained using electronic medical records: MLR, logistic least absolute shrinkage and selection operator regression (LLR), random forest, extreme gradient boosting (XGB) tree, and two support vector machine models (kernel = linear function and radial basis function). In order to detect drug-drug interactions, the XGB and LLR models that showed good predictive performance were interpreted by SHapley Additive exPlanations (SHAP) and relative excess risk due to interaction (RERI), respectively.

Results: Among approximately 2.5 million patients, 65,667 patients were extracted from the electronic medical records, and assigned to case (N = 5,319) and control (N = 60,348) groups. In the XGB model, a combination of loop diuretic and histamine H_2 blocker [mean (|SHAP|) = 0.011] was identified as a relatively important risk factor for AKI. The combination of loop diuretic and H_2 blocker showed a significant synergistic interaction on an additive scale (RERI 1.289, 95% confidence interval 0.226–5.591) also in the LLR model.

Conclusion: The present population-based case-control study using interpretable machine-learning models suggested that although the relative importance of the individual and combined effects of loop diuretics and H_2 blockers is lower than that of well-known risk factors such as older age and sex, concomitant use of a loop diuretic and histamine H_2 blocker is associated with increased risk of AKI.

KEYWORDS

drug-drug interaction (DDI), machine learning, artificial inteligence, relative excess risk due to interaction, nephrotoxic drugs, acute kidney injury

1 Introduction

Acute kidney injury (AKI) is one of four phenotypes of drug-induced kidney disease (DIKD), and is diagnosed by serum creatinine (SCr)-based definitions proposed in the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines (Mehta et al., 2015; Ostermann et al., 2020). Various clinical studies have been conducted to assess the effect of individual drugs (e.g., platinum-based agents and antibiotics) on risk of AKI, and those drugs associated with increased risk of AKI are listed as nephrotoxic drugs (Usui et al., 2016; Huang et al., 2022). Recently, Gray et al. (2022) have classified the nephrotoxic potential of 167 medications into seven phased nephrotoxicity categories (ranging from "No potential" to "Definite"), and 41 medications (25%) had nephrotoxic potential (rating ≥ 1). In Japan, society is aging rapidly because of the declining birth rate, and while individuals aged 20–34 account for 4.9% of total cases of polypharmacy, individuals aged 65 and older account for 69.0% (Onoue et al., 2018). Therefore, it is possible that multiple drugs with nephrotoxic potential are prescribed to patients, especially elderly patients. In fact, it has been reported that in elderly patients, concomitant use of two drug classes with nephrotoxic potential, for example, antibiotics and proton pump inhibitors, is the 3rd leading cause of acute interstitial nephritis (AIN), which is an important cause of AKI (Muriithi et al., 2015; Pierson-Marchandise et al., 2017). Hence, it is important to evaluate the combined effect of two drug classes on the risk of AKI.

In 2000, a case report of two patients who had taken a diuretic, angiotensin receptor blocker, and non-steroidal anti-inflammatory drug (NSAID) in combination, so-called "triple whammy," and experienced a rise in SCr was published (Thomas, 2000). Subsequently, a number of clinical studies worldwide have investigated whether concurrent use of these drug classes increases SCr level and decreases estimated glomerular filtration rate (Loboz and Shenfield, 2005; Lapi et al., 2013; Camin et al., 2015; Kunitsu et al., 2019; Imai et al., 2022). Besides the triple whammy, clinical studies have tried to detect drug-drug interactions between two or more drug classes in acute kidney injury (Bird et al., 2013; Gandhi et al., 2013; Gul et al., 2016; Inaba et al., 2019; Okada et al., 2019; Liu et al., 2021; Salerno et al., 2021). However, most of these studies used a multivariable logistic regression (MLR) model, which is a traditional statistical model, and evaluation metrics such as discrimination, calibration, and robustness of the regression model have not been evaluated. Machine learning (ML) is an alternative analytical approach that can handle complex relationships between a number of variables in real-world big data. ML algorithms have been used to predict AKI, and the predictive performance of ML models is often superior to that of traditional statistical models (Song et al., 2021; Peng et al., 2022; Yue et al., 2022). Furthermore, interpretable ML has been applied to detect variables affecting the development of an outcome (Jiang et al., 2023). Hence, the aim of the present study was to investigate whether there is a combination of two drug classes that has combined effects on the increased risk of AKI, by mining electronic medical records using interpretable ML models.

2 Materials and methods

2.1 Data source

The present study was based on a population-based case-control study utilizing electronic medical records from the Nihon University School of Medicine's Clinical Data Warehouse (NUSM's CDW) between 1 April 2004 and 1 September 2021. NUSM's CDW is a centralized data repository that integrates separate databases, including patient demographics, diagnoses, and laboratory data of approximately 2.5 million patients, from the hospital information systems at three hospitals affiliated with the NUSM; Nihon University Itabashi Hospital, Nerima Hikarigaoka Hospital, and Surugadai Nihon University Hospital. To protect patient privacy, patient identifiers are replaced by anonymous identifiers in all databases of the CDW.

2.2 Definition of acute kidney injury as binary outcome

Sample size flow in this study is shown in Figure 1. Firstly, 74,016 Japanese patients who underwent kidney function tests at least three times within 14 days (the interval between each measurement date was 7 days or less) and whose serum creatinine (SCr) showed a <50% change between the 1st and 2nd measurement dates were extracted from NUSM's CDW, and the 2nd measurement date was regarded as baseline. Among the 74,016 patients, those who met any of the following two conditions were regarded as patients with acute kidney injury complying with the KDIGO criteria: 1) SCr increased by 0.3 mg/dL within 48 h from baseline, or 2) SCr increased to ≥1.5 times higher than baseline within the prior 7 days. These patients with acute kidney injury were assigned to the case group (N = 7,203; outcome = 1) and the date that AKI occurred was regarded as the event date. On the other hand, the remaining 66,813 patients were assigned to the control group (outcome = 0), and the 3rd measurement date was regarded as the reference date in the control group. Next, patients who met the following exclusion criteria were excluded: 1) under 18 years old, 2) baseline SCr >5.0 mg/dL, and 3) patients with pre-existing kidney disease [chronic kidney disease stage ≥3, diabetic nephropathy, other kidney disease; International Classification of Disease 10 (ICD-10) codes are shown in Supplementary Table S1A]. Then the clinical information from 65,667 patients was used for training and testing of ML models.

2.3 Features

In order to detect interactions between two drug classes for risk of AKI, we obtained use or non-use of 32 therapeutic drug classes, and 496 (=32C2) product terms of these drug classes as features from the eligible patients. However, because none of the 88 product terms included patients who developed AKI (i.e., these product terms contained only "0"), the number of product terms reduced to 408. The drug classes were classified based on the Anatomical Therapeutic Chemical (ATC) code published by the WHO

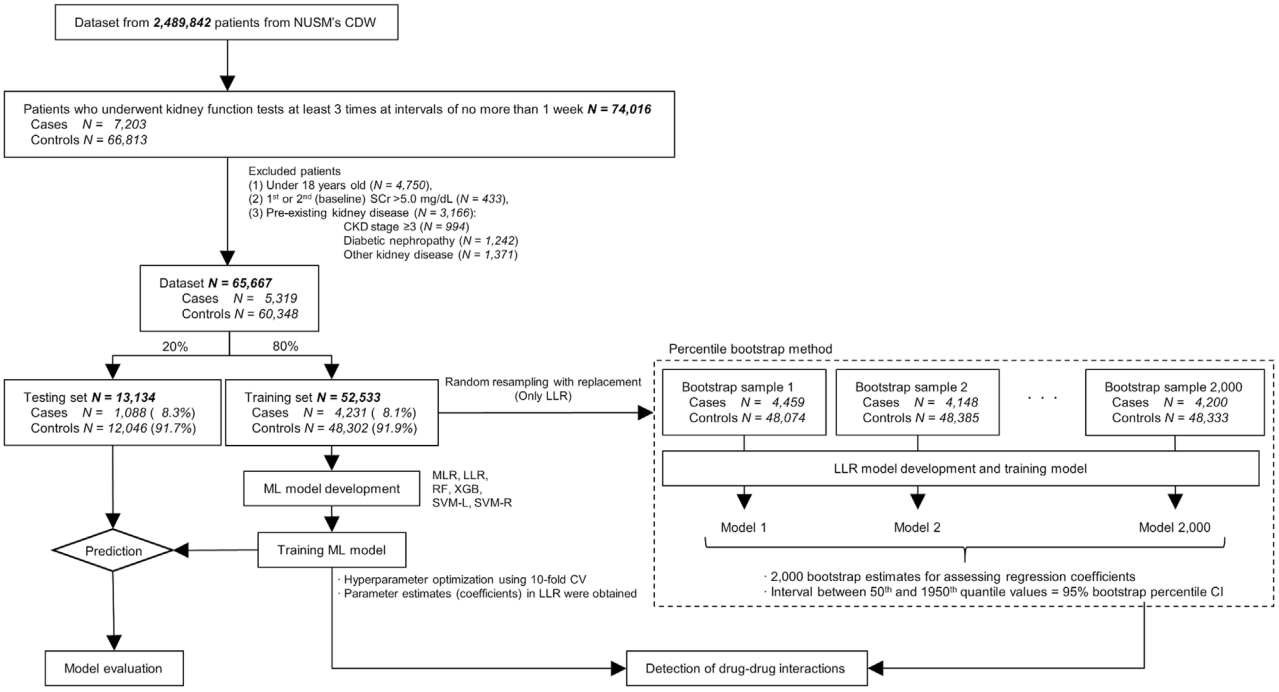

FIGURE 1
Sample size flowchart. Abbreviations: NUSM's CDW, Nihon University School of Medicine's Clinical Data Warehouse; SCr, serum creatinine; CKD, chronic kidney disease; CI, confidence interval; LLR, logistic least absolute shrinkage and selection operator regression; CV, cross-validation; ML, machine-learning; MLR, multivariable logistic regression; RF, random forest; SVM-L, support vector machine (linear function); SVM-R, support vector machine (radial basis function); XGB, extreme gradient boosting.

Collaborating Centre for Drug Statistics Methodology (Supplementary Table S2). AKI tends to occur within 7 days from the initiation of a culprit drug, and sub-acute kidney injury occurs within 4 weeks (Mehta et al., 2015). In fact, it has been reported that several nephrotoxic drugs are more likely to induce acute kidney injury within 7 days, and most cases of acute kidney injury occur within 30 days from the initiation of the drug (Khalili et al., 2013; Miano et al., 2018; Ide et al., 2019; Kunitsu et al., 2022; Wu et al., 2022). Hence, if a drug class was newly started within 1–7 days before the event date, the drug class was regarded as "use." If a drug class was newly started on the event date, the drug class was regarded as "non-use," to prevent reverse causality bias. A drug class newly started within 8+ days before the event date was regarded as "non-use." When the included product term is "1," it means that the two drug classes were newly started at about the same time within 7 days before the event date, whereas when it is "0," it means that one of the two drug classes was used or neither of them was newly started. That is, the present study detected whether any of the 408 combinations of the 32 drug classes had an interaction for increased risk of AKI.

Five demographic characteristics and medical history which included seven diagnoses as features were obtained to adjust for the effect of these features on the risk of AKI. The demographic information was composed of age, sex, and three hospitals (Itabashi, Hikarigaoka, and Surugadai; dummy variables). The medical history was composed of hypertension, diabetes, heart failure, anemia, sepsis, chronic kidney disease (stage ≤2), and chronic liver disease, which are known risk factors for AKI (ICD-10 codes are shown in Supplementary Table S1B) (Poston and Koyner, 2019; Ostermann et al., 2020; Yu et al., 2020; Cullaro et al., 2022). A diagnosis was regarded as "present" if there was a diagnosis before baseline. We investigated 32 therapeutic drug classes commonly associated with risk of acute kidney injury (Usui et al., 2016; Nast, 2017; Ostermann et al., 2020). Finally, a two-dimensional dataset (65,667 patients × 452 features) for ML was generated. Data imputation was not performed because all the observations in the dataset had no missing values.

2.4 Construction of ML models and model evaluation

The dataset for ML was randomly split into a training set for the development of ML models (80%; $N = 52,533$) and a testing set for evaluation (20%; $N = 13,134$). To evaluate the effects of individual drug classes and their product terms on the risk of AKI, six ML models were utilized in this study: 1) MLR model and 2) logistic least absolute shrinkage and selection operator regression (LLR) model which are linear algorithms, 3) random forest (RF) model and 4) extreme gradient boosting (XGB) tree model which are tree-based algorithms, and 5) and 6) two support vector machine models [kernel = linear function (SVM-L) and radial basis function (SVM-R)]. All the supervised ML models were developed using R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

The supervised ML models were performed with AKI occurring as a binary dependent variable and the 452 features as independent variables; that is, 449 features excluding the individual effects of the two drug classes of interest and their product terms were regarded as co-variables. When constructing the four ML models except for the MLR model, we ran 10-fold cross-validation to perform hyperparameter tuning. In the LLR model, a lambda (λ) value, which is the penalty term in the loss function, was determined to minimize misclassification error for the training set and to avoid over-fitting to the training set using the R "glmnet" package. A regularized logistic regression equation was obtained using the optimized λ value (Supplementary Figure S1). The RF model was constructed using the R "randomForest" package. Hyperparameters such as the number of features randomly sampled as candidates at each tree (mtry) and the number of trees to grow (ntree) were optimized by grid search (Supplementary Table S3). The XGB model was constructed using the R "xgboost" package. The hyperparameters of the XGB model are roughly divided into the following four parameters: general, booster, learning task, and command line parameters. Of these parameters, booster parameters were optimized by grid search. Finally, the XGB model with the optimized hyperparameters was constructed (Supplementary Table S4). The two SVM models were constructed using the R "e1071" package, and the hyperparameters were optimized using a grid search (Supplementary Table S5).

Area under the receiver operating characteristic curve (AUROC) and area under the precision-recall curve (AUPR) were calculated to evaluate the discrimination and robustness of each ML model. To evaluate model calibration, the calibration slope and intercept were calculated for each ML model from a calibration plot with actual probabilities on the *X*-axis and log odds on the *Y*-axis. The calibration slope and intercept have target values of 1 and 0, respectively. A slope <1 indicates that predictive risk is too extreme, i.e., too high for patients who are at high risk and too low for patients who are at low risk, and an intercept <0 indicates overestimation of predicted risk (Van Calster et al., 2019). Additionally, Brier score, which is an evaluation metric to verify the accuracy of predicted probabilities, was calculated for model calibration using the R "scoring" package. Brier score is the mean squared error between the actual binary outcome and the predicted probabilities, as shown in Formula 1 (Huang et al., 2020):

$$\textbf{\textit{Brier score}} = \frac{\sum_{i=1}^{N} (\boldsymbol{E_i} - \boldsymbol{O_i})}{\boldsymbol{N}} \tag{1}$$

where N is the number of patients, E_i is the predicted probability for patient i, and O_i is the actual outcome for patient i. Brier score ranged from 0 to 1, and a Brier score of 0 indicates the best possible calibration. Sensitivity (recall), positive predictive value (PPV, precision), specificity, negative predictive value (NPV), and F1-score were also calculated as evaluation metrics. The R "pROC" and "PRROC" packages were used to calculate these metrics.

2.5 Detection of drug-drug interactions for risk of acute kidney injury

In the present study, the following two ML models were interpreted to detect interactions between two drug classes for increased risk of AKI: 1) the XGB model, which had the best predictive performance, and 2) the LLR model, which had the second-best predictive performance and can detect synergistic interactions on an additive scale. Although the complexity of the models of ML makes it hard to provide interpretability, some interpretation algorithms such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) have been used (Hu et al., 2022). In this study, SHAP values were calculated to detect features that affect the increased risk of AKI using the R "SHAPforxgboost" package.

In the LLR model, relative excess risk due to interaction (RERI) was used to evaluate synergistic interaction on an additive scale between two drug classes. RERI has been used to detect whether there are combined effects of two exposures on an outcome and can be calculated by substituting coefficients in the regression equation into the following Formulas 2, 3 (Knol et al., 2007; Knol and VanderWeele, 2012). RERI of 0 indicates no interaction on an additive scale. $\widehat{\beta_1}$, $\widehat{\beta_2}$, and $\widehat{\beta_3}$ represent regression coefficients for drug class 1, drug class 2, and a product term of drug classes 1 and 2, respectively.

$$\left(e^{\widehat{\beta_1}+\widehat{\beta_2}+\widehat{\beta_3}} - \mathbf{1}\right) \neq \left(e^{\widehat{\beta_1}} - \mathbf{1}\right) + \left(e^{\widehat{\beta_2}} - \mathbf{1}\right) \tag{2}$$

and

$$\textbf{\textit{RERI}} = e^{\widehat{\beta_1}+\widehat{\beta_2}+\widehat{\beta_3}} - e^{\widehat{\beta_1}} - e^{\widehat{\beta_2}} + \mathbf{1} \tag{3}$$

However, in the LLR model built using the glmnet package, a point estimate for each feature is calculated, but its standard error is not. Hence, 95% confidence intervals (95% CIs) of regression coefficients, adjusted odds ratio (OR), and RERI were estimated with a percentile bootstrap method (Figure 1) (Jung et al., 2019). To calculate 95% CIs, 2,000 bootstrap samples, each of which was the same size as the training set, were generated by resampling with replacement from the training set. After a parameter estimate was calculated from each bootstrap sample, 2,000 parameter estimates in all the bootstrap samples were sorted in ascending order. The interval between the 50th and 1950th quantile values of the 2,000 parameter estimates was regarded as the 95% CI. In this study, combinations that had a product term with a lower limit of adjusted OR 95% CI > 1 and had a lower limit of RERI 95% CI > 0 were considered to have a positive interaction for the risk of AKI. However, it is invalid to calculate RERI if the adjusted OR for at least one of two drug classes in a combination is less than 1.

2.6 Statistical analysis

To compare the patient characteristics between the case and control groups and between the training and testing sets, unpaired two-tailed Welch's *t*-test or Wilcoxon rank-sum test for continuous data and chi-squared test for categorical data were performed. DeLong's test and bootstrap test were performed to compare AUROC and AUPR, respectively. The level of statistical significance was set at 5.0% for all statistical analyses. All statistical analyses were performed using R software.

2.7 Sensitivity analyses

Sensitivity analyses were performed to evaluate the robustness of the detected potential drug-drug interactions. Since most cases of

TABLE 1 Patients' characteristics in case and control groups.

Characteristics	Case group (N = 5,319)	Control group (N = 60,348)	*p* value
Age (years), median (IQR)	69 (59–78)	65 (51–74)	<0.001
Male, n (%)	3,519 (66.2)	32,726 (54.2)	<0.001
Hospital, n (%)			<0.001
Itabashi	3,924 (73.8)	43,998 (72.9)	
Surugadai	884 (16.6)	9,284 (15.4)	
Hikarigaoka	511 (9.6)	7,066 (11.7)	
Medical history, n (%)			
Hypertension	1,379 (25.9)	8,544 (14.2)	<0.001
Diabetes	1,602 (30.1)	13,994 (23.2)	<0.001
Heart failure	1,079 (20.3)	4,830 (8.0)	<0.001
Anemia	746 (14.0)	5,858 (9.7)	<0.001
Sepsis	620 (11.7)	1,107 (1.8)	<0.001
Chronic kidney disease	72 (1.4)	244 (0.4)	<0.001
Chronic liver disease	109 (2.0)	625 (1.0)	<0.001
Use of therapeutic drug classes, n (%)			
Antibiotic drugs			
Penicillins	462 (8.7)	2,731 (4.5)	<0.001
Cephalosporins	500 (9.4)	8,144 (13.5)	<0.001
Carbapenems	161 (3.0)	349 (0.6)	<0.001
Aminoglycosides	37 (0.7)	37 (0.1)	<0.001
Glycopeptides	228 (4.3)	86 (0.1)	<0.001
Tetracyclines	13 (0.2)	87 (0.1)	0.107
Fluoroquinolones	105 (2.0)	844 (1.4)	0.001
Macrolides	97 (1.8)	591 (1.0)	<0.001
Sulfamethoxazole/trimethoprim	58 (1.1)	104 (0.2)	<0.001
Azoles	21 (0.4)	29 (0.0)	<0.001
Amphotericin B	15 (0.3)	12 (0.0)	<0.001
Anti–herpes virus drugs (nucleoside analogues)	20 (0.4)	175 (0.3)	0.330
Interferons	3 (0.1)	31 (0.1)	1.000
Antihypertensive drugs			
Calcium channel blockers	495 (9.3)	4,628 (7.7)	<0.001
ACE inhibitors	225 (4.2)	2,164 (3.6)	0.018
ARBs	104 (2.0)	519 (0.9)	<0.001
α–adrenergic receptor blockers	35 (0.7)	185 (0.3)	<0.001
β–adrenergic receptor blocker	107 (2.0)	584 (1.0)	<0.001
Loop diuretics	516 (9.7)	1,170 (1.9)	<0.001

(Continued on following page)

TABLE 1 (*Continued*) Patients' characteristics in case and control groups.

Characteristics	Case group (N = 5,319)	Control group (N = 60,348)	*p* value
Aldosterone antagonists	246 (4.6)	658 (1.1)	<0.001
Other diuretics	24 (0.5)	277 (0.5)	1.000
Antineoplastic drugs			
Folate antimetabolites	16 (0.3)	11 (0.0)	<0.001
Platinum–based agents	133 (2.5)	125 (0.2)	<0.001
Immunosuppressive drugs			
Calcineurin inhibitors	8 (0.2)	23 (0.0)	0.001
Sulfhydryl compounds (DMARDs)	1 (0.0)	27 (0.0)	0.595
Drugs for alimentary tract			
Histamine H_2 receptor blockers	637 (12.0)	7,391 (12.2)	0.577
Proton pump inhibitors	680 (12.8)	4,382 (7.3)	<0.001
Drugs for dyslipidemia			
Statins	142 (2.7)	1,966 (3.3)	0.022
Fibrates	11 (0.2)	203 (0.3)	0.143
Others			
NSAIDs	706 (13.3)	9,491 (15.7)	<0.001
SGLT2 inhibitors	5 (0.1)	52 (0.1)	1.000
Vitamin D_3 preparations	2 (0.0)	100 (0.2)	0.036
Serum creatinine on event date (mg/dL), median (IQR)			
Male	1.7 (1.3–2.3)	0.8 (0.7–0.9)	<0.001
Female	1.3 (0.9–2.0)	0.6 (0.5–0.7)	<0.001

Since continuous data such as age and serum creatinine level were not normally distributed, Wilcoxon rank–sum test was performed for differences in the features. Chi–squared test was performed for categorical data. Abbreviations: DMARD, disease modifying anti–rheumatic drug; IQR, interquartile range; NSAID, non–steroidal anti–inflammatory drug; SGLT2, sodium glucose cotransporter 2.

AKI occur within 4 weeks regardless of drug class, we redefined new exposures to the drug classes within 1–14 and 1–30 days from the event date as "use" and reconstructed the XGB and LLR models using the same procedure as above. SHAP and RERI values were calculated from the two reconstructed models, and potential interactions between two drug classes of interest were evaluated.

3 Results

3.1 Patients' characteristics

A total of 65,667 eligible patients were extracted from NUSM's CDW and assigned to the case ($N = 5,319$) and control ($N = 60,348$) groups. Their clinical characteristics are presented in Table 1. Age in the case group was significantly older than that in the control group ($p < 0.001$), and the case group contained significantly more male patients than the control group ($p < 0.001$). All seven medical diagnoses were significantly more prevalent in the case group than in the control group (all $p < 0.001$). With regard to therapeutic drug classes, most of the drug classes were significantly different between the case and control groups. SCr levels on the event date were within normal range (male, 0.65–1.07 mg/dL; female, 0.46–0.79 mg/dL) for both male and female subjects in the control group. On the other hand, most patients in the case group had SCr levels above the normal range, and SCr levels in the case group were significantly higher than those in the control group regardless of sex ($p < 0.001$, respectively). Additionally, patients' characteristics were homogeneous between the training and testing sets in both the case and control groups (Supplementary Tables S6, S7).

3.2 Comparison of predictive performance among six ML models

Discrimination, robustness, and calibration of each ML model are shown in Figure 2, and other classification metrics are shown in Table 2. Among the six ML models, the XGB model had the highest AUROC (0.827, 95% CI 0.814–0.840), and the LLR model had the second highest AUROC (0.801, 0.787–0.816) (Figure 2A). The XGB model had the highest AUPR (0.384, 0.352–0.414) followed by the LLR (0.348, 0.319–0.379) and RF (0.336, 0.305–0.367) models (Figure 2B). The

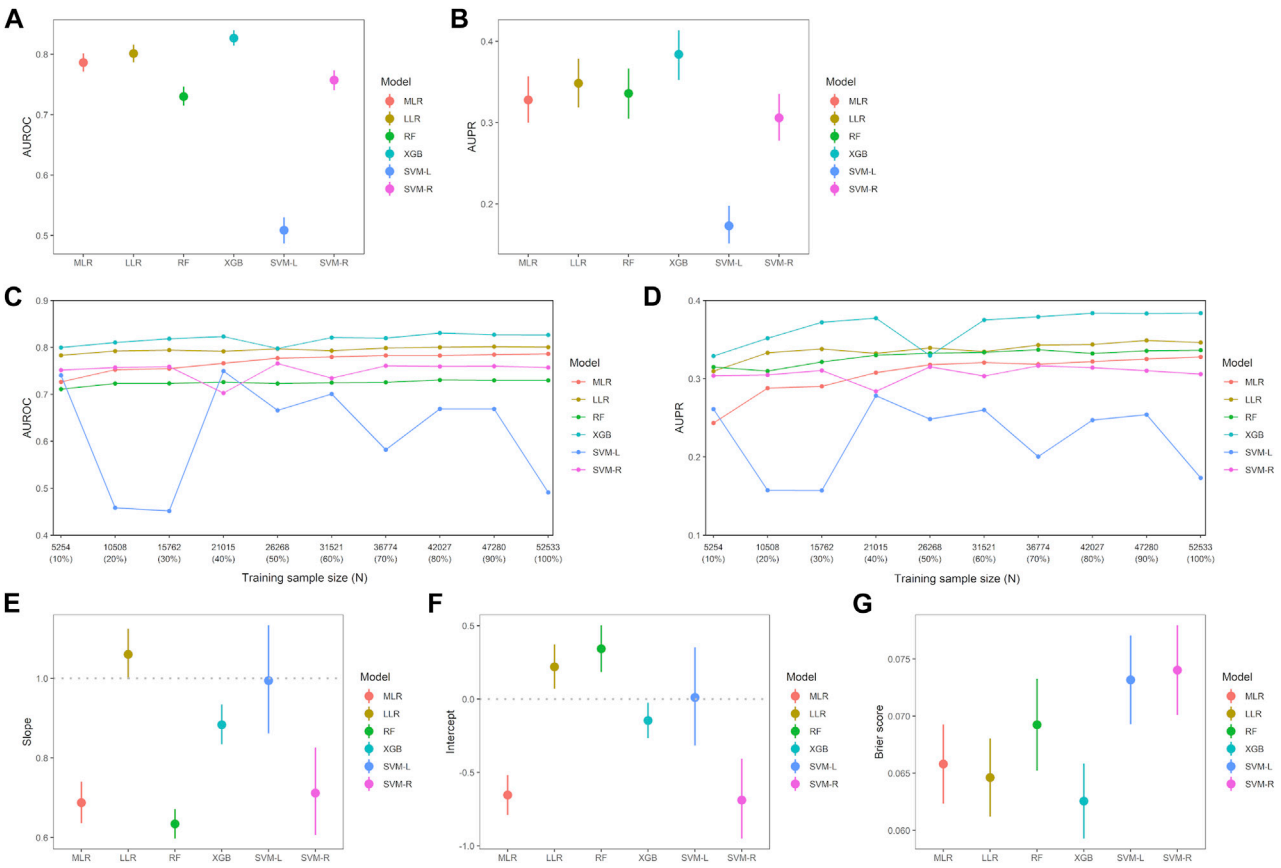

FIGURE 2
Comparison of evaluation metrics among six machine-learning models. **(A)** Each point indicates area under the receiver operating characteristic curve (AUROC) and error bar indicates 95% confidence interval (CI). There were significant differences between all six machine-learning models ($p < 0.001$, respectively). **(B)** Each point indicates area under the precision-recall curve (AUPR) and error bar indicates 95% CI. There were significant differences between all machine-learning models ($p < 0.01$, respectively) except between MLR and SVM-R models ($p = 0.435$), between MLR and RF models ($p = 0.466$), and between RF and LASSO model ($p = 0.222$). Robustness of the machine-learning models in AUROC **(C)** and AUPR **(D)**, respectively. AUROC for each training sample size was calculated by increasing the sample size by 10%. Calibration slope **(E)** and intercept **(F)** were calculated from the calibration curve, and error bar indicates 95% CI. **(G)** Brier score in each machine-learning model. Error bar indicates 95% CI and smaller Brier score indicates a stronger fit of the model. Abbreviations: LLR, logistic least absolute shrinkage and selection operator regression; MLR, multivariable logistic regression; RF, random forest; SVM-L, support vector machine (linear function); SVM-R, support vector machine (radial basis function); XGB, extreme gradient boosting.

TABLE 2 Classification performance metrics of each machine-learning model.

Evaluation metrics	Machine-learning models					
	MLR	LLR	RF	XGB	SVM-L	SVM-R
Sensitivity (recall), %	72.2	76.6	64.8	77.4	46.5	67.6
PPV (precision), %	18.7	18.9	18.0	20.5	10.1	18.7
Specificity, %	71.7	70.3	73.3	72.9	62.6	73.5
NPV, %	96.6	97.1	95.8	97.3	92.8	96.2
F1-score	0.297	0.303	0.281	0.324	0.166	0.293
AUROC (95% CI)	0.786 [0.771, 0.802]	0.801 [0.787, 0.816]	0.730 [0.715, 0.746]	0.827 [0.814, 0.840]	0.509 [0.487, 0.530]	0.757 [0.741, 0.773]
AUPR (95% CI)	0.328 [0.300, 0.357]	0.348 [0.319, 0.379]	0.336 [0.305, 0.367]	0.384 [0.352, 0.414]	0.173 [0.151, 0.198]	0.306 [0.278, 0.335]

Abbreviations: AUPR, area under precision-recall curve; AUROC, area under receiver operating characteristic curve; CI, confidence interval; LLR, logistic least absolute shrinkage and selection operator regression; MLR, multiple logistic regression; NPV, negative predictive value; PPV, positive predictive value; RF, random forest; SVM-L, support vector machine with linear function kernel; SVM-R, support vector machine with radial basis function kernel; XGB, extreme gradient boosting.

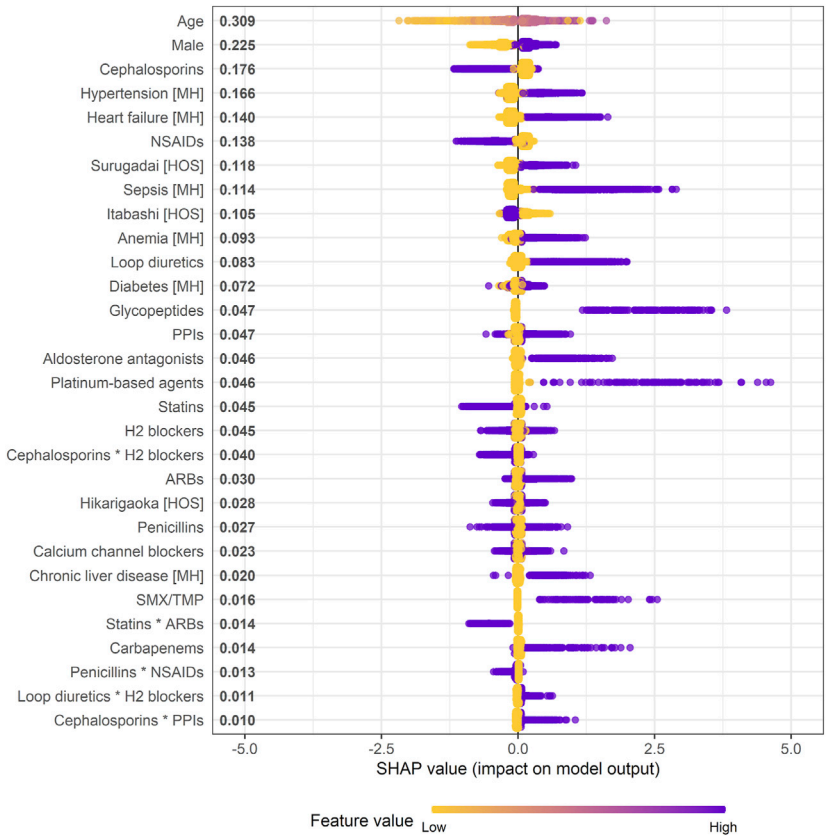

FIGURE 3
Effect of features on increased risk of AKI in XGB model (SHAP summary plot). * indicates product term of two drug classes. When a feature is continuous, the higher the feature value, the more purple it is. When a feature is binary, it is represented in purple if the feature is present. Each dot represents one patient on the line for each feature. Mean absolute SHAP value is shown to the right of a feature. Abbreviations: ARB, angiotensin receptor blocker; H_2 blocker, histamine H_2 receptor blocker; HOS, hospital; MH, medical history; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SHAP, SHapley Additive exPlanation; SMX/TMP, sulfamethoxazole/trimethoprim.

XGB model had the highest classification performance, with sensitivity of 77.4%, PPV of 20.5%, specificity of 72.9%, NPV of 97.3%, and F1-score of 0.324 (Table 2). After this model, the LLR model had sensitivity of 77.6%, PPV of 18.9%, specificity of 70.3%, NPV of 97.1%, and F1-score of 0.303. As for model robustness, the XGB and LLR models maintained high AUROC and AUPR even with small training sample sizes (10%–30% of the training set). The MLR model had low AUPR for very small training sample sizes, such as 10% of the training set, and the SVM-L model showed a lack of robustness (Figures 2C, D). With regard to model calibration, the LLR and SVM-L models had a good calibration slope (1.06, 1.00–1.12; 0.99, 0.86–1.13, respectively), and the latter also had a good calibration intercept (0.01, −0.32 to 0.35). On the other hand, the MLR, RF, XGB, and SVM-R models had slopes less than 1, and these three models other than the RF model had intercepts less than 0 (Figures 2E, F). The XGB model had the lowest Brier score (0.063, 0.059–0.066), followed by the LLR model (0.065, 0.061–0.068) (Figure 2G). Therefore, the XGB and LLR models, which had the best and second-best evaluation metrics, were interpreted to detect interactions between two drug classes with increased risk of AKI.

Supplementary Figure S2 shows the effect of the 408 product terms on model discrimination of the six ML models. AUROC values of the five models, except for the MLR model, with these product terms were significantly higher than those of the models without them. AUPR values of the LLR, SVM-L, and SVM-R models with these product terms in the training set were significantly higher than those of the models without them. That is, the product terms between two drug classes affected model discrimination.

3.3 Evaluation of features affecting increased risk of AKI in XGB model

A SHAP summary plot of the XGB model was made to identify features that affect the risk of AKI in the prediction model, and the top 30 important features are shown in Figure 3. All 110 features with non-zero mean (|SHAP|) values are shown in Supplementary Figure S3. This plot shows how strongly or weakly the features were related to the SHAP values. For example, the older the patient, the more purple it becomes. As another example, in the case of binary features such as sex and use or non-use of the drug classes, “male” and “use” are shown in purple. Age, male, hypertension, heart failure, and sepsis were detected as the most important predictors of increased risk of AKI, and their feature importance scores, as measured by mean (|SHAP|), were 0.309, 0.225, 0.166, 0.140, and 0.114, respectively. In particular, the locally-weighted

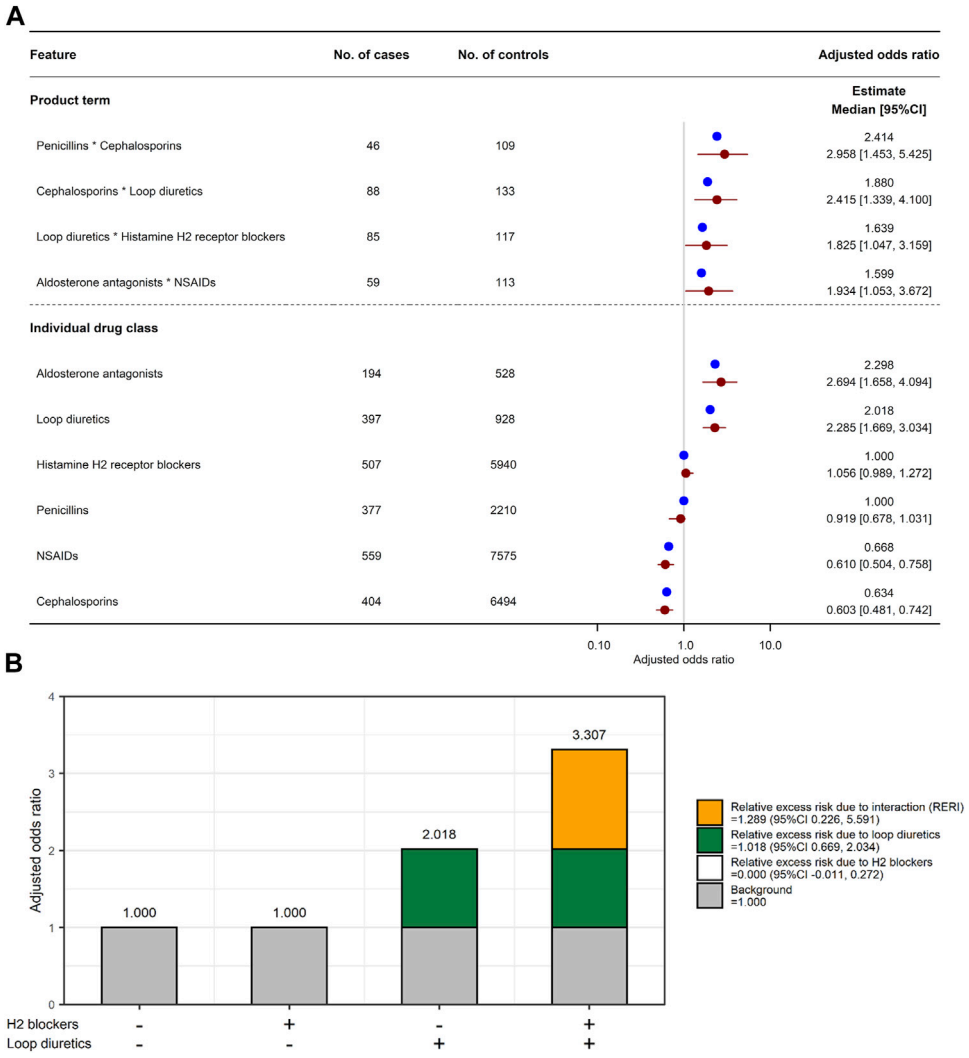

FIGURE 4
Combined effects of two drug classes on increased risk of AKI. **(A)** Adjusted odds ratio for six individual drug classes and their four product terms. Blue and red circles represent estimated adjusted odds ratio in the original training set and median of adjusted odds ratio in 2,000 bootstrap replicates, respectively. Red horizon indicates adjusted odds ratio 95% confidence interval calculated by a percentile bootstrap method. **(B)** Relative excess risk due to interaction (RERI) between histamine H_2 blockers and loop diuretics. Gray bar indicates background (i.e., non-use of H_2 blockers and loop diuretics). White and green bars indicate relative excess risk due to H_2 blockers ($e^{\hat{\beta}_1} - 1$) and loop diuretics ($e^{\hat{\beta}_2} - 1$), respectively. Orange bar indicates RERI ($e^{\hat{\beta}_1+\hat{\beta}_2+\hat{\beta}_3} - e^{\hat{\beta}_1} - e^{\hat{\beta}_2} + 1$). Abbreviations: CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

scatterplot smoothing curve exceeded the SHAP value of 0 for ages from 60 to 93 years according to the SHAP dependence plot (Supplementary Figure S4). Regarding the individual drug classes, loop diuretics, glycopeptides, aldosterone antagonists, platinum-based agents, and sulfamethoxazole/trimethoprim were identified as important predictors of increased risk of AKI. Of the five product terms in the top 30 important features, the product term of loop diuretics and histamine H_2 blockers [mean (|SHAP|) = 0.011], and that of cephalosporins and proton pump inhibitors (0.010) were identified as relatively important risk factors for AKI because SHAP values of most of the patients with these product terms were positive.

Supplementary Figure S5 shows the SHAP values of the reconstructed XGB models in which the drug classes newly started within 1–14 and 1–30 days were considered "use." The product term of loop diuretics and H_2 blockers was consistently included in the top 30 important features in the reconstructed models, and rather the SHAP values tended to be higher than those in the original model. Moreover, the individual effects of these drug classes on increased risk of AKI in the reconstructed models were also greater than those in the original model: mean (|SHAP|) of loop diuretics = 0.083 within 1–7 days, 0.116 within 1–14 days, and 0.161 within 1–30 days; that of H_2 blockers = 0.045, 0.051, and 0.071, respectively.

3.4 Detection of drug-drug interactions for increased risk of AKI in LLR model

One hundred and thirty-four features were selected in the LLR model, with an optimized value λ of 0.0015275. All the selected features are shown in Supplementary Table S8. Of the

408 combinations, four combinations had a product term with a lower limit of adjusted OR 95% CI > 1 (Figure 4A): penicillins*cephalosporins (adjusted OR 2.414, 95% CI 1.453–5.425), cephalosporins*loop diuretics (1.880, 1.339–4.100), loop diuretics*H_2 blockers (1.639, 1.047–3.159), and aldosterone antagonists*non-steroidal anti-inflammatory drugs (NSAIDs; 1.599, 1.053–3.672). Among the four combinations, only the combination of loop diuretics and histamine H_2 blockers had a lower limit of RERI 95% CI > 0 (RERI 1.289, 95% CI 0.226 to 5.591 in Figure 4B): individual effect of loop diuretics, $e^{\hat{\beta}_1} = 2.018$; that of histamine H_2 blockers, $e^{\hat{\beta}_2} = 1.000$; product term, $e^{\hat{\beta}_3} = 1.639$; combined effect of these drug classes, $e^{\hat{\beta}_1+\hat{\beta}_2+\hat{\beta}_3} = 3.307$. On the other hand, RERIs could not be calculated for the remaining three combinations because the adjusted ORs for the individual drug classes that were included in the product terms were less than 1 (e.g., NSAIDs; adjusted OR 0.668, 95% CI 0.504–0.758) (Knol and VanderWeele, 2012).

Supplementary Figure S6 shows the adjusted ORs for the four combinations of the six individual drug classes in the reconstructed LLR models. Similarly to the XGB model, the product term of loop diuretics and histamine H_2 blockers and the individual effect of loop diuretics were consistently associated with increased risk of AKI in the reconstructed models. Moreover, exposure to H_2 blockers within 1–30 days before the event date was significantly associated with increased risk of AKI (adjusted OR 1.485, 95% CI 1.089, 1.790).

4 Discussion

In the present study, six ML models were constructed for the prediction of AKI. Although the XGB model tended to overestimate the risk of AKI, this model had the best discrimination and the lowest Brier score among the six ML models. After the XGB model, the LLR model showed good discrimination and low Brier score. On the other hand, AUROC and AUPR of the SVM-L model were the lowest among these ML models. The reason for this is thought to be that the sample size was extremely large compared to the number of features, making it difficult to calculate a hyperplane that can clearly discriminate the presence or absence of AKI in the feature space. In fact, the SVM-R model, which maps the 452-dimensional feature space (input space) to a higher-dimensional feature space by using the radial basis function kernel, had significantly greater AUROC and AUPR than the SVM-L model. Therefore, we detected the combined effect of two therapeutic drug classes on increased risk of AKI by interpreting the XGB and LLR models, with good predictive performance.

In the XGB model, well-known risk factors for AKI such as older age (Xu et al., 2021), male sex (Neugarten, et al., 2018), and six medical diagnoses (Poston and Koyner, 2019; Ostermann et al., 2020; Yu et al., 2020; Cullaro et al., 2022) were included in the top 30 important predictors. Especially, the risk of AKI increased in Japanese elderly patients aged 60–93 years (Supplementary Figure S4). Similarly to the XGB model, age, male, and five diagnoses except for diabetes and chronic kidney disease were significantly associated with increased risk of AKI in the LLR model (Supplementary Table S8). Since life expectancy at birth in Japan is 81.1 years for men and 87.1 years for women (Tsugane, 2021), the range from 60 to 93 years associated with increased risk of AKI covers most of the Japanese elderly population; that is, Japanese elderly patients are at high risk of AKI. Regarding individual drug classes, five drug classes (loop diuretics, glycopeptides, aldosterone antagonists, platinum-based agents, and sulfamethoxazole/trimethoprim) were associated with increased risk of AKI in the XGB model. Furthermore, all of these drug classes associated with the risk of AKI in the XGB model were also significantly associated with the risk of AKI in the LLR model. The five drug classes associated with increased risk of AKI are known to be nephrotoxic drug classes (Usui et al., 2016; Nast, 2017; Ostermann et al., 2020). On the other hand, NSAIDs were associated with decreased risk of AKI in both the XGB and LLR models. Although NSAIDs are well-known risk factors for DIKD, recent studies suggest that the coexistence of other risk factors in patients who take NSAIDs contributes to the development of AKI. For example, the risk of NSAID-induced AKI in patients with CKD and elderly people tended to be higher than that in the general population (Zhang et al., 2017). Moreover, adding NSAIDs in patients with hypertension further increases blood pressure due to reduction of renal vasodilator prostanoids such as prostaglandin E_2 (PGE_2) and PGI_2, which are formed predominantly by cyclooxygenase (COX)-2, leading to renal vascular damage (Drożdżal et al., 2021; Spence et al., 2022). Because these factors that modify the risk of NSAID-induced AKI were adjusted in this study, NSAIDs may not be associated with increased risk of AKI. Therefore, it is conceivable that the ML models constructed using electronic medical records can successfully explain the factors that affect the increased risk of AKI reported in various clinical studies to date.

In the LLR model, four product terms were significantly associated with increased risk of AKI. However, of these product terms, since three included a drug class with an adjusted OR <1 (e.g., NSAIDs and cephalosporins), RERI could not be calculated, suggesting that these three combinations are unlikely to have an interaction for the risk of AKI. In the XGB model, two product terms were identified as relatively important risk factors for AKI: loop diuretics * H_2 blockers and cephalosporins * proton pump inhibitors. Although the product term of cephalosporins and proton pump inhibitors tended to be associated with increased risk of AKI, the individual effects of cephalosporins were suggested to reduce the risk, contrary to the product term. Therefore, this combination may not have an interaction for the risk of AKI. The product term of loop diuretics and H_2 blockers was identified as an important predictor in both the XGB and LLR models, and the latter model suggested that concomitant use of these drug classes has a potential drug-drug interaction for AKI. Furthermore, the individual and combined effects of these drug classes on the risk of AKI were robust in the sensitivity analyses. To our knowledge, no clinical studies have evaluated the association between H_2 blockers and AKI in a large population, but Fisher et al. have summarized more than 20 case reports of H_2 blocker-induced AIN (Fisher and Le Couteur, 2001). Since drug-induced AIN is a common cause of AKI (Perazella and Markowitz, 2010), it is not surprising that H_2 blockers are one of the risk factors for AKI. According to the drug-drug interaction checker by DrugBank, the combination of loop diuretic and H_2 blocker is suggested to have a drug-drug interaction that affects organic anion transporter 3 (OAT3), and its severity is moderate. SCr is excreted into urine through renal drug transporters such as OAT2, organic cation transporter 2 (OCT2), OCT3, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K (Nakada et al., 2019). Loop diuretics including furosemide and torasemide are known to be

human OAT1 (hOAT1), hOAT3, and hOAT4 inhibitors (Vormfelde et al., 2006; Jeong et al., 2015; Gharibkandi et al., 2022), and it has been reported that uptake of H_2 blockers such as famotidine and cimetidine into hOAT3-expressing cells decreases in the presence of an hOAT3 inhibitor (Tahara et al., 2005). That is, concomitant use of loop diuretics, which are OAT inhibitors, with H_2 blockers may increase the concentration of H_2 blockers in the blood. H_2 blockers including famotidine, cimetidine, and nizatidine are known as *in vitro* OAT2-, OCT2-, OCT3-, MATE1-, and MATE2-K-inhibitors, and these drugs increase SCr in healthy subjects (Nakada et al., 2019). For these reasons, we speculate that loop diuretics reduce renal excretion of H_2 blockers, and then OATs and OCTs expressed at the basolateral membrane of proximal tubule cells of the human kidney are inhibited by these drugs, resulting in elevated SCr. Therefore, although the relative importance of the individual and combined effects of loop diuretics and H_2 blockers in the XGB model was lower than that of well-known risk factors such as older age, sex, and medical history, it was suggested that the interaction between loop diuretics and H_2 blockers can increase the risk of AKI.

The present study has several limitations. First, there is a possibility of sampling bias because this study was a case-control study design using non-randomized data. Second, this study controlled potential confounding factors that were available and measurable, but failed to adjust for non-observed risk factors. For example, AKI is a common complication after cardiac surgery, and percutaneous coronary intervention is a known risk factor for AKI, and the incidence of cardiac surgery-induced AKI in Japanese patients is similar to that in other countries (Marenzi et al., 2013; Karrowni et al., 2016; Ikemura et al., 2020). However, no surgical information is recorded in NUSM's CDW. As another example, acute physiologic assessment and chronic health evaluation (APACHE) II, which is a scoring system for assessing the severity of ICU inpatients, is a risk factor for AKI in patients with severe sepsis (Chawla et al., 2007). Unfortunately, since there are no APACHE 2 scores recorded in our database, it is very difficult to adjust for APACHE II score as a covariate in this study. Finally, the database cannot access clinical information stored at other medical institutions. In this study, drug classes that were newly started within 1–7 days from the event date in the three hospitals were considered as suspected drug classes for AKI, but the drug classes may have been previously prescribed by another medical institution. However, the two ML models showed better predictive performance than the traditional statistical model, and the clear drug-drug interactions detected by interpreting these models may be useful for drug prescribing decision making.

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 human participants were reviewed and approved by The Ethics Committee of the Nihon University School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HA and SA contributed to the conception of the study. HA and TH performed data analysis. All authors were involved in the interpretation of the results. HA wrote the first version of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.2023.1176096/full#supplementary-material

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Safety profile of vascular endothelial growth factor receptor tyrosine-kinase inhibitors in pediatrics: a pharmacovigilance disproportionality analysis

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Introduction: existing research on children consists primarily of phase I/II clinical trials for VEGFR-TKI. System reports of safety on the use of VEGFR-TKI in pediatrics are lacking.

Aim: to investigate the safety profiles of VEGFR-TKI in pediatrics via the FDA Adverse Event Reporting System (FAERS).

Method: data regarding VEGFR-TKIs were extracted from the FAERS between 2004Q1 to 2022Q3 and categorized by the Medical Dictionary for Regulatory Activities (MedDRA). Population characteristics were analyzed, and reporting odds ratio (ROR) was performed to identify risk signals associated with VEGFR-TKI.

Results: 53,921 cases containing 561 children were identified in the database from 18 May 2005, to 30 September 2022. Among those in the system organ class, skin, subcutaneous tissue disorders, and blood and lymphatic system disorders in pediatrics contributed to over 140 cases. Palmar-plantar erythrodysesthesia syndrome (PPES) in VEGFR-TKI presented the most significant 340.9 (95% 229.2–507.0). And pneumothorax also gave a high reporting odds ratio of 48.9 (95% 34.7–68.9). For a specific drug, musculoskeletal pain gave a ROR of 78.5 (95% 24.4–252.6) in cabozantinib and oesophagitis in lenvatinib with a ROR of 95.2 (95% 29.5–306.9). Additionally, hypothyroidism presented a high signal, especially sunitinib, with a ROR of 107.8 (95% 37.6–308.7).

Conclusion: the present study explored the safety profile of VEGFR-TKI in pediatrics using the FAERS database. Multiple skin and subcutaneous tissue disorders, as well as blood and lymphatic system disorders, were common VEGFR-TKI-related AEs in system organ class. No serious hepatobiliary AEs were detected. For the specific AEs, PPES and pneumothorax were VEGFR-TKI-related AEs that presented significantly higher signals than those in the general population.

KEYWORDS

pharmacovigilance, FDA adverse event reporting system (FAERS), VEGFR tyrosine kinase inhibitors, pediatrics, adverse event (AE)

1 Introduction

Vascular endothelial growth factor (VEGF) and its receptor have crucial roles in the growth and subsequent physiologic homeostasis in endothelial cell neogenesis, angiogenesis, and neovascularization, as well as pathologic processes, such as cancer and ophthalmic disorders (Folkman, 1972; Ferrara, 2004). Widespread use of these agents has improved survival rates and is well-tolerated by a range of advanced adult cancers (Ferrara and Adamis, 2016). The reported efficacy of pazopanib, lenvatinib, and anlotinib also supported clinical use in children with solid tumors (Weiss et al., 2020; Gaspar et al., 2021a; Xu et al., 2021). Multiple meta-analyses have demonstrated that multi-target VEGFR-TKI in adults was linked to hand-foot skin reactions (HFSR), rashes, bleeding, hypertension, and cardiotoxicity in adults (Massey et al., 2015; Das et al., 2021; Hou et al., 2021). However, given the low prevalence and heterogeneity of pediatric cancers (Spini et al., 2022), there has not yet been enough research on the safety profile of anti-angiogenesis therapy in pediatric patients.

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem (Bohm et al., 2021). Pharmacovigilance is an essential component of drug safety monitoring, providing early identification of potential drug-related adverse events (AE) through active and voluntary surveillance efforts in a real-world setting (Dhodapkar et al., 2022). The FDA adverse event reporting system (FAERS) is a well-known AE spontaneous reporting system that documents numerous drug AE reports and medication errors and contains the largest and most normative data (Sakaeda et al., 2013). Disproportionality analysis in data mining algorithms (DMAs) such as proportionality reporting ratio (PRR) with associated χ^2 value and reporting odds ratio (ROR) with 95% confidence interval (CI) are used to generate a hypothesis for risk signals using FAERS database (Sharma et al., 2023). We sought to explore the safety of VEGFR-TKI via FAERS while focusing on potential AEs associated with using these drugs in pediatric patients.

The objective of this real-world pharmacovigilance for children aimed to systemically investigate the association of reported AEs and FDA-approved multi-target VEGFR-TKI based on the FAERS database. Clarifying potential AEs associated with VEGFR-TKI of the study can provide evidence for future clinical research and enable clinicians to select the most effective therapies in clinical practice.

2 Methods

2.1 Date source

Seven VEGFR-TKI, including sunitinib, sorafenib, pazopanib, regorafenib, axitinib, cabozantinib, and lenvatinib, have partly similar targets to anlotinib, were selected as study drugs. In the FAERS database, drug names are arbitrary, and both generic and brand names are included as the keyword in the subsequent analysis. In OpenVigil, drugs are named according to the U.S. Adopted Name (USAN) scheme. Hence, we directly leveraged OpenVigil to rely on the FAERS database for mapping the drug names to USAN. Finally, OpenVigil 2.1-MedDRA-v24 was implemented, comprising 258,346 children (age 1–17) in 5,236 256 cases with case_id deduplicated of FAERS data from 2004Q1 to 2022Q3. Because it is impossible to identify individual patients, informed consent was not required.

2.2 Data cleaning of FAERS

The data cleaning and mapping of drug names in FAERS were done by OpenVigil 2.1 (Bohm et al., 2016; Bohm et al., 2021). This step filtered all duplicate and ambiguous reports that contain misspelled names of drugs and pharma products that are not corrected according to Drugbank or Drug@FDA. The AEs related to disease progression, tumor recurrence, off-label use, and other product use errors were excluded from the analysis. In addition, the Medical Dictionary for Regulatory Activities (MedDRA [v25.0]) was utilized to classify the AEs automatically into the broadest system organ class (SOC) and specific preferred term (PT) categories. In the FAERS database, PT is well-accepted and utilized, and both PT and SOC will be adopted to identify any possible AE.

2.3 Statistical analysis

Data mining to measure the association of VEGFR-TKI with specific AEs in the PT category was performed by disproportionality analysis. The reporting odds ratio (ROR) based on the 2 × 2 crosstab (Supplementary Table S1) was utilized to identify the signals which indicate a potentially increased risk of drug-associated AEs. And risk-signal detection ratio (RSR) was defined as the ratio of a risk signal to all PT reports in each drug. The computation of ROR and the criteria of a significant signal are shown as follows:

$$ROR = \frac{(DE / dE)}{(De / de)} \times 100\%$$

$$SE(ln\,ROR) = \sqrt{\frac{1}{DE} + \frac{1}{De} + \frac{1}{dE} + \frac{1}{de}}$$

$$95\%CI = e^{ln(ROR) \pm 1.96 \times SE}$$

In population-specific outcomes, DE is the number of interest drug reports for suspect AE; dE is the number of other drug reports for suspect AE; De is the number of interest drug reports for other AE; de is the number of other drugs for other AE. It was considered significant if a potential risk signal simultaneously had ≥3 report cases, a ROR ≥2, a lower 95% confidence interval (CI) limit ≥1, and a Chi-square test (χ^2) ≥ 4. Any death or pharmacodynamic-related PTs, such as disease and tumor progression, were excluded from the result of detection presentation.

2.4 Subgroup analysis

In the subgroup analysis, the risk signal results of patients in each age group would be counted according to the SOC level. Then the results of each age group were arranged according to the number of cases, and the top 10 AEs for VEGFR-TKI comprehensive results in each age group were compared. Due to the small number of cases

TABLE 1 Clinical characteristics of pediatric patients using VEGFR-TKI.

Characteristics	Case number (n)	Case proportion (%)
All cases	53,921	
Pediatric cases	561	
Gender		
Male	275	49.02
Female	246	43.85
Unknown	40	7.13
Age		
1–4	34	6.06
5–11	160	28.52
12–17	367	65.42
Regions		
Asia	59	10.52
Europe	129	22.99
North America	352	62.75
Oceania	7	1.25
South America	3	0.53
Unspecified	11	1.96
Drugs		
Sorafenib	212	37.79
Pazopanib	145	25.85
Cabozantinib	82	14.62
Lenvatinib	59	10.52
Sunitinib	27	4.81
Regorafenib	25	4.46
Axitinib	11	1.96
Outcomes		
Hospitalization	154	27.45
Death	114	20.32
Life-Threatening	19	3.39
Disability	4	0.71

of young patients in the FAERS database at this stage, patients aged 1–4 and those aged 5–11 were combined for discussion, and subgroup analysis was performed with the group aged 12–17.

3 Results

3.1 Data population characteristics for VEGFR-TKI

The characteristics of patients and AEs are presented in Table 1. We retrieved 53,921 cases involving 193,477 AE reports between 18 May 2005 and 30 September 2022. Moreover, 561 cases (1.04%, 561 of 53,921) involved pediatric patients, in which females made a total of 246 cases (43.85%), and 40 of 561 (7.13%) were unknown. Hospitalization in outcome analysis was most frequent in 154 cases (27.45%). Sorafenib was the drug that generated the most reports among the 7 VEGFR-TKI (37.79%, 212 of 561), followed by pazopanib (25.85%, 145 of 561). At least 33 countries and regions were represented in the FAERS data, with North America contributing the majority of reports (62.75%, 352 of 561), followed by Europe (22.99%, 129 of 561). Additionally, the indication used for osteosarcoma took most cases (15.15%, 85 of 561), followed by acute myeloid leukemia (8.20%, 46 of 561).

3.2 Disproportionality analysis characteristics for VEGFR-TKI

We detected AE signals for seven VEGFR-TKI in pediatrics. Figure 1 shows how the risk signals were distributed according to the SOC, and the quantity of cases is shown in Supplementary Table S3.

Disproportionality analysis results detected 5,276 PTs, and the pediatrics caught a total of 561 PTs, in which 99 potential risk signals (PTs) targeted 17 organ systems sorted by MedDRA. In pediatrics, 283 of 561 (50.45%) were injury, poisoning, and procedural complications (Supplementary Table S3), which took most cases at the SOC level, but most at the PT level were associated with off-label use. Compared to the results of the general population (3.21%, 1,389 of 53,921), the proportion of blood and lymphatic system disorders (27.27%, 153 of 561) was significantly higher.

Figure 2 represents the RSR for each drug in the general population and pediatrics. The RSR for regorafenib (20.43%) was the highest among all included VEGFR-TKI in the general population. Axitinib detected the fewest risk PTs (9.23%) among the VEGFR-TKI. For pediatric patients, lenvatinib had the highest RSR detected (24.21%), followed by sorafenib (22.77%). Except for no significant difference in sorafenib, regorafenib, pazopanib, and cabozantinib between all populations and children, sunitinib in children were significantly lower than in the general population, whereas sorafenib and lenvatinib results were significantly higher (Supplementary Table S4).

3.3 Risk signal distribution in pediatric patients

We additionally presented the top 50 from a total of 99 risk signals in Table 2 for pediatrics and the comprehensive results of VEGFR-TKI based on adverse event reports. Skin and subcutaneous tissue disorders (n = 147) and blood and lymphatic system disorders (n = 153) were these steps' two most prevalent SOCs. None of the risk signals has been identified in the result of axitinib.

3.3.1 Investigations

Increased alanine aminotransferase (ALT) was the most commonly reported PT (ROR 5.0, 95%CI [3.1–8.1], n = 17) for the SOC level, followed by increased aspartate aminotransferase (AST; ROR 3.5, 95%CI [1.9–6.4], n = 11; Table 2). The strongest signal in this step was increased thyroid stimulating hormone (TSH, ROR 23.5, 95%CI [10.3–53.5], n = 6), and cabozantinib contributed most of the cases (ROR 138.8, 95%CI [55.3–348.1], n = 5). Although the increased blood pressure was a risk signal according to the combined result, no single VEGFR-TKI had a risk definition.

3.3.2 Blood and lymphatic system disorders

Blood and lymphatic system disorders (27.27%, 153 of 561) at the SOC level were also prevalent. Among this SOC in

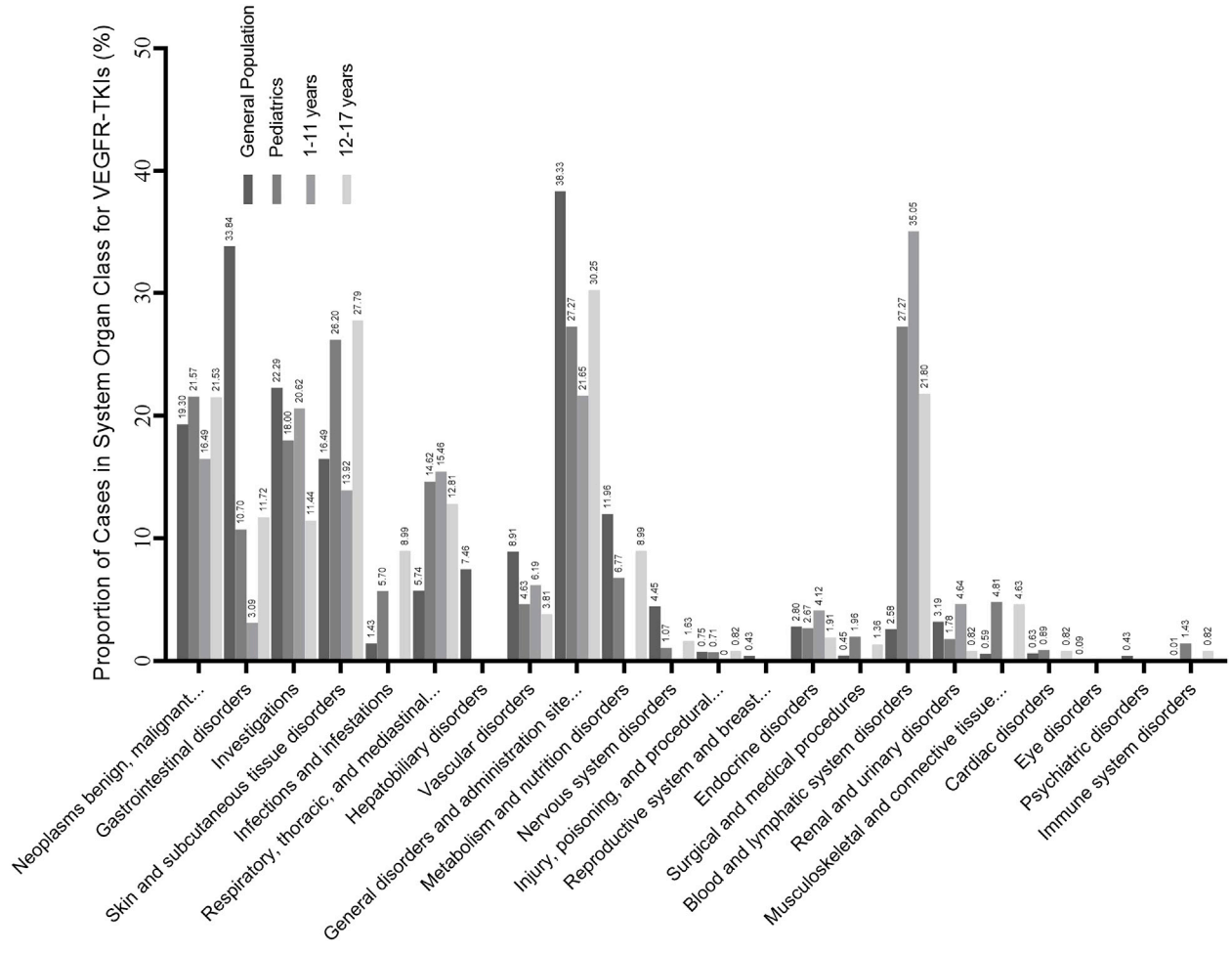

FIGURE 1
Proportion of cases in the risk preferred terms (PTs) identified in system organ class (SOC) level. The result is the ratio of the number of cases involved in the risk signal to the total number of cases. The general population contains all the records exported from the FAERS database. Subgroup analysis is also contained, and pediatrics is divided into the younger age group (1–11 years) and the older age group (12–17 years).

Table 2, anemia had the most cases (ROR 6.9, 95%CI [4.4–10.6], n = 21) and bone marrow failure (ROR 12.4, 95%CI [11.1–25.8], n = 23) presented a strong signal, followed by lymphopenia (ROR 11.6, 95%CI [5.5–24.6], n = 7). Sorafenib gave strong signals for all 9 PTs, especially bone marrow failure (ROR 36.2, 95%CI [22.2–59.0], n = 18), pancytopenia (ROR 29.8, 95%CI [18.7–47.4], n = 20) and lymphopenia (ROR 26.6, 95%CI [11.7–60.2], n = 6). Furthermore, lenvatinib had stronger signals for anemia (ROR 15.6, 95%CI [6.2–39.0], n = 5), febrile neutropenia (ROR 24.2, 95%CI [11.9–49.2], n = 9) and neutropenia (ROR 8.3, 95%CI [3.0–22.9], n = 4) than the other VEGFR-TKI.

3.3.3 Skin and subcutaneous tissue disorders

Cases of skin and subcutaneous tissue disorders (26.20%, 147 of 561) were second only to injury, poisoning, and procedural complications. In the SOC level of Skin and subcutaneous tissue disorders, palmar-plantar eythrodysesthesia syndrome (PPES) was the most frequent PT with the highest ROR (340.9, 95%CI [229.2–507.0], n = 41) and sorafenib contributed most of the PPES cases and had the strongest signal (ROR 745.4, 95%CI [484.4–1,146.9], n = 34). In addition, the high RORs were also detected in alopecia (ROR 10.9, 95%CI [7.1–16.8], n = 22) and hair color changes (ROR 143.4, 95%CI [73.3–280.5], n = 11). For hair color changes, both pazopanib (ROR 220.6, 95%CI [86.5–562.7], n = 5) and cabozantinib (ROR 225.4, 95%CI [68.8–737.9], n = 3) presented high-risk signals respectively.

3.3.4 Other SOCs

Moreover, VEGFR-TKI showed a strong signal for pneumothorax (ROR 48.9, 95%CI [34.7–68.9], n = 38; Table 2), particularly for cabozantinib (ROR 104.0, 95%CI [54.8–197.5], n = 11) and lenvatinib (ROR 185.2, 95%CI [99.6–344.4], n = 13). In musculoskeletal disorders, the signal of musculoskeletal pain was also with a high ROR (13.7, 95%CI [5.6–33.4], n = 5), particularly in lenvatinib (ROR 78.5, 95%CI [24.4–252.6], n = 3). And oesophagitis of gastrointestinal disorders (ROR 95.2, 95%CI [29.5–306.9], n = 3) in lenvatinib was higher than in any other VEGFR-TKI. In endocrine disorders, hypothyroidism presented the highest ROR (21.3, 95%CI [12.6–35.9], n = 15), especially for sunitinib (ROR 107.8, 95%CI [37.6–308.7], n = 4).

TABLE 2 The ROR of the top 50 AE reports in pediatrics.

SOC	PT	VEGFR-TKI		Sunitinib		Sorafenib		Pazopanib		Cabozantinib		Regorafenib		Lenvatinib	
		N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
Investigations	ALT increased	17	5.0 (3.1, 8.1)	1	5.1 ✗ (0.7, 37.3)	7	5.4 (2.5, 11.4)	2	2.2 ✗ (0.5, 8.8)	6	12.3 (5.4, 28.4)	1	6.6 ✗ (0.9, 48.7)		
	AST increased	11	3.5 (1.9, 6.4)	1	5.7 ✗ (0.8, 41.5)	3	2.5 ✗ (0.8, 7.8)			6	13.7 (6.0, 31.5)	1	7.3 ✗ (1.0, 54.1)		
	weight decreased	11	2.3 (1.3, 4.2)	3	11.9 (3.6, 38.9)	4	2.2 ✗ (0.8, 5.9)	3	2.4 ✗ (0.8, 7.5)	1	1.4 ✗ (0.2, 10.0)				
	platelet count decreased	10	4.3 (2.3, 8.0)	1	7.6 ✗ (1.0, 55.7)	2	2.2 ✗ (0.6, 9.0)	2	3.2 ✗ (0.8, 13.1)	1	2.9 ✗ (0.4, 20.6)			4	16.6 (6.0, 45.7)
	blood pressure increased	8	5.6 (2.8, 11.3)	2	25.7 ✗ (6.1, 107.9)	1	2.6 ✗ (0.4, 13.0)	1	2.6 ✗ (0.4, 18.9)	2	9.5 ✗ (2.3, 38.8)	2	33.6 ✗ (7.9, 142.7)		
	LDH increased	6	7.4 (3.3, 16.6)			4	13.1 (4.8, 35.3)	1	4.6 ✗ (0.6, 33.2)			1	28.2 ✗ (3.8, 209.2)		
	TSH increased	6	23.5 (10.3, 53.5)							5	138.8 (55.3, 348.1)	1	87.6 ✗ (11.8, 652.2)		
	neutrophil count decreased	6	4.7 (2.1, 10.5)			3	6.2 (2.0, 19.3)							3	22.3 (7.0, 71.3)
	blood bilirubin increased	5	4.1 (1.7, 9.9)			4	8.7 (3.2, 23.4)			1	5.5 ✗ (0.8, 39.5)				
	ejection fraction decreased	5	18.6 (7.6, 45.6)			3	29.2 (9.2, 92.3)	2	28.0 ✗ (6.9, 114.1)						
	hepatic enzyme increased	5	2.8 (1.2, 6.8)			4	6.0 (2.2, 16.1)	1	2.1 ✗ (0.3, 15.3)						
Blood and Lymphatic	anaemia	21	6.9 (4.4, 10.6)			10	8.6 (4.6, 16.3)	3	3.6 ✗ (1.2, 11.4)	1	2.1 ✗ (0.3, 15.3)	2	15.2 ✗ (3.6, 64.4)	5	15.6 (6.2, 39.0)
	bone marrow failure	23	12.4 (11.1, 25.8)	1	12.4 ✗ (1.7, 90.9)	18	36.2 (22.2, 59.0)	1	2.6 ✗ (0.4, 18.8)					3	19.9 (6.2, 63.7)
	febrile neutropenia	20	5.2 (3.3, 8.1)			10	6.9 (3.6, 13.0)	1	1.0 ✗ (0.1, 6.8)					9	24.2 (11.9, 49.2)
	neutropenia	18	3.9 (2.5, 6.3)	1	3.8 ✗ (0.5, 27.9)	12	7.1 (4.0, 12.7)	1	0.8 ✗ (0.1, 5.8)	1	1.4 ✗ (0.2, 10.4)			4	8.3 (3.0, 22.9)
	pancytopenia	21	11.2 (7.2, 17.4)	1	9.1 ✗ (1.2, 66.8)	20	29.8 (18.7, 47.4)								
	thrombocytopenia	16	4.6 (2.8, 7.6)	3	16.2 (4.9, 53.2)	6	4.5 (2.0, 10.2)	1	1.1 ✗ (0.2, 7.7)	4	7.9 (2.9, 21.7)	2	13.6 ✗ (3.2, 57.8)	2	5.3 ✗ (1.3, 21.7)
	lymphadenopathy	14	8.6 (5.0, 14.6)			13	21.8 (12.4, 38.3)	1	2.3 ✗ (0.3, 16.2)						
	lymphopenia	7	11.6 (5.5, 24.6)			6	26.6 (11.7, 60.2)					1	37.6 ✗ (5.1, 278.8)		
	myelosuppression	9	9.1 (4.7, 17.7)			5	16.5 (6.8, 40.4)	2	9.4 ✗ (2.3, 38.2)					1	11.4 ✗ (1.6, 82.3)
Skin	PPES	41	340.9 (229.2, 507.0)	2	183.5 ✗ (43.3, 777.4)	34	745.4 (484.4, 1,146.9)	1	18.7 ✗ (2.6, 134.6)	2	67.9 ✗ (16.5, 279.9)	2	239.3 ✗ (55.7, 1,027.7)		

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TABLE 2 (*Continued*) The ROR of the top 50 AE reports in pediatrics.

SOC	PT	VEGFR-TKI		Sunitinib		Sorafenib		Pazopanib		Cabozantinib		Regorafenib		Lenvatinib	
		N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
	rash	29	2.3 (1.6, 3.3)			22	5.4 (3.5, 8.4)			5	3.0 (1.2, 7.4)	2	4.1 ✗ (1.0, 17.2)		
	alopecia	22	10.9 (7.1, 16.8)	2	17.6 ✗ (4.2, 73.6)	11	14.5 (7.9, 26.6)	8	15.2 (7.5, 31.2)			1	11.0 ✗ (1.5, 81.1)		
	skin toxicity	15	128.2 (72.5, 226.5)			14	323.5 (178.5, 586.5)			1	46.6 ✗ (6.4, 339.3)				
	hair colour changes	11	143.4 (73.3, 280.5)	1	186.3 ✗ (25.0, 1,390.6)	2	55.8 ✗ (13.5, 230.8)	5	220.6 (86.5, 562.7)	3	225.4 (68.8, 737.9)				
	dry skin	9	4.0 (2.0, 7.7)	1	7.8 ✗ (1.1, 57.1)	8	9.5 (4.7, 19.3)								
Respiratory	pneumothorax	38	48.9 (34.7, 68.9)	2	44.5 ✗ (10.6, 186.6)	4	12.8 (4.7, 34.6)	4	18.7 (6.9, 50.8)	11	104.0 (54.8, 197.5)	2	58.0 ✗ (13.6, 246.7)	13	185.2 (99.6, 344.4)
	pleural effusion	13	9.1 (5.2, 15.8)			5	9.1 (3.7, 22.1)	4	10.6 (3.9, 28.6)	3	14.2 (4.5, 44.9)				
	respiratory failure	12	3.1 (1.7, 5.5)	2	9.4 ✗ (2.2, 39.3)	3	2.0 ✗ (0.6, 6.3)	4	3.9 (1.5, 10.7)	1	10.7 ✗ (1.5, 77.4)			2	4.8 ✗ (1.2, 19.5)
	hypoxia	8	4.4 (2.2, 8.9)	1	9.8 ✗ (1.3, 71.9)	2	2.9 ✗ (0.7, 11.6)							5	27.2 (10.9, 68.2)
	respiratory distress	8	2.6 (1.3, 5.2)			3	2.6 ✗ (0.8, 8.0)			1	2.2 ✗ (0.3, 15.7)			5	16.0 (6.4, 40.1)
General disorders	fatigue	23	2.4 (1.6, 3.6)	4	8.0 (2.8, 22.8)	8	2.2 ✗ (1.1, 4.4)	4	1.6 ✗ (0.6, 4.2)	5	3.6 ✗ (1.5, 8.9)	4	10.7 (3.7, 31.1)		
	drug intolerance	18	16.6 (10.3, 26.7)			18	46.2 (28.3, 75.4)								
	mucosal inflammation	15	9.3 (5.6, 15.7)			6	9.8 (4.3, 22.1)	6	14.3 (6.3, 32.6)					3	17.4 (5.4, 55.6)
	asthenia	10	2.4 (1.3, 4.5)	2	8.8 ✗ (2.1, 37.0)	4	2.5 ✗ (0.9, 6.8)	3	2.8 ✗ (0.9, 8.7)	1	1.6 ✗ (0.2, 11.6)				
	general physical health deterioration	7	3.6 (1.7, 7.6)	2	18.9 ✗ (4.5, 79.4)	5	6.8 (2.8, 16.7)								
Musculoskeletal	pain in extremity	11	2.9 (1.6, 5.3)	1	4.7 ✗ (0.6, 34.4)	3	2.1 ✗ (0.7, 6.5)	3	3.0 ✗ (0.9, 9.5)	1	1.8 ✗ (0.2, 12.7)	1	6.1 ✗ (0.8, 44.8)	2	4.9 ✗ (1.2, 20.2)
	myalgia	6	3.1 (1.4, 7.0)	1	9.2 ✗ (1.3, 67.7)	1	1.3 ✗ (0.2, 9.6)	2	3.9 ✗ (0.9, 16.0)	1	3.5 ✗ (0.5, 25.1)			1	4.8 ✗ (0.7, 34.4)
	bone pain	5	9.0 (3.7, 21.8)			4	19.0 (7.0, 51.5)							1	16.4 ✗ (2.3, 118.7)
	musculoskeletal pain	5	13.7 (5.6, 33.4)	1	48.4 ✗ (6.6, 356.7)							1	62.6 ✗ (8.4, 464.9)	3	78.5 (24.4, 252.6)
Gastrointestinal	diarrhoea	36	3.9 (2.8, 5.5)	4	8.2 (2.9, 23.3)	14	4.0 (2.3, 6.9)	8	3.3 (1.6, 6.7)	8	6.1 (2.9, 12.7)	1	2.4 ✗ (0.3, 17.6)	1	1.0 ✗ (0.1, 6.9)
	stomatitis	11	8.7 (4.8, 15.9)	2	28.7 ✗ (6.8, 120.3)	5	10.4 (4.3, 25.3)	1	2.9 ✗ (0.4, 21.1)	1	5.2 ✗ (0.7, 37.7)			2	14.6 ✗ (3.6, 59.8)

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TABLE 2 (*Continued*) The ROR of the top 50 AE reports in pediatrics.

SOC	PT	VEGFR-TKI		Sunitinib		Sorafenib		Pazopanib		Cabozantinib		Regorafenib		Lenvatinib	
		N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)	N	ROR (95% CI)
	oesophagitis	5	16.6 (6.8, 40.6)					1	12.7 ✗ (1.8, 91.5)	1	22.2 ✗ (3.1, 160.2)			3	95.2 (29.5, 306.9)
Metabolism	decreased appetite	18	2.7 (1.7, 4.4)	2	6.5 ✗ (1.6, 27.4)	9	4.3 (2.2, 8.5)	2	1.4 ✗ (0.3, 5.5)	2	2.4 ✗ (0.6, 9.9)	2	8.5 ✗ (2.0, 36.2)		
	dehydration	11	3.7 (2.1, 6.8)	1	6.0 ✗ (0.8, 44.0)	1	0.9 ✗ (0.1, 6.3)	2	2.6 ✗ (0.6, 10.4)	2	4.6 ✗ (1.1, 18.7)	1	7.8 ✗ (1.0, 57.4)	3	9.6 (3.0, 30.8)
	hypophosphataemia	5	15.7 (6.4, 38.4)	1	55.2 ✗ (7.5, 406.7)					1	20.9 ✗ (2.9, 150.8)	1	71.3 ✗ (9.6, 530.2)	2	58.4 ✗ (14.1, 240.7)
Vascular	hypertension	20	4.7 (3.0, 7.4)	1	4.1 ✗ (0.6, 29.9)	10	6.3 (3.3, 11.8)	3	2.6 ✗ (0.8, 8.3)	3	4.7 ✗ (1.5, 15.0)	1	5.3 ✗ (0.7, 39.0)	2	4.3 ✗ (1.0, 17.6)
Infections	gastroenteritis	5	5.5 (2.3, 13.2)			4	11.6 (4.3, 31.4)							1	10.1 ✗ (1.4, 72.8)
Nervous system	paraesthesia	6	3.2 (1.4, 7.2)			6	8.6 (3.8, 19.4)								
Endocrine	hypothyroidism	15	21.3 (12.6, 35.9)	4	107.8 (37.6, 308.7)	1	3.5 ✗ (0.5, 25.2)	4	21.1 (7.8, 57.3)	3	28.2 (8.9, 89.7)	1	31.2 ✗ (4.2, 231.1)	2	25.4 ✗ (6.2, 104.5)

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; To obtain robust results and reduce the false positive signals, signal values were only calculated for complications with at least 3 records. A signal was defined as both $\chi^2 > 4$ and lower 95% CI > 1. Negative signals were highlighted in white with✗.

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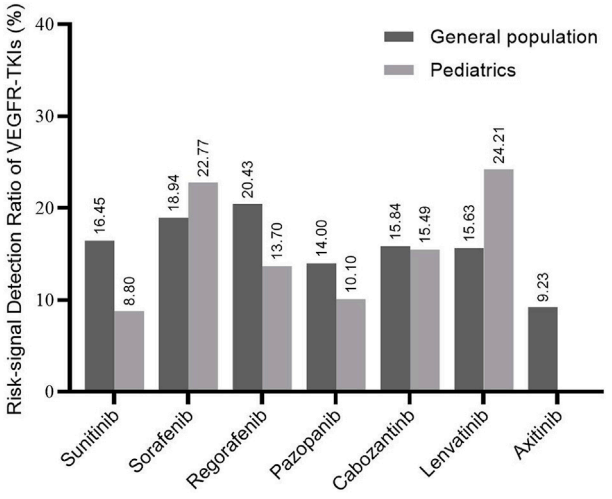

FIGURE 2
Risk-signal detection ratio for each VEGFR-TKI. The result is the ratio of the number of risk signals involved in each kind of VEGFR-TKI to the total recorded signals. The general population contains all the records exported from the FAERS database.

3.3.5 Subgroup analysis

As shown in Figure 1. Pediatrics in the younger age group (1–11 years) and the older age group (12–17 years) had similar results in SOC level AEs such as respiratory, thoracic, and mediastinal disorders and blood and lymphatic system disorders. However, the younger age group had a higher proportion of blood and lymphatic system diseases (35.05%, 68 of 194) than the older group (21.80%, 80 of 367). In comparison, the older group had a lower proportion of skin and subcutaneous tissue diseases (27.79%, 102 of 367). AEs in specific PT levels are shown in Table 3. PPES had a higher risk signal in both groups (ROR 222.70 and 324.26, respectively). For hypothyroidism, pediatrics in the younger group showed a significant risk signal (ROR 35.65, 95%CI [17.34–73.30], n = 8), whereas the older group had a strong risk signal for pneumothorax (ROR 71.63, 95%CI [47.83–107.27], n = 30).

TABLE 3 Subgroup analysis of the top 10 specific risk signals in the younger age group (1–11 years) and older age group (12–17 years) for VEGFR-TKI.

PT	ROR	95% CI	Case reports	(%)
1–11 (n = 194)				
drug intolerance	43.95	26.10–74.01	16	8.25
bone marrow failure	26.19	15.38–44.58	15	7.73
pancytopenia	20.98	12.34–35.66	15	7.73
skin toxicity	252.87	136.88–467.13	14	7.22
lymphadenopathy	24.26	13.75–42.82	13	6.70
ALT increased	9.32	5.19–16.73	12	6.19
pleural effusion	18.87	9.93–35.83	10	5.15
AST increased	6.76	3.33–13.74	8	4.12
hypothyroidism	35.65	17.34–73.30	8	4.12
PPES	222.70	100.64–492.81	8	4.12
12–17 (n = 367)				
PPES	324.26	201.59–521.57	33	8.99
pneumothorax	71.63	47.83–107.27	30	8.17
diarrhoea	5.54	3.76–8.16	28	7.63
pyrexia	2.33	1.52–3.59	22	5.99
Rash	2.60	1.67–4.04	21	5.72
anaemia	10.20	6.39–16.28	19	5.18
febrile neutropenia	10.07	6.23–16.26	18	4.90
alopecia	9.65	5.90–15.78	17	4.63
Fatigue	2.08	1.27–3.38	17	4.63
hypertension	4.93	2.88–8.44	14	3.81

4 Discussion

Malignancies in pediatrics present a significant challenge to physicians, partly because of the rarity of occurrence and the relative scarcity of data compared with adult tumors. Vincristine, cyclophosphamide, and irinotecan are chemotherapeutic drugs that have emerged as part of therapeutic regimens in various solid tumors in the last 60 years (Tsakatikas et al., 2021). As previous clinical studies described, combing anti-angiogenesis therapy could provide strong synergistic effects (Weiss et al., 2020; Gaspar et al., 2021b; Xu et al., 2021). Gradually, these drugs have become an increasingly common practice in the setting of limited pediatric oncology treatment options. Most anti-angiogenic treatments targeting VEGFR in pediatrics have been investigated up to phase I/II study, and at least four of these relevant clinical studies discuss safety in detail (Wetmore et al., 2016; Verschuur et al., 2019; Brose et al., 2021; Geoerger et al., 2021). Of the VEGFR-TKI included in our analysis, only cabozantinib has been approved by the FDA for children over 12 with differentiated thyroid cancer (DTC) (Duke et al., 2022). Therefore, clinicians' awareness of common and uncommon VEGFR-TKI-related AEs is of great importance to improve the quality of healthcare for pediatrics.

According to the SOC conducted by disproportionality analysis, the proportion of blood and lymphatic system disorders and skin and subcutaneous tissue disorders in children was significantly higher than in the general population, but the gastrointestinal disorders proportion was significantly lower. Except for axitinib, without any risk signal being detected due to its limited case of uses, the safety profiles of each VEGFR-TKI were not similar for the limited data and biased drugs used. Notably, although sunitinib presented a low RSR, its safety in children remained to be further studied, considering only 22 cases with 124 PT reports.

At the SOC level, although ALT and AST increases were universal for AEs among these drugs in the investigations, few severe hepatobiliary disorders were detected compared to the general population. Skin and subcutaneous tissue disorders and blood and lymphatic system disorders were the most common SOCs in pediatrics. As for blood and lymphatic system disorders, anemia presented a high

signal in many cases. In clinical practice, anemia is a common but often underestimated and undertreated event. Anemia and its related fatigue are associated with poor prognosis in cancer patients and were shown to be correlated with a 65% overall increase in the risk of mortality (Harper and Littlewood, 2005; Lang et al., 2017). Barni S et al. revealed that TKIs were associated with higher and more significant risk ratios (RR) (Barni et al., 2012). One possible explanation was that blockade of FLT-3 and Kit by TKIs leads to anemia-induced hematopoietic insufficiency (Weisel et al., 2007; Kent et al., 2008; Williams et al., 2013; Lang et al., 2017). Secondly, microvascular thrombotic hemolytic anemia was also found in some studies (Talebi et al., 2012; Haksöyler and Paydaş, 2021). In addition, we also found that bone marrow failure, lymphopenia, pancytopenia, *etc.*, 9 PTs were risk AEs. However, given the high risk of etoposide (ROR 23.21) in combined use and being reported as a primary suspect drug, the relationship between the risk and VEGFR-TKI remains to be clarified.

Our analysis of the single AE found that the PPES, also named hand-foot skin reaction (HFSR), was the most frequent in pediatrics, followed by pneumothorax and diarrhoea, with over 30 case reports.

Among the 50 included PTs, the PPES signal was the strongest. We observed that sorafenib contributed to most of the cases, and among all included VEGFR-TKI, only sorafenib was judged to be associated with the occurrence of PPES; the signal was much higher than other agents. VEGFR was reported to be the primary cause of PPES, which was consistent with the findings of our study (Lacouture et al., 2008; Chanprapaph et al., 2016). In addition, significantly improved clinical benefit was found in this population compared to patients with advanced HCC who did not develop the HFSR (Vincenzi et al., 2010). The mechanism of PPES is not yet clear cause PPES most commonly occurs on palmoplantar surfaces, so in general, PPES is related to the repair of skin damage (Lacouture et al., 2008; Chanprapaph et al., 2016). Some previous studies have proved that its occurrence may result from a combination of multiple factors. First, TKI is cytotoxic to keratinocytes (Yamamoto et al., 2014; Zimmerman et al., 2016), and second, it also inhibits angiogenesis in wound repair (Eming and Krieg, 2006; Apte et al., 2019). Third, inhibiting immune downmodulate after VEGF is inhibited may also lead to one of the factors of PPES(Motz and Coukos, 2013; Apte et al., 2019). Effective wound repair would be hampered by the inhibition of VEGF in downregulating immune responses brought on by these agents, which could result in PPES.

Intriguingly, we discovered that the pneumothorax signal following VEGFR-TKI use in kids was second only to PPES. This phenomenon was generally prevalent in the six included VEGFR-TKI and significantly higher than the signal in the general population (ROR 6.09). The signal strength was also significantly more than that of the same event in adults and not listed on the label. In two retrospective studies and a phase II single-arm multicenter study involving anti-angiogenesis agents used in children and adolescents, the incidence of pneumothorax during treatment ranged from 13.3% to 33% (Interiano et al., 2015; Italiano et al., 2020; Bodea et al., 2022). Subsequent research proved peripheral lung lesions or necrosis of pleural lesions due to the tumor directly involving the pleura after chemotherapy might be the cause of pneumothorax rather than the direct toxicity of chemotherapy drugs (Sabath et al., 2018; Aiba et al., 2021), and solid tumors account for 30% of all pediatric cancers (Spini et al., 2022). Factually, after reviewing the raw data, we found the indications of cases who reported pneumothorax with VEGFR-TKI were all soft tissue sarcoma. Second, the ROR results for the drugs in the combined medications, like ifosfamide, etoposide, everolimus, *etc.*, were much lower when the above method was used to calculate them than the former. The existing literature confirmed that sarcoma usually metastasizes with a stable frequency, most children treated with VEGFR-TKI are already advanced, and lung metastases are more likely (Burnei et al., 2013; Interiano et al., 2015; Murugan et al., 2018; Andión Catalán et al., 2020). Considering the data from FAERS depends on spontaneous reporting, a significant bias would be presented after correlating the presence or not of metastases from sarcoma with the occurrence of pneumothorax. Thus, in conjunction with the previous article, the incidence of pneumothorax is associated with the clinical benefit of using these drugs, but due to its high risk, one should be alert and preventative against the occurrence of this AE during therapy with VEGFR-TKI.

We found that cabozantinib carries a higher risk signal of musculoskeletal pain than other drugs and that lenvatinib also carries a greater risk of oesophagitis. But because these two AEs were only reported in a small number of children, the final ROR seemed too high. More research needs to be done to determine if two AEs are linked to using VEGFR-TKI. In addition, we also noticed that VEGFR-TKI, especially sunitinib, pazopanib, and cabozantinib, presented a significant signal of hypothyroidism. The possible mechanisms of TKI-induced hypothyroidism include the degeneration of the capillaries in the thyroid; the TKI-induced apoptosis of the thyroid follicular cells; and altered thyroid hormone metabolism (Liao et al., 2021; Basolo et al., 2022). These results showed that TKI-induced hypothyroidism was more related to thyroid atrophy caused by the first two situations. Therefore, because of the effect on child growth, thyroid function needs to be closely monitored when using VEGFR-TKI, then reduced or stopped according to the situation above.

However, due to its characteristics, FAERS data only represents a portion of the healthcare population. The trial sponsor, affected participant, and general practitioner may report this data because it was spontaneously reported. The information on disease severity or outcomes is lacking, and the data may contain duplicate, incomplete, inaccurate, and omitted reports. Second, we utilized the ROR method in the analysis. Although the ROR method is simple and easy to understand, the results are highly susceptible to individual values. The statistic fluctuates greatly if the cell frequency is small. Thus, when signal detecting according to the standard, we focused on AEs with many cases to avoid false positives. Finally, Due to the particularity of children, VEGFR-TKIs are usually combined with conventional radiotherapy and chemotherapy for advanced-stage tumors for children in clinical practice. They are rarely used as a monotherapy. Therefore, the sensitivity analysis of these concomitant drugs' effect on this population could not be performed.

Overall, our study showed that the risk profiles of VEGFR-TKI vary. By analyzing the comprehensive characterization of these drugs based on the FAERS, new, severe, or unexpected AE signals can be identified. Although using the FAERS database has limitations, the comparative exploration of VEGFR-TKI and background factors through disproportionality analysis can partially avoid the influence of confounding factors in cancer patients (Uetake et al., 2018). These results can provide evidence for future clinical research and enable clinicians to choose the optimal therapies in clinical practice.

5 Conclusion

The present study explored the safety profile of VEGFR-TKI in pediatrics using the FAERS database. Multiple skin and subcutaneous tissue disorders, as well as blood and lymphatic system disorders, were common VEGFR-TKI-related AEs in SOC. No serious hepatobiliary AEs were detected. For the specific AEs, PPES and pneumothorax were VEGFR-TKI-related AEs that presented significantly higher signals than those in the general population. Future observational studies, population cohorts, and clinical trials are required to validate the AEs of pediatric VEGFR-TKI used off-label.

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

YX, CZ, and GL conceptualized and designed the study. YX and GL provisioned study material. YX and SF assembled and interpreted the data, and YX drafted the manuscript. YX, SF, GL, and CZ revised and approved the final 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

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1160117/full#supplementary-material

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Utilisation of drugs for the treatment of psychiatric diseases in the pediatric population: focus on off-label use

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Psychotropics are increasingly used in pediatrics, often as off-label medicines. The guarantees of safety and efficacy are not always granted in clinical practice compared to adult authorised indications. A retrospective observational study was done to estimate the prevalence of psychotropic use in pediatric subjects of Catalonia (Spain). Anonymised data on dispensation of psychotropics to pediatric patients, demography and other related data were obtained by the local healthcare management for the period 2008–2017. Estimation of off-label use was done through description of drug dispensations with no authorised use related to age range. The prevalence of psychotropics was 40.8–64.2 per 1,000 pediatric inhabitants. Hydroxyzine-only represented two-thirds of dispensations, and when removed, the prevalence dropped to 26.4–32.2 per 1,000 pediatric inhabitants. Adolescents and boys were more likely to receive a psychotropic. Psychostimulants had the highest exposure rate, mainly due to methylphenidate. Off-label use was observed in 12% of subjects, corresponding to 4.6% of all dispensed psychotropics with boys being more exposed. The proportion of off-label use vs. labelled use was higher in younger populations. Aripiprazole had the highest off-label frequency. Our data support the frequent reality of off-label use in pediatrics, despite the potential underestimation related to the selected off-label definition. There is an urgent need to systematically ascertain effectiveness and any potential adverse events in the off-label pediatric setting, and to generate valuable information for risk-benefit assessment in these populations where extrapolation from adults is not reliable.

KEYWORDS

children, adolescents, pediatric, psychiatry, drugs, psychotropics, prevalence, off-label

1 Introduction

There is a great relevance in ensuring that appropriate efforts are directed to preserve, promote, restore and protect mental health, as a key axis of the overall subject and community wellbeing and functionality (World Health Organization, 2018). Global estimates suggest that roughly 1 in 5 children and adolescents present with a mental

health condition, that half of the mental conditions start by the age of 14 years old, while suicide is considered the third leading cause of death in adolescents aged 15–19 years old (World Health Organization, 2021; World Health Organization, 2023). Hence, the epidemiology of mental disorders in the pediatric population still has room for improvement, while few and generally fragmented data are available on the prevalence of the different conditions and their treatments, since many countries do not have the appropriate information systems to obtain them.

Children and adolescents have been traditionally considered a neglected population from a therapeutic perspective. Reasons include the intrinsic clinical difficulty to identify mental signs and symptoms in pediatric patients along with the developmental changes, the lack of awareness on the frequency and importance of mental conditions in children, social stigma on mental disorders (World Health Organization, 2013), as well as several other reasons acting as barriers to the development of new drugs and evidence-based treatment options for this population (Koelch et al., 2008; Hoffman et al., 2014).

Data on the use of drugs are important to understand the epidemiology of a specific health problem, especially in a population for which the participation in clinical studies is often not considered ethical or easily manageable. Therefore, real-world evidence can be useful for prescribers and patients by complementing the information derived from randomised clinical trials. Moreover, data on effectiveness in clinical practice may complement efficacy and safety data in groups of patients not included in clinical trials, wider samples and diverse cultural and social settings, allowing to clarify uncertainties and to complete missing information (Lapeyre-Mestre et al., 2013). In a literature search for studies describing the use of psychotropics in children and adolescents in Spain, we found only one population-based study, but the subjects were of the age of 15 years and above (Barceló et al., 2016).

We aimed to describe the use of psychotropics in the pediatric population in the region of Catalonia (Spain) and their trends in time, in order to identify the main areas of exposure to psychotropic drugs used in this vulnerable population in our setting.

2 Materials and methods

We conducted a retrospective observational population-based quantitative study of psychotropic consumption in the population below 18 years of age residing in the region of Catalonia (Spain) and covered by the social security. Pharmacy billing data from the Catalan Health Service (*CatSalut*) for a 10-year period (2008–2017) were used and linked as per the single identification number of the Catalan Health Service to the data contained in the central insurance registry for demographics and insurance status. The pharmacy reimbursement data are considered representative of the region's population, since all residents in Catalonia (approximately 7.72 million, 16.4% of Spain's total population) (Instituto Nacional de Estadística, 2018) are covered by the public system. The data used for this analysis were provided by the *Agència de Qualitat i Avaluació Sanitàries de Catalunya* (*AQuAS*) through the *PADRIS* program (*Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya*) upon records linkage, by personnel not linked to the study team and anonymised the data following a procedure aiming to maintain the data confidentiality via double encryption and removal of personal identifiers.

The extracted data were reviewed for their quality and completion. No further action was done concerning the missing data as their collection was not feasible due to the retrospective design of the study. Before the actual analysis, duplicate cases were detected and deleted. The analysis of the study was descriptive: categorical variables were described using frequencies and percentages, while the use of psychotropics was defined as per the pharmacy dispensed number of medicines following their prescription by a physician and given as prevalence by 1,000 Catalan inhabitants aged less than 18 years. As psychotropics we included the following ATC groups as defined by WHO: antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A), psychostimulants (N06B) and drugs used in addictive disorders (N07B). The off-label use was approached through analysis of drugs dispensed out of the authorised age range (if any) for each product as defined from products labelling, in a subset of data between 2015 and 2017 and was presented using percentages. The listing of the most frequently off-label dispensed psychotropics was described for 1 year (2017).

The statistical analysis was performed using the statistical package SAS v9.4 (SAS Institute, Cary, NC, United States).

The protocol of this observational study was authorised by the relevant ethics committee in Catalonia, but no further authorisation or signed patient consents were needed according to national regulation.

3 Results

3.1 Prevalence of psychotropics use

During the study period (2008–2017) 449,196 subjects with at least one psychotropic drug dispensed from the Catalan health reimbursement system were identified in the concerned region; 137 patients were excluded as they had potential errors as regards the sex variable, and therefore our initial sample was finally of 449,059 pediatric subjects.

The annual prevalence of use of psychotropics was between 40.8 and 64.2 per 1,000 pediatric inhabitants with at least one psychotropic dispensed within the 10-year period of this study. Pediatric subjects under hydroxyzine-only treatment represented two-thirds of the dispensations. After removing the hydroxyzine-only dispensations data, the prevalence of psychotropic use in the pediatric population of this targeted exposure was between 26.4 and 32.2 per 1,000 pediatric inhabitants. Adolescents and boys were more likely to receive a psychotropic drug. Table 1 presents in detail the prevalence of use in the Catalan pediatric population of our setting in total and per age groups.

Psychostimulants had the highest prevalent exposure in our setting (Figure 1) and boys were much more exposed compared to girls. Methylphenidate was found to be the most prevalent psychotropic dispensed to the Catalan pediatric population, but antipsychotics and antidepressants were also highly ranked (see Supplementary Material S1).

3.2 Off-label use

The subset of the pediatric population used for the off-label analysis consisted of 66,824 outpatient pediatric subjects with at

TABLE 1 Prevalence of psychotropics use in Catalonia's pediatric population from 2008 to 2017 (per 1,000 pediatric inhabitants).

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Pediatric inhabitants	***1,281,777***	***1,322,462***	***1,346,516***	***1,367,382***	***1,384,978***	***1,389,763***	***1,386,458***	***1,388,261***	***1,391,507***	***1,398,400***
Any exposure										
All Girls - Boys	***63.7*** 57.6–69.5	***40.8*** 33.5–47.6	***53.6*** 46.5–60.3	***60.7*** 52.4–68.4	***60.5*** 52.0–68.4	***56.9*** 48.7–64.7	***63.7*** 55.8–71.1	***64.2*** 56.4–71.4	***62.0*** 54.5–68.9	***55.2*** 47.7–62.1
Target exposures										
All Girls - Boys	***26.4*** 19.4–32.9	***27.2*** 19.8–34.1	***30.9*** 23.3–37.9	***31.3*** 22.9–39.2	***31.5*** 22.8–39.6	***31.8*** 23.1–39.9	***32.2*** 23.9–39.9	***31.4*** 23.5–38.9	***30.3*** 22.6–37.5	***29.6*** 22.2–36.6
< 1 year Girls - Boys	***0.0*** 0.0–0.0	***0.0*** 0.0–0.0	***1.3*** 1.3–1.4	***1.1*** 0.9–1.3	***1.7*** 1.3–2.1	***2.4*** 1.9–2.7	***2.2*** 1.8–2.5	***2.1*** 1.9–2.3	***1.7*** 1.6–1.7	***1.9*** 1.6–2.3
1–2 years Girls - Boys	***1.0*** 0.9–1.1	***4.4*** 3.9–4.8	***8.3*** 7.4–9.1	***7.0*** 6.1–7.8	***5.3*** 4.7–6.0	***5.0*** 4.2–5.9	***4.7*** 3.8–5.6	***4.8*** 4.0–5.5	***4.9*** 4.4–5.3	***4.6*** 4.2–4.9
3–5 years Girls - Boys	***14.9*** 12.2–17.5	***11.4*** 9.7–12.9	***12.0*** 9.7–14.2	***11.0*** 9.0–12.8	***8.9*** 6.8–10.9	***7.9*** 6.0–9.7	***6.7*** 5.5–7.9	***6.2*** 5.1–7.3	***5.8*** 4.6–6.8	***5.6*** 4.4–6.8
6–8 years Girls - Boys	***21.4*** 17.2–25.5	***18.4*** 13.5–23.1	***23.7*** 16.1–30.9	***22.9*** 14.8–30.5	***21.0*** 13.7–27.9	***23.8*** 14.4–32.6	***22.4*** 13.8–30.5	***19.9*** 12.1–27.2	***17.7*** 10.9–24.1	***16.8*** 10.3–22.8
9–11 years Girls - Boys	***37.0*** 25.9–47.5	***38.9*** 24.8–52.2	***44.4*** 28.5–59.4	***45.5*** 28.8–61.4	***43.7*** 26.9–59.7	***45.4*** 27.1–62.6	***43.2*** 26.1–59.3	***40.5*** 24.2–55.8	***37.5*** 22.6–51.4	***34.8*** 20.8–47.8
12–14 years Girls - Boys	***45.6*** 30.6–59.8	***47.8*** 29.8–64.8	***50.9*** 33.3–67.3	***54.2*** 34.9–72.0	***55.8*** 36.4–73.9	***57.2*** 37.9–75.2	***58.8*** 39.8–76.8	***58.0*** 39.3–75.6	***55.3*** 37.0–72.6	***53.2*** 35.9–69.5
15–17 years Girls - Boys	***48.5*** 36.8–59.5	***55.3*** 46.7–63.3	***60.4*** 56.1–64.4	***62.8*** 55.6–69.6	***69.2*** 60.5–77.2	***63.5*** 59.3–67.3	***66.8*** 63.5–69.7	***66.1*** 62.9–69.0	***65.2*** 61.1–69.0	***63.7*** 59.5–67.6

Bold italic figures refer to the overall (Girls+Boys) data

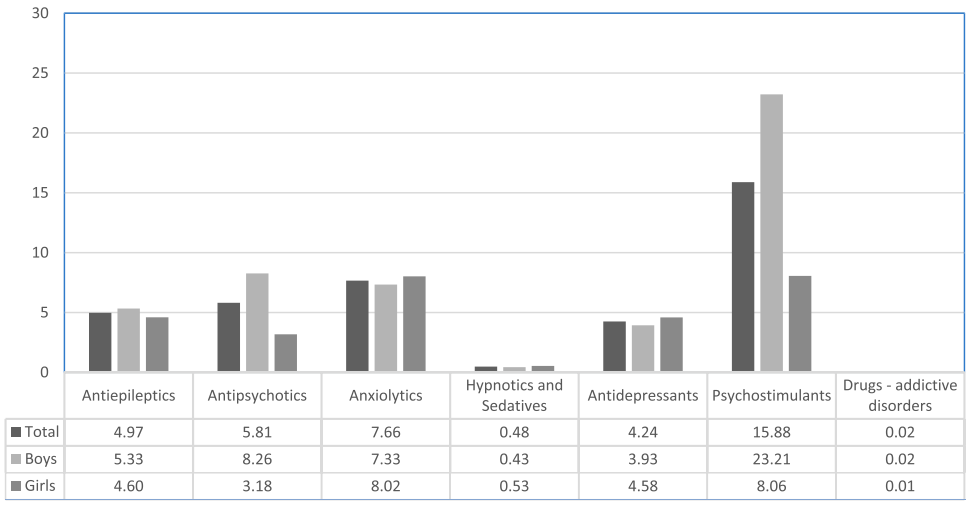

FIGURE 1
Prevalence (per 1,000 inhabitants) of psychotropics use by ATC groups..

least one psychotropic drug dispensed between 2015 and 2017, corresponding to 950,395 drug dispensations. Off-label use was observed in 12% of pediatric subjects and was more frequent in boys (Table 2).

The proportion of off-label use vs. labelled use was higher in younger populations as described in Figure 2. Considering data only in 2017, aripiprazole was the active substance most frequently used under an off-label status followed by two other antipsychotics (Table 2).

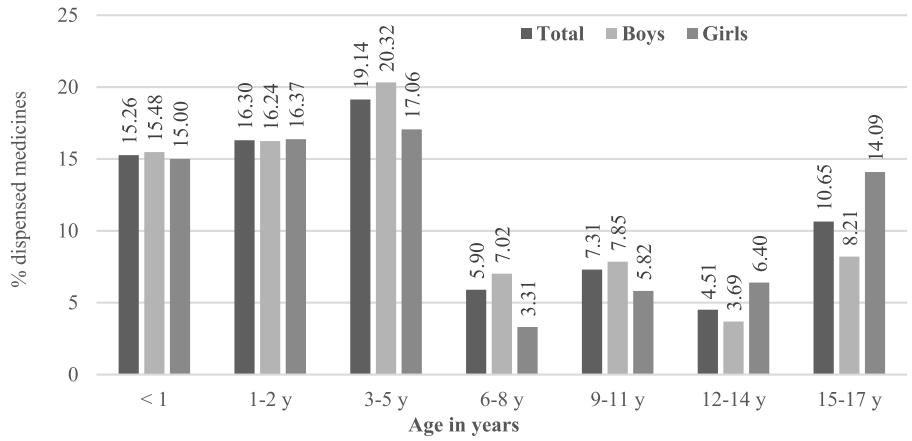

FIGURE 2
Off-label use considering labelled age-range, by age groups of subjects.

TABLE 2 Off-label use considering labelling age range and most frequently off-label drugs.

a. Off-label use considering labelling age (patients)			
	Girls	**Boys**	**Total**
	n (%)	**n (%)**	**n (%)**
In the authorised age range	21,910 (82.93)	36,880 (91.28)	58,790 (87.98)
Out of authorised age range	4,510 (17.07)	3,524 (8.72)	8,034 (12.02)
Overall	26,420	40,404	66,824

b. Most frequent off-label drugs in 2017				
ATC		**Dispensed psychotropics** (*n = 310,078*)		
Code	**Name**	**n**	**%**	**D/P[a]**
N05AX12	aripiprazole	5,496	1.77	4.8
N05AH04	quetiapine	4,380	1.41	3.9
N05AH03	olanzapine	2,654	0.86	3.6
N06AB10	escitalopram	1,165	0.38	3.6
N05BA12	alprazolam	1,036	0.33	1.8
N05AX13	paliperidone	1,024	0.33	6.7
N05BA09	clobazam	872	0.28	6.6
N06AB04	citalopram	743	0.24	3.5
N06AX11	mirtazapine	659	0.21	2.9
N03AF02	oxcarbazepine	622	0.20	6.5

[a]Dispensed drug per patient ratio.

4 Discussion

4.1 Psychotropic use in paediatrics

We analysed anonymised data on dispensed drugs covered by the national health system of Catalonia. The overall prevalence of psychotropic use was between 4.1% and 6.4% in Catalonia and was led by a high rate of short-term use of hydroxyzine, an H1 antihistaminic which is used for several acute indications such as skin allergies and itching. To focus the analysis on psychotropic use in mental conditions, subsequent analyses excluded patients who had only hydroxyzine dispensations. In the population with this targeted exposure, the prevalence of psychotropics use in the pediatric population ranged between 2.6% and 3.2%, and was more frequent in adolescents as well as in boys, mostly due to the use of psychostimulants. A significant amount of the dispensed psychotropic drugs was used out of the authorised age range, with higher proportions of the overall use being not covered by labelling age range in younger patients. Aripiprazole was the most frequent drug dispensed off-label, since in Europe it is authorised for use in children older than 13 years of age.

The rates of exposure to psychotropic drugs in Catalonia were found to be within the ratio reported in other European countries as well as the United States of America (Zito et al., 2003; Safer et al., 2004; Zito et al., 2008; Zoëga et al., 2009). A study in France reported a lower prevalence for the year 2010 compared to Catalonia (25.0 vs. 30.9 per 1,000 respectively) (Kovess Masfety et al., 2015). The current study also demonstrated that boys are more exposed to psychotropics than girls, confirming the trend that has been reported in previous studies (Zito et al., 2003; Zito et al., 2008; Kovess Masfety et al., 2015; Hartz et al., 2016; Piovani et al., 2016). Psychostimulants use rate was 15.88 per 1,000 inhabitants, similar to the rates reported in Germany (7.1–22.0 per 1,000) (Zito et al., 2008; Bachmann et al., 2017), the Netherlands (1.5–39.0 per 1.000) (Schirm et al., 2001; Faber et al., 2005; Zito et al., 2008; Bachmann et al., 2017) and Israel (7.0–25.0 per 1,000) (Vinker et al., 2006), slightly higher than Denmark (0.9–15.0 per 1,000) (Pottegård et al., 2012; Bachmann et al., 2017) and lower than the ones reported in Iceland (21.7–28.4 per 1,000) (Zoëga et al., 2009), whereas in France (2.0 per 1,000) (Kovess Masfety et al., 2015), Italy (0.1–1.9 per 1,000) (Piovani et al., 2016) and the United Kingdom (3.0–5.0 per 1,000) (Bachmann et al., 2017), the reported prevalence rates for psychostimulants were lower.

We had exhaustive information on drug dispensation from the public healthcare in Catalonia for a period of 10 years, which can be considered representative for the region since the system covers almost all inhabitants and was fully available across the whole study period (Modol et al., 2017). Prescription data might be a better option to describe the use of drugs, since they may involve information on indication. Advantages of using pharmacy invoicing data render the observations to be more representative of the actual exposure in specific drugs, considering that these data enclose information on patients that have actually collected the prescribed treatment. Hence, data on reimbursement can define better the prevalence on the use of a drug, even though one cannot still be reassured in absolute terms about the actual adherence to the dispensed medications. While the actual use may differ compared to the purchase of drugs and may also change in time, invoicing data are useful to define the trends and any relevant change throughout the evaluated period. Nonetheless, the extent of information in the present study was limited, since the type of variables available in healthcare databases is predetermined and focused on the management of invoicing and healthcare services (Andersen, 2014). Another limitation from the source of the data used here is the fact that databases of reimbursements are limited to drugs in need of prescription; since in Spain all psychotropics are prescription-only medications, this limitation is unlikely a source of bias in our study. Linking the use of drugs and the disease for which they have been prescribed, would have permitted to analyse more in depth the proportion of off-label use, considering the indication of the treatment. However, since these data were not available for the current study, we approached the off-label analysis through the perspective of the age range only.

4.2 Off-label use of psychotropics

Medication used under an off-label status is often considered a common practice in pediatric patients which imposes this vulnerable population into a high-risk situation due to uncertainties in the efficacy and safety of the concerned treatments. Psychotropic medication is often not studied in underaged patients due to a large list of reasons like barriers regarding pharmacological treatments to obtain evidence-based treatment options for children (Koelch et al., 2008) or lower epidemiology of mental health disorders as opposed to adults. The lack of research for many decades has led to a situation where many drugs currently used in children are lacking clinical evidence in pediatric conditions, and physicians need to extrapolate their practice from the adult studies or the knowledge acquired by clinical experience along the years, to be able to treat their pediatric patients (Kern, 2009).

The off-label use in both Spain (and subsequently Catalonia) is somehow regulated, as there are legal measures in place to regulate requirements for an off-label use. A law established in 2009 states that a drug could be given as off-label in both hospitals and primary care settings, provided that physicians justify the need and absence of commercialised alternatives suitable for the patient, as well as they should obtain the consent from the patient after informing him or her on the benefits and risks (Ministerio de SanidadPolítica Social, 2009). In certain circumstances for repeated uses, physician's obligations may be waived if approved protocols are in place (Ministerio de SanidadPolítica Social, 2009). However, available evidence in Europe demonstrates that there is a relationship between off-label use in children and an increased percentage and severity of adverse drug reactions (ADRs); in particular, neuro-psychiatric ADRs are detected more frequently in children compared to adults (European Medicines Agency, 2004). According to other studies, between 23% and 60% of all ADRs in children may be related to drugs used out of their authorised conditions (Neubert et al., 2004; Cuzzolin et al., 2006; Fabiano et al., 2012).

The off-label use of psychotropics in pediatric population has been previously reported in several countries. The extent of off-label use depends on the setting and the applied off-label definition: small studies used to focus on a given indication or drug, provide more detailed descriptions and include information on formulation, dose and indication that allow a more accurate

definition of the off-label use, hence leading to higher rates of off-label use than the ones identified in our study (Braüner et al., 2016; Deng et al., 2018; Kornø and Aagaard, 2018). In the present study, the data did not permit a very precise definition of off-label use, since they did not allow linking dispensed medications to a clinical indication. In addition, information on the age of the subjects was received as being aggregated into fixed age groups due to confidentiality purposes. Therefore, we had to limit the analysis of the off-label use to the age range for which each active substance was approved, leading to a partial description of the off-label rates driven only by the approved age and not by the approved indication of psychotropics.

Considering all these limitations, we observed that 12% of Catalan pediatric subjects received at least one psychotropic as off-label related to any pediatric approval of at least one product with the same active substance. Our study results may be compared only to one study reporting the off-label psychotropic prescriptions in the Icelandic pediatric population (Zoëga et al., 2009). Nonetheless, the much higher off-label use in Iceland compared to the one described in our sample, can be explained by our methods based on age only and the study periods that do not coincide.

To date there is still a huge need of appropriate and consistent regulatory information for the use of available psychotropic drugs in children and adolescents. We have shown that such use of available drugs is far from being rare, but this off-label use is currently done empirically and in the absence of the regulatory guarantees that are granted through strict product labelling processes (Christiansen et al., 2022). The present study provide an overview on the psychotropic use and highlights that pediatric patients are in need of special attention. The data generated in this study could be a basis to start working towards an improved environment for pediatric healthcare with treatments having the guarantees of quality, safety and efficacy for pediatric patients at the same level as the ones existing for adults. Our study could be considered as a starting point to identify the most frequent off-label use in pediatric mental healthcare, in order to inform guidelines on how psychotropic off-label use can be minimised, especially for those substances with no robust evidence in the particularly vulnerable underaged patient group. Moreover, the information described in our study could be also useful to regulatory authorities in order to define if there is still a need to further harmonise the requests for granting or extending an authorisation in psychiatric indications for the pediatric population, and subsequently to foster further the implementation of the pediatric regulation in Europe which was recently under revision (European Medicines Agency, 2021). Real-world evidence data could also play an important part to fill in the gap especially for all those medicines that are used for a long period under an off-label status in this patient population. Finally, our data could support actions aimed to align the incentives for pharmaceutical industry with the needs to extend the labelling of existing psychotropics, many under an off-patent status and approved for use only in adults, and thus to regulate current established uses and patient age groups (Lepola et al., 2020).

Data availability statement

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

Author contributions

CP contributed to conception and design of the study. SP and MF organized the database and informed the analyses to be conducted. BR and FT performed the statistical analysis. CP and SP wrote the first draft 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

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1157135/full#supplementary-material

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Active surveillance and clinical analysis of anaphylaxis based on the China Hospital Pharmacovigilance System

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Objective: This study aimed to develop active surveillance programs (ASPs) for anaphylaxis using the China Hospital Pharmacovigilance System (CHPS) and analyze the characteristics, allergens, and management strategies for anaphylaxis within a tertiary hospital setting in China.

Methods: We retrospectively analyzed the anaphylaxis cases reported to the National Adverse Drug Reaction Monitoring System in our hospital from 2014 to 2021. Characteristic medical orders, progress notes, and diagnoses in these cases were recorded to identify initial anaphylaxis trigger entries. Based on these initial entries, the questionnaire was developed, and the Delphi method was used to establish consensus entries for anaphylaxis triggers. The CHPS was used to program these trigger entries and construct ASPs, which were then tested on the 238,194 discharged patients to evaluate their performance and analyze the related clinical data.

Results: Ten anaphylaxis triggers and three ASPs were ultimately identified. The ASPs captured 309 cases, out of which 94 cases were confirmed as anaphylaxis following manual screening. After removing duplicates, we noted 76 patients who experienced anaphylaxis 79 times. The positive rate of triggers and the positive predictive value of the programs were 0.13% and 30.42%, respectively. The incidence of anaphylaxis in our study was 0.03%, and the number of anaphylaxis cases detected by the ASPs was 5.64 times higher than those detected by the spontaneous reporting system. Anaphylaxis was more common among female patients. Antibacterial drugs, antineoplastic drugs, and contrast media were the most prevalent allergens in clinical practice. Anaphylaxis to antineoplastic drugs had the highest incidence (0.6%) when compared with patients admitted during the same period. Our study revealed a significant underuse of epinephrine and overuse of second-line therapy (glucocorticoids and antihistamines) in the management of anaphylaxis. Furthermore, we found the use and dosage of epinephrine to be inappropriate.

Conclusion: The CHPS can effectively utilize both structured and unstructured data to construct anaphylaxis ASPs, and this could counteract the under-reporting by the spontaneous reporting system, the primary adverse reaction monitoring method in China. The treatment and management of anaphylaxis are currently inadequate and require improvement to reduce mortality risk.

KEYWORDS

active surveillance, anaphylaxis, China Hospital Pharmacovigilance System, epinephrine, Delphi method

1 Introduction

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance (Sampson et al., 2006), and it can lead to serious consequences if there is a delayed diagnosis and inappropriate treatments. Drugs are generally considered to be the main cause of anaphylaxis (Tejedor-Alonso MA et al., 2015), and despite its relative rarity as an adverse drug reaction (ADR), drug-induced anaphylaxis remains a leading cause of allergy-related deaths in adults (Lee and Vadas, 2011; Jerschow et al., 2014). In addition, with the introduction of new medications such as biologics, small-molecule drugs, and chemotherapeutic drugs, the incidence of hospitalization caused by drug-induced anaphylaxis continues to increase (Cardona et al., 2020; Muraro et al., 2022). During the past decade, there has been an advanced understanding of the diagnosis, pathogenesis, and treatment management of anaphylaxis (Dribin and Castells, 2022; Weiler et al., 2023), but significant data and knowledge gaps remain in key clinical care and research domains, such as population science, validated clinical or biomarker-based models that predict disease outcome, and acute management (Dribin and Castells, 2022; Dribin et al., 2022). These shortcomings are especially acute in China (Li et al., 2019), where there is a dearth of active surveillance studies and epidemiological data on anaphylaxis. Additionally, studies showed gaps in the initial treatment of anaphylaxis between China and international guidelines (Jiang et al., 2020).

The China Hospital Pharmacovigilance System (CHPS), launched and promoted by the China National Center for ADR Monitoring since 2016, possesses the capability to automatically collect and analyze data extracted from electronic hospital information systems (HISs) in sentinel hospitals (Figure 1) (Li et al., 2018). These data include a myriad of information, spanning diagnoses, medical orders, progress notes, test and examination results, and other information. The connection to the HIS makes it possible to simply, actively, and comprehensively obtain real-world drug safety data. At present, the CHPS encompasses more than 400 hospitals across China and is utilized in drug safety research owing to its high operability and accessibility (Li et al., 2018; Sun et al., 2020). Sun et al. (2020) utilized the CHPS to conduct a retrospective analysis of ADRs among 217 COVID-19 patients in China. The study underscored the CHPS's critical role in actively monitoring and detecting ADR signals that reflect real-world ADRs during COVID-19 treatment, thereby providing valuable insights for ensuring safe medication in clinical settings.

This study aims to develop anaphylaxis triggers using the Delphi method and construct ASPs based on the CHPS. These ASPs are

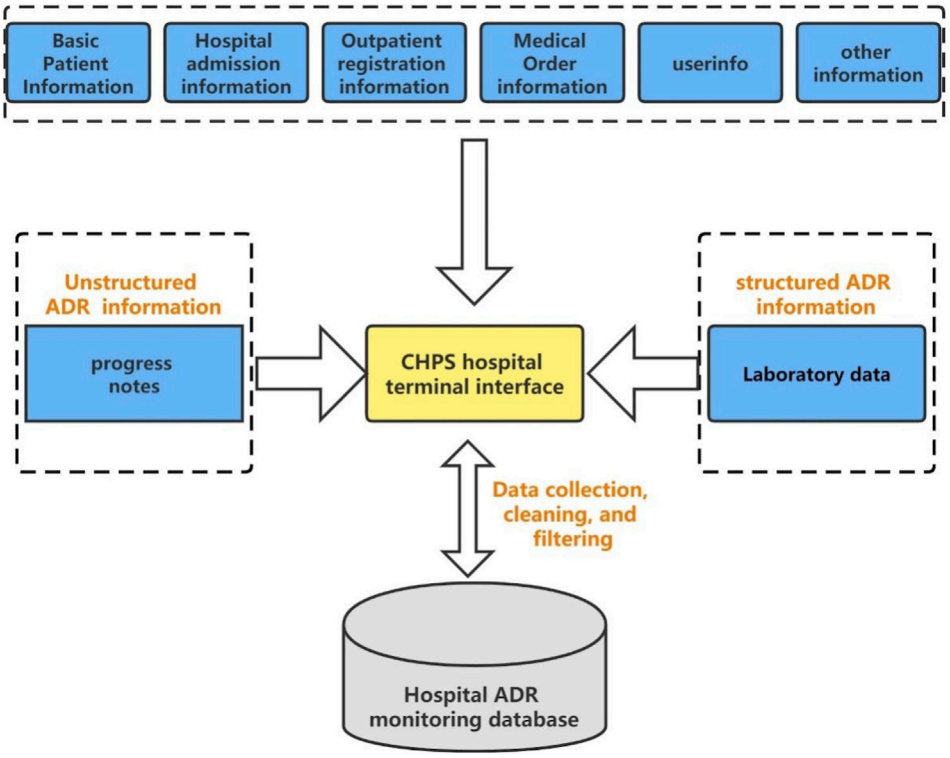

FIGURE 1
Data acquisition structure diagram of the CHPS.

TABLE 1 Diagnostic criteria for anaphylaxis.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
1. Acute onset of illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, and swollen lips, tongue, or uvula)
AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), and hypoxemia)
b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, and incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, and swollen lips, tongue, or uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, and hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, and incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain and vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

then applied to a cohort of 238,194 discharged patients, thereby facilitating an evaluation of their effectiveness and a detailed analysis of anaphylaxis characteristics, implicated allergens, and associated management practices within the Chinese population.

2 Materials and methods

2.1 Retrospective analysis of ADR reports

ADR reports from our hospital, spanning from January 2014 to December 2021, were retrieved from the National Adverse Drug Reaction Monitoring System. These reports were then retrospectively reviewed by both a pharmacist (CCW) and an allergist (ZJL). In reference to the diagnostic criteria for anaphylaxis (Sampson et al., 2006) (Table 1) and the Technical Specifications and Evaluation Criteria for Common Serious Adverse Drug Reactions issued by the National Center for ADR, China, the reviewers identified anaphylaxis cases and filled in the electronic case report forms. These forms included various details, such as diagnoses, departments, characteristic medical orders, and progress notes. After analyzing the relevant data, we formulated initial trigger entries for anaphylaxis.

2.2 Designing the expert consultation questionnaire

An expert consultation questionnaire was conceived, taking into account the initial entries. The questionnaire was structured in two sections; the first collected fundamental information about the experts, encompassing their field of specialization, educational background, years of professional experience, and academic title. The second section sought expert evaluation on the importance, familiarity, and judgment basis of trigger entries. A multidisciplinary panel of experts, each representing the fields of allergology, dermatology, emergency medicine, cardiology, intensive care, respiratory medicine, neurology, and pharmacy, was assembled. All panelists were selected based on their extensive experience in the diagnosis and treatment of anaphylaxis.

2.3 Employing the Delphi method for trigger entries

All experts were asked to rate the importance and familiarity of each item on a 5-point Likert scale (with 1 meaning strongly disagree, 2 meaning agree, 3 meaning neutral, 4 meaning agree, and 5 indicating strongly agree). The basis of judgment was classified into four categories: theoretical analysis, practice, informed by domestic and foreign peers, and intuition. A gradation from 0.1 to 0.5 points was allocated in accordance with the degree of impact on expert judgment, with the highest score of 0.5 being awarded when practice considerably influenced expert opinion. Furthermore, panel members were encouraged to submit free-text comments to clarify their responses to every question, suggest additional questions, or recommend modifications to the existing queries. The indicators of the Delphi method include the experts' positive coefficient, the degree of expert authority, the concentration of expert opinions, and the degree coordination among expert opinions (Huan-huana et al., 2017). The positivity coefficient of experts was represented as the recovery rate of the questionnaire. The authority coefficient of experts, denoted as Cr, was dictated by the judgment basis of the entries (Ca) and the degree of familiarity with the consultation content (Cs), wherein Cr was given by the equation $Cr = (Ca + Cs)/2$, and Cr values of 0.7 or higher were generally considered to carry a high degree of credibility. The concentration of expert opinion was depicted by the mean value of the importance score (Mj) and full score frequency (Kj) of the trigger entries. The cut-off value of Mj and Kj = mean-standard deviation, and those with scores higher than the cut-off value were included. The degree of expert opinion coordination was expressed as the coefficient of variation (Vj). The cut-off values of Vj = mean + standard deviation and those with scores lower than the cut-off value were included. Entries that failed to satisfy any of the three criteria were subsequently eliminated (Zeng, 1996).

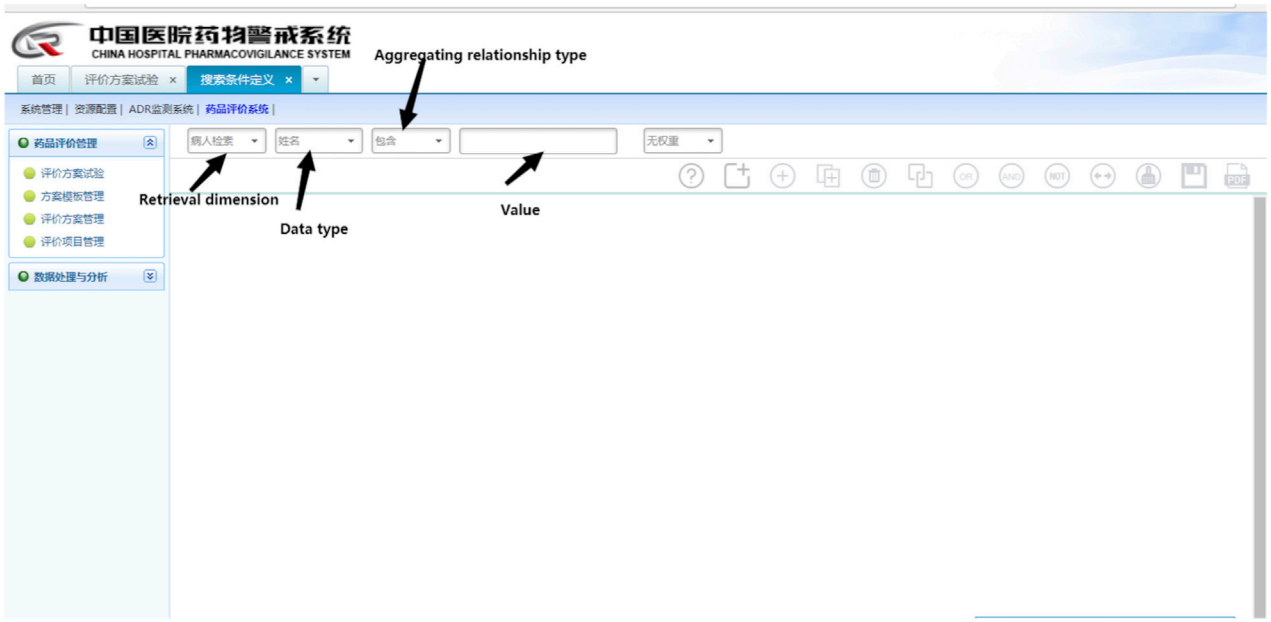

FIGURE 2
Website of the CHPS drug evaluation system.

2.4 Construction of ASPs

The CHPS Drug Evaluation System (Figure 2), a subsystem of the CHPS, procures seven dimensions of clinical data from the HIS. These dimensions include patient information retrieval (basic information about patients), test retrieval (test items and test values), medical order retrieval (drug ID), medical record retrieval (admission records and progress notes), diagnosis retrieval, physical sign retrieval, and examination retrieval, and these seven dimensions can be easily connected with each other by Boolean logic operators. In this study, we utilized Boolean logic programming to formulate retrieval rules for triggers within medical orders, diagnoses, and progress notes. To augment the positive rate, triggers embedded in the progress notes and medical orders were conjoined by an "AND"operator.

These retrieval rules were then applied to discharged patients to obtain trigger-positive patient cases. Two reviewers, a pharmacist (CCW) and an allergist (ZJL), independently examined the results of the automated screening and jointly decided whether the cases were anaphylaxis. Cases were categorized as false positive if both reviewers considered them to be non-anaphylaxis. In the event of disagreement, a third more sophisticated reviewer with more experience (MYF) was consulted to make the final decision. Thereafter, the cases of false positives were analyzed, and exclusion rules were established to enhance the performance of the triggers. Ultimately, ASPs were constructed by integrating retrieval rules and exclusion rules (Figure 3).

2.5 Performance evaluation of ASPs

Upon running the ASPs, we manually reviewed the positive-triggered cases one by one, consequently establishing a comprehensive database for patients suffering from anaphylaxis. Furthermore, we calculated the count of anaphylaxis cases identified by ASPs to assess the performance of our system. The positive predictive value (PPV) of the ASPs was computed by dividing the number of anaphylaxis cases identified by the ASPs by the number of cases with positive triggers. The incidence of anaphylaxis was determined by dividing the number of anaphylaxis cases identified by ASPs by the total number of discharged patients. To quantify the efficiency of the ASPs relative to the spontaneous reporting system, we devised a ratio of the anaphylaxis cases detected by the ASPs to the anaphylaxis reports lodged within the spontaneous reporting system over an identical time frame.

2.6 Analysis of clinical data

We created additional electronic case report forms to extract various patient information, including patient ID, gender, age, the department of hospitalization, the time of anaphylaxis occurrence, descriptions of anaphylaxis processes in progress notes, suspected drugs, and the types and usage of therapeutic drugs. Furthermore, the suspected drugs were classified according to their pharmacological effects, and patients in the anaphylaxis database were categorized based on whether they experienced anaphylactic shock.

2.7 Statistic analysis

Categorical data were described by frequency counts and percentages. Continuous variables were depicted as means with standard deviation. Numerical differences between groups were

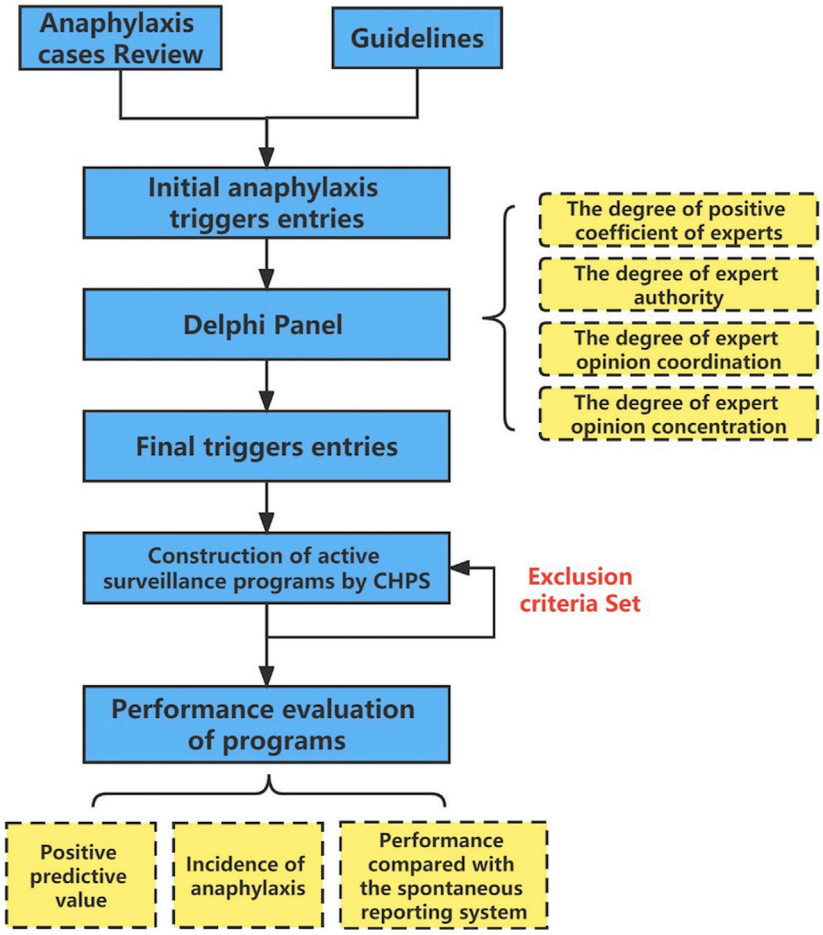

FIGURE 3
Flow chart of active surveillance for anaphylaxis.

assessed by the Chi-square test for categorical variables. The threshold for statistical significance was defined as $p < 0.05$. All statistical analyses were conducted using SPSS, Version 25.0 (SPSS Inc., Chicago, IL, United States)

3 Results

3.1 Trigger entries of anaphylaxis

From 2014 to 2021, our hospital reported 1827 ADR cases to the National Adverse Drug Reaction Monitoring System, and 22 cases were identified as anaphylaxis. We designed initial triggers using diagnoses, medical orders, and descriptions of progress notes. To refine trigger performance, we formulated exclusion rules. These included (1) the exclusion of descriptions of progress notes containing "anaphylactic shock" in informed consent prior to invasive procedures (such as anesthesia, bronchoscopy, and hematopoietic stem cells) and records aimed at preventing allergies, conducting allergy tests, and documenting allergy history; (2) the exclusion of the long-term medical order type for rescue drugs or when the interval between different rescue drug usage exceeded a day.

We distributed a 28-question online questionnaire to experts, and all eight questionnaires were effectively recovered, with a questionnaire recovery rate of 100%. Questionnaire data analysis yielded an expert authority coefficient of 0.92 ± 0.10, demonstrating high expert authority. The Mj, Kj, and Vj of the triggered entries are shown in Table 2. Finally, 10 trigger entries were developed by the Delphi method (Table 2).

3.2 ASPs and performance

After using Boolean logic programming to integrate the trigger entries and optimizing the rules, the final surveillance programs were obtained (Table 3). The programs ran for approximately 3 min, automatically monitoring 238,194 medical records of discharge patients from 2018 to 2021, and 309 cases were positive for triggers, with a positive rate of 0.13%. After the manual screening, 94 cases of anaphylaxis were obtained, and the PPV was 30.42%. In total, 76 patients with 79 cases of anaphylaxis were finally obtained after removing the duplicates, including 37 cases of anaphylactic shock and 42 cases of no anaphylaxis shock. The incidence of anaphylaxis detected by the ASPs was 0.03%. During the same period, 14 cases of anaphylaxis were

TABLE 2 Trigger entries and scores for anaphylaxis.

Trigger entries	Mj (Cut-off = 3.90)	Kj (Cut-off = 0.36)	Vj (Cut-off = 0.37)
Diagnosis contains “anaphylactic shock”	5.00	1.00	0.00
Medical orders contain “epinephrine”	4.88	0.88	0.07
Medical orders contain “glucocorticoids (dexamethasone or methylprednisolone) combined with promethazine”	4.13	0.50	0.31
Progress notes contain “anaphylactic shock”	4.88	0.88	0.07
Progress notes contain “allergy”	4.38	0.63	0.17
Progress notes contain “cutaneous adverse reactions” (e.g., rash, flushing, pruritus)	4.38	0.63	0.20
Progress notes contain “respiratory system adverse reactions” (e.g., chest tightness, dyspnea, suffocation)	4.88	0.88	0.07
Progress notes contain “nervous system adverse reactions” (e.g., dizziness, irritability, unconsciousness, confusion)	3.80	0.50	0.63
Progress notes contain “digestive system adverse reactions” (e.g., nausea, vomiting, diarrhea)	3.50	0.13	0.22
Progress notes contain “circulatory system adverse reactions " (e.g., reduced BP, palpitation, precordial discomfort)	4.25	0.38	0.13

TABLE 3 Active surveillance programs for anaphylaxis and its performance.

Items in surveillance programs	Positive frequency of triggers	Frequency of anaphylaxis	PPV (%)
Diagnosis contains “anaphylactic shock”	31	30	96.78
Progress notes contain “anaphylactic shock" and medical orders contain “epinephrine or glucocorticoids combined with promethazine”	19	11	57.89
Progress notes contain “allergy" and “adverse skin or respiratory or nervous system or digestive or circulatory system reactions,” and medical orders contain “epinephrine or glucocorticoids combined with promethazine”	259	53	20.46
Total	309	94	30.42

reported to the National Adverse Drug Reaction Monitoring System in our hospital. The number of anaphylaxis cases detected by the ASPs was 5.64 times higher than that detected by the spontaneous reporting system, and the under-reporting rate of the spontaneous reporting system was 83.72%.

3.3 Characteristics of anaphylaxis

Among the detected cases (Table 4), 25 (31.65%) were males and 54 (68.35%) females, with a mean age of 55.78 years (range: 4–79 years). The highest incidence of anaphylaxis occurred in the emergency department (19 cases, 24.05%), succeeded by the oncology (12 cases, 15.19%) and gynecology departments (8 cases, 10.13%). It should be noted that all anaphylaxis in the gynecology department was caused by antineoplastic drugs.

3.4 Anaphylaxis allergens

Out of the 79 anaphylaxis cases, 66 were drug-induced, constituting 83.54% of all anaphylaxis cases (Table 5). Others included eight cases with unidentified allergens, three cases were animal-induced (insect and shrimp allergens), and two cases were caused by absolute alcohol and irritating odors. Antibacterial drugs were the most common class of allergenic drugs, with cephalosporins being the most frequent, followed by antineoplastic drugs and contrast media. The drug with the highest individual frequency identified by the ASPs was oxaliplatin (5 cases, 7.58%), followed by carboplatin (4 cases, 6.06%). Additionally, traditional Chinese medicine injections, a class of drugs under special management in China due to safety concerns, were also commonly associated with anaphylaxis.

3.5 Treatment regimen

Glucocorticoids (66 cases, 83.54%) were the most commonly used therapeutic drugs for patients with anaphylaxis, followed by promethazine (46 cases, 58.23%) and epinephrine (35 cases, 44.30%). Other drugs, including vitamin C injection (18 cases, 22.78%) and calcium gluconate (16 cases, 20.25%), were also utilized in the treatment of anaphylaxis (Table 6).

A total of 35 anaphylaxis cases treated with epinephrine were analyzed, and there was a statistically significant difference in the

TABLE 4 Demographic characteristics of anaphylaxis.

Demographic characteristics	Numbers
Age	55.78 ± 17.56
Gender	
Male	25 (31.65%)
Female	54 (68.35%)
Department(n ≥ 2)	
Emergency department	19 (24.05%)
Oncology department	12 (15.19%)
Gynecology department	8 (10.13%)
Cardiology department	5 (6.33%)
Neurology department	4 (5.06%)
Hepatology department	4 (5.06%)
Critical care medicine	3 (3.80%)
Neurosurgery department	3 (3.80%)
Respiratory department	3 (3.80%)
Hematology department	2 (2.53%)
Gastroenterology department	2 (2.53%)
Bone tumor department	2 (2.53%)
Pediatrics department	2 (2.53%)
Obstetrics department	2 (2.53%)
Anorectal department	2 (2.53%)

epinephrine usage rate between patients with anaphylactic shock and those with non-anaphylactic shock ($p < 0.01$) (Table 7). The main route of epinephrine administration was intramuscular injection (45.71%), with subcutaneous injection (28.57%), bolus (25.71%), and other routes, but the epinephrine dose varied widely (Table 8).

4 Discussion

Anaphylaxis constitutes an acute, potentially fatal systemic allergic reaction. Measuring and evaluating epidemiological data related to anaphylaxis is an important way to identify disease burden trends and risk factors. At present, epidemiological data sources for anaphylaxis encompass the purchase of epinephrine auto-injectors, national databases, primary care databases, representative sample surveys from the general population, hospital admissions, and emergency department visits (Tejedor Alonso et al., 2015; Tejedor-Alonso MA et al., 2015; Tanno et al., 2018), and hospital admission datasets were deemed the largest and most robust data available to understand trends in anaphylaxis (Turner et al., 2020). Research grounded on hospitalizations typically employs structured data such as the International Classification of Diseases (ICD)-9 and ICD-10 to identify patients with anaphylaxis (Mulla et al., 2011). Nonetheless, such studies are prone to drawbacks like misdiagnosis and misclassification (Tanno et al., 2018), which subsequently lead to an underestimation of anaphylaxis incidence. For example, Klein and Yocum (1995) undertook a retrospective analysis of patient records from the emergency department, uncovering 17 cases of anaphylaxis. However,

TABLE 5 Drugs that induced anaphylaxis.

Drug classification	Drug	Number
Antibacterial drugs	11 cephalosporins (four unspecified cephalosporins, three cefoperazone–sulbactam, three cefotiam, and one cefuroxime), three piperacillin–tazobactam, two amoxicillin, one metronidazole, and one levofloxacin	18
Antineoplastic drugs	Five oxaliplatin, four carboplatin, three doxorubicin liposome, two cetuximab, one nedaplatin, and one infliximab	16
Contrast media	Three iodixanol, three iopromide, and one iodine contrast agent with unknown details	7
Traditional Chinese medicine injections	Two Shenmai injections and one Xingnaojing injection	3
Glucocorticoid	Two dexamethasone and one methylprednisolone	3
Blood products	Two plasma and one platelet	3
Other drugs	One potassium sodium dehydroandroandrographolide succinate for injection, one extract of *Ginkgo biloba* leaf injection and citicoline, one reduced glutathione, one combined with compound paracetamol and amantadine hydrochloride, Qingre Sanjie capsule, Ganmao Qingre granule, one muscle relaxant, one lansoprazole, one epinastine and pantoprazole, one lidocaine, one domperidone, one iron sucrose, two transcatheter artery chemoembolization related drugs, one radionuclide, and one Zhenggu Zijin Wan	14
Unclear drugs	2	2
Total		66

TABLE 6 Drugs for the treatment of anaphylaxis.

Treatment drugs	Case numbers (%)
Glucocorticoids (dexamethasone, methylprednisolone, and betamethasone	66 (83.54%)
Promethazine	46 (58.23%)
Epinephrine	35 (44.30%)
Vitamin C	18 (22.78%)
Calcium gluconate	16 (20.25%)
Others (dopamine, norepinephrine, etc.)	17 (21.52%)

only four of these 17 patients received an anaphylaxis diagnosis identifiable by ICD-9.

In this study, we devised trigger entries for anaphylaxis encompassing both structured (e.g., medical orders and diagnostic data) and unstructured (e.g., progress notes). This incorporation of unstructured data led to a two-fold rise in the anaphylaxis detection rate compared to the reliance solely on diagnosis-based structured data, thereby substantially augmenting the performance of the programs. Concurrently, when compared with the spontaneous reporting system of our hospital during the same period, it was evident that 83.72% of anaphylaxis cases were under-reported. This finding underscores the significant potential of ASPs to rectify the deficiencies of the spontaneous reporting system, the primary monitoring method for adverse reactions in China. The study by Panesar et al. (2013) illustrated that the incidence rates for anaphylaxis in Europe fluctuated between 1.5 and 7.9 per 100,000 person-years. Our research found the incidence of anaphylaxis in the Chinese population to be 8.29 episodes per 100,000 person-years, a figure surpassing other studies (Bann et al., 2021; Nunes et al., 2022) reliant on electronic medical records, which signals the efficacy of the ASPs. However, the sensitivity of our programs remained suboptimal. We analyzed 4,874 medical records of discharged patients from our hospital from 1 December to 31 December 2020 and recorded all suspected ADRs (based on the progress notes and diagnoses). Out of these, three cases were identified as anaphylaxis, and only one case could be effectively tracked by the ASPs. Analysis of undetected anaphylaxis in the aforementioned discharged patients and the spontaneous reporting system (see Supplementary Table S1) revealed that all eight patients were not diagnosed with anaphylactic shock. Among these, five cases either received only dexamethasone treatment or did not receive any pharmacological intervention post-anaphylaxis. Furthermore, two cases lacked progress notes indicating an "allergy," and one case, although marked as "allergy," also had a "prevention" note, which accounts for their exclusion from ASP monitoring. Hence, it is crucial to standardize the management of anaphylaxis and medical record documentation to enhance the sensitivity of the detection method.

Regarding demographic characteristics, our study demonstrated that the incidence of anaphylaxis was significantly higher in females than in males. Taking into account the gender composition of patients during the same period, the ratio of male-to-female anaphylaxis incidence was 1: 2.1. Banerji et al. (2014) reported a similar gender disparity, with 71% of 716 anaphylaxis patients being female. Studies have indicated that anaphylaxis in females is less frequent than in males before puberty but increases rapidly and surpasses male incidence with age, although the exact mechanism is yet to be deciphered (Simons et al., 2002; Sheikh et al., 2008).

Death rates from drug-induced anaphylaxis have risen 300% over the last decade (Tejedor Alonso et al., 2015), and drugs associated with anaphylaxis vary based on different populations, time, geographic regions, drug usage patterns, genetic factors, anaphylaxis definitions, case registries, and study designs (Giavina-Bianchi et al., 2018). In our study, drugs were responsible for a significant 83.54% of all anaphylaxis cases, and the leading drug classes linked with anaphylaxis were antibacterial drugs, antineoplastic drugs, and contrast media. When compared with the number of patients treated at our hospital during the same period, we observed that anaphylaxis triggered by antineoplastic drugs had the highest proportion (0.06%), trailed by antibacterial drugs (0.02%) and contrast media (0.02%). Among the antineoplastic drugs, oxaliplatin emerged as the most common trigger, a finding consistent with results from the Korean population (Park et al., 2017). Indeed, hypersensitivity reactions induced by oxaliplatin have garnered substantial attention (Aroldi et al., 2015; Otani et al., 2017; Rogers et al., 2019), leading the China National Medical Products Administration to revise the package insert in August 2021 (Administration and N.M.P, 2021). This revision included a black-box warning about potential severe allergic reactions, even death, associated with oxaliplatin. Antibacterial drugs, particularly beta-lactams, are recognized as the primary causes of anaphylaxis, with previous studies suggesting a lower incidence of anaphylaxis with cephalosporins than penicillins (Park et al., 2017; Giavina-Bianchi et al., 2018), and drugs containing amoxicillin have been reported as the most frequent anaphylaxis triggers to the FDA (Yu et al., 2021). However, our study observed that cephalosporins were the most frequently implicated drugs, likely due to prescription practices in our hospital. As routine skin tests are not advocated prior to the administration of cephalosporins, future research should focus on devising prediction methods for allergic reactions with heightened sensitivity and specificity.

TABLE 7 Epinephrine use in patients with anaphylaxis.

Patient classification	With epinephrine	Without epinephrine	*p*-value
Anaphylactic shock	29	8	<0.01
Non-anaphylactic shock	6	36	

TABLE 8 Dosage and administration of epinephrine.

Dosage and administration of epinephrine		Number (%)
Intramuscular injection	0.5 mg	10 (28.57%)
	0.3 mg	3 (8.57%)
	4 mg	1 (2.86%)
	1 mg	1 (2.86%)
	0.4 mg	1 (2.86%)
Subcutaneous injection	0.5 mg	4 (11.43%)
	0.3 mg	3 (8.57%)
	1 mg	2 (5.71%)
	0.15 mg	1 (2.86%)
Bolus	1 mg	2 (5.71%)
	0.02 mg	2 (5.71%)
	0.25 mg	1 (2.86%)
	0.2 mg	1 (2.86%)
	0.1 mg	1 (2.86%)
	0.03 mg	1 (2.86%)
	Unknown	1 (2.86%)

Administering an immediate intramuscular injection of epinephrine into the mid-thigh area is the primary treatment strategy for anaphylaxis, regardless of the presence of shock, as outlined in multiple guidelines (Cardona et al., 2020; Muraro et al., 2022). For adults, the recommended dosage is 0.01 mg/kg of body weight, not exceeding a total dose of 0.5 mg. Importantly, subcutaneous injection is not recommended for emergency intervention because of its slower onset of action (Li et al., 2019). Furthermore, although glucocorticosteroids and antihistamines are frequently employed in managing anaphylaxis, they are only recommended as secondary treatment options per guidelines, and their routine usage remains a contentious issue. Current evidence suggests that glucocorticosteroids may not provide any benefit or might even be detrimental in the acute management of anaphylaxis (Cardona et al., 2020). In our study, we noted that the use of glucocorticosteroids and antihistamines significantly outpaced that of epinephrine in anaphylaxis management (83.54% vs. 44.30%, 58.23% vs. 44.30%, $p < 0.01$). Notably, the employment of epinephrine was significantly less common in non-shock cases compared to shock incidents. Moreover, the application and dosage of epinephrine were not rational, reflected by a high percentage of subcutaneous epinephrine injections and considerable dosage inconsistency. Jiang et al. (2020) similarly underscored the significant underutilization, inappropriate usage, and dosage of epinephrine and the unreasonably high employment of glucocorticoids in China. Hence, it is crucial to improve anaphylaxis management and treatment by medical professionals to reduce mortality from this severe allergic reaction.

Our study does possess several limitations. Primarily, as a single-center study, the formulation of triggers in medical orders was based on the prescribing habits of doctors in our hospital; this context-specific design may compromise its external validity. Thus, when attempting to apply these triggers to other hospitals, certain elements may require modification. Additionally, our ASPs may not have captured all anaphylaxis cases due to certain inherent limitations, which could potentially affect the thoroughness of our results. This factor may have subtly influenced the outcomes of our research.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

CW, ZL, and AL contributed to the conception and design of the study. CW, ZL, and MF reviewed the ADR reports and formulated the initial triggers. CW and YY performed the statistical analysis. CW wrote the first draft 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.

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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.2023.1180685/full#supplementary-material

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Major adverse cardiovascular events associated with testosterone treatment: a pharmacovigilance study of the FAERS database

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Background and purpose: Testosterone is an essential sex hormone in maintaining masculine characteristics, which is prescribed for male hypogonadism as testosterone replacement treatment (TRT). Herein, we investigated long-standing controversies about the association between TRT and major adverse cardiovascular events (MACEs), based on real world adverse event (AE) reports, registered in the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: Publicly available FAERS data from 1 January 2004 to 31 December 2022 were retrieved from the Food and Drug Administration (FDA) website. The data mining protocol including the reporting odds ratio (ROR) and the Bayesian confidence propagation neural network (BCPNN) was applied to analyze overreporting caused by risk factors and MACEs, including TRT, morbidities, and ages. The ROR and the BCPNN were also applied to investigate the annually developing trend of pharmacovigilance (PV) signals in the real world, retrospectively.

Results: A total of 3,057 cases referring to MACEs, with a median age of 57 years old (yo), were identified from 28,921 cases of testosterone users. MACEs related to PV signals have emerged since 2014, including cardiac death, non-fatal myocardial infarction, and non-fatal stroke. Myocardial infarction (MI) (ROR: 9.46; IC_{025}: 3.08), acute myocardial infarction (AMI) (ROR: 16.20; IC_{025}: 3.72), ischemic cardiomyopathy (ROR: 11.63; IC_{025}: 2.20), and cardiomyopathy (ROR: 5.98; IC_{025}: 1.96) were the most significant signals generated, and weaker signals included cardiac failure acute (ROR: 4.01; IC_{025}: 0.71), cardiac arrest (ROR: 1.88; IC_{025}: 0.56), and ventricular fibrillation (VF) (ROR: 2.38; IC_{025}: 0.38). The time-to-onset (TTO) of MACEs was calculated with a median of 246 days for AMI.

Conclusion: For myocardial infarction and cardiomyopathy, TRT statistically tended to increase the risk of MACEs, while for cardiac arrhythmia, cardiac failure, and stroke, TRT demonstrated beneficial effects among the population with morbidities, such as testosterone deficiency (TD), diabetes mellitus (DM), and hypertension. MACEs were rare but led to serious outcomes including significant increase in death and disability. Since 2018, and before 2014, reports referring to TRT associated with MACEs were relatively scarce, which indicated that there might be a considerable number of cases that went unrecorded, due to

neglection. Health workers and testosterone users might pay more attention to testosterone-induced MACEs.

KEYWORDS

pharmacovigilance, testosterone treatment, TT, major adverse cardiovascular events, MACE, FAERS

1 Introduction

Testosterone is essential for the maintenance of muscle mass, sex drive, bone density, and fertility of men. Testosterone deficiency (TD) could be caused by various conditions, and testosterone is widely used for testosterone replacement therapy (TRT), to restore the testosterone level of men with hypogonadism or with low testosterone levels (low-T), which is considered as a safe and effective hormone supplement (Elliott et al., 2017; Bhasin et al., 2018) and treatment for certain types of cancers, such as hormone therapy for prostate cancer (Bhasin et al., 2018).

However, the necessity of testosterone treatment (TT), especially the association between TRT and major adverse cardiovascular events (MACEs) remains controversial. MACEs refer to negative outcomes related to the heart and blood vessels, including cardiac death, non-fatal infarction, and non-fatal stroke, which is a significant concern in the management of various medical conditions, including heart diseases and diabetes (Casas et al., 2021; Rini et al., 2022). Although there are a few available guidelines up till date, no conclusions were given on the association between TT and MACE risk (Minhas et al., 2021; Isidori et al., 2022). Various reviewed experimental studies on androgen administration in animal models concluded that androgen exposure increases the cardiotoxicity of androgens via mROS generation and NLRP3 inflammasome activation, while it also demonstrates cardioprotective effects of resistance training on the heart tissue by increasing the level of malondialdehyde (MDA) and protein carbonyl and reducing the risks of heart injuries and other issues affecting the heart including hypertrophy, fibrosis, autonomic imbalance, and the irreversible destruction of the heart tissue (Sessa et al., 2022).

Skeptical opinions were publicized claiming that TT might induce sudden cardiac death (Esposito et al., 2023), cardiomyopathy (Doleeb et al., 2019), and venous thrombosis (Bertola et al., 2017; Poirier-Blanchette et al., 2021), increasing the risk of myocardial infarction (MI), stroke (Vigen et al., 2013), and non-fatal myocardial infarction (Finkle et al., 2014). In 2014, the Food and Drug Administration (FDA) Advisory Committee agreed that enough attention should be paid to the potential testosterone-induced cardiovascular (CV) risks (Garnick, 2015; Seftel, 2015). In 2022, Bhasin et al. (2022) excised a study including 6,000 subjects and determined that TT in middle-aged and older men with hypogonadism was with or at increased risk of CV diseases. On the contrary, there were other publications that pointed out that TT has no effect on MACEs or that it even presented some beneficial effects (Wang et al., 2011; Baillargeon et al., 2015; Cheetham et al., 2017), including statements that TT is associated with a decrease in atherosclerosis, hypertension, intima–media thickness of carotid arteries, insulin resistance, and mortality in men due to all causes (Morgentaler et al., 2015) and no short-term increased risk of adverse events (AEs) is observed among subjects with hypogonadism (Elliott et al., 2017).

Herein, based on the FDA Adverse Event Reporting System (FAERS), we aim to solve long-standing controversies about the association between TRT and MACEs, using the reporting odds ratio (ROR) method in tandem with the Bayesian confidence propagation neural network (BCPNN).

2 Methods

2.1 Data source and the scheme

Publicly available FAERS data from 1 January 2004 to 31 December 2022 were downloaded as raw data. Criteria of exclusion were demonstrated in the scheme of the study (Figure 1): all reports that were officially deleted by the FDA authority, duplicated, missing case ID and date, or with inaccurate data for gender and age were removed. The data process was conducted using SPSS version 19.0 (Statistical Product and Service Solutions) and R Studio 4.1.2 (R Studio), using a logistic regression model.

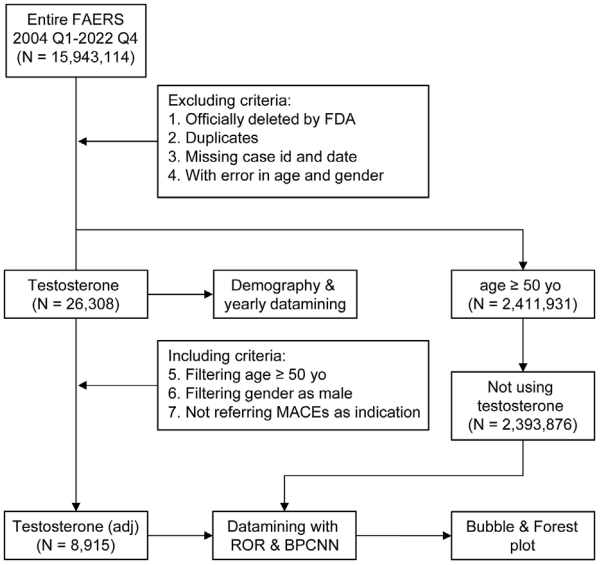

FIGURE 1
Scheme of the study with the including/excluding criteria. Publicly available FAERS data from 1 January 2004 to 31 December 2022 were filtered using this including/excluding criterion. N, case number of each drug or control group; testosterone stands for reports referring to testosterone treatment (TT), the dataset of TT; testosterone (adj) stands for reports referring to TT without major adverse cardiovascular events (MACEs) as indications and concomitants that were able to generate MACE signals.

2.2 Definition of TT and control groups

RxTerms, which is maintained by the US National Library of Medicine, was used as the dictionary database of drug names (Nelson et al., 2011), and the dataset of TT was composed of all reports referring to generic and brand names of testosterone, which were further filtered with testosterone as the primary suspected (PS) drug, and was used for description and statistical analysis later on. The dataset of TT was further stratified into three subgroups according to age, which were non-age [TT: 0–17 years old (yo)], adult (TT: 18–49 yo), and elderly (TT >50 yo). All cases referring to men above 50 yo, without records of TT and without indications referring to MACEs, who were probably undergoing a decrease in their testosterone levels (Petering and Brooks, 2017; Bhasin et al., 2018; Grober et al., 2021), were extracted to represent the population with TD (or with low-T) but without TT (NT >50 yo), as FAERS data do not offer any information about the testosterone level. All cases with the age above 65 yo among the low-T population were further extracted to represent the population with an extended low-T status (NT >65 yo). The dataset of TD was composed of all reports with indications referring to testicular dysfunction, hypogonadism, male andropause, and other preferred terms (PTs) (Supplementary Table S1, indications) provided by the Standardized MedDRA Queries (SMQs) (MedDRA version 23.0) (Katsuhara and Ikeda, 2021), which could logically result in low-T. All concomitant drugs were extracted and evaluated for their association with MACEs, as well as the top 10 indications alongside TT, which could be considered as morbidities. Reports referring to concomitant drugs that could generate valid pharmacovigilance (PV) signals of MACEs or indications referring to MACEs were dropped, and the cleansed dataset of TT was subjected to a data mining procedure to get the adjusted ROR. The datasets of the control groups including TD, NT >50 yo, and NT >65 yo, and morbidities and other risk factors mentioned previously were also calculated for their association with MACEs; a bubble map was created to demonstrate the panorama of interfering effects. The intensity of the PV signal was defined using a value of the lower limit of the information component (IC_{025}) and was demonstrated with the size of the bubble. Chi-square (Chi^2) tests were used to compare patterns of signals generated by different risk factors and assess whether the differences observed are statistically significant.

2.3 Definition of MACEs

MACEs were defined using International Classification of Diseases, Clinical Modification, Tenth Revision (ICD-10-CM) diagnosis codes, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (Bosco et al., 2021; Zhang et al., 2021), including acute myocardial infarction (AMI)-induced left heart failure (LHF), ventricular fibrillation (VF)-induced sudden death, and cordial arrhythmia induced by valvular diseases, myocardiopathy, and myocarditis. Thus, MACEs can be detailed as all of the preferred terms containing the keywords "card," "heart," "ventricular," "cereb," "brain" coupled with "infarction," "stroke," "death," "itis," "pathy," "failure," and "fibri," which were determined by the Standardized MedDRA Query (version 23.0) terminology (Katsuhara and Ikeda, 2021) (Supplementary Table S1, MACEs). The PTs mapped in "Embolic and thrombotic events (SMQs)" were also used to screen for pharmacovigilance signals.

2.4 Descriptive analysis and demography

Qualified reports that underwent exclusion criteria described in Section 2.1 were stratified by gender, age, reporting year, TTO, outcomes, AEs, concomitant drugs, and indications to investigate the demographic profile of testosterone users, especially for reports referring to MACEs. The TTO of each MACE, which could generate PV signals when associated with testosterone, was demonstrated by a box plot. Due to lack of information about testosterone levels in AE reports, age is a notable factor for indicating TD among the male population. The dataset of TT was stratified into subgroups according to the age including 0–9 yo, 10–17 yo, 18–29 yo, 30–49 yo, 50–64 yo, 65–75 yo, 76–85 yo, and above 86 yo. Reports referring to testosterone users from 0–17 yo, 18–49 yo, and above 50 yo were subjected to statistical analyses, and a bubble map of PV signals generated by TT–MACE pairs was plotted. Chi^2 tests were induced to compare the differences between each age group.

2.5 Statistical analysis and signal detection

The data mining procedure using the ROR method was introduced to investigate the disproportionality in reporting the ratio caused by interested drug–AE pairs compared with random drug–AE pairs (detailed in previous publications (Min et al., 2018; Moreland-Head et al., 2021)), which were tandem in with the BCPNN method introduced by Bate et al. (1998), deducing the linkage between the target drug and event by a prior possibility. The association among risk factors including age, morbidities such as diabetes mellitus (DM), and MACEs was also investigated. For the ROR, a positive signal was determined as the count of the targeted drug–AE pair (a) more than three, plus the value of the ROR higher than 1 and the lower limit of the 95% confidence interval (95% CI) exceeding 1. For the BCPNN, a valid PV signal was defined as the value of the lower limit of the information component (IC_{025}) exceeding 0, that is, to be specific, the IC_{025} value between 0 and 1.5 was defined as a weak signal, while the IC_{025} value between 1.5 and 3 was considered as a medium signal, and the IC_{025} value >3 was considered as a strong signal.

To demonstrate the developing trend of PV signals generated by TT–MACE pairs, myocardial infarction was picked as an example of testosterone-induced MACEs and was subjected to the calculation of the natural logarithm value of the ROR (ln ROR) and IC_{025} annually with two approaches, including calculations based on the reports of each single year separately and on reports accumulated over time on a yearly basis, mimicking the accumulation of AE reports in the FAERS.

3 Results

3.1 Demography of TT-associated MACEs

From 1 January 2004 to 31 December 2022, a total of 15,943,114 valid cases were retrieved as raw data. The dataset of TT was composed of 28,921 cases, which referred to testosterone as the PS drug and was used for specific indications, among which

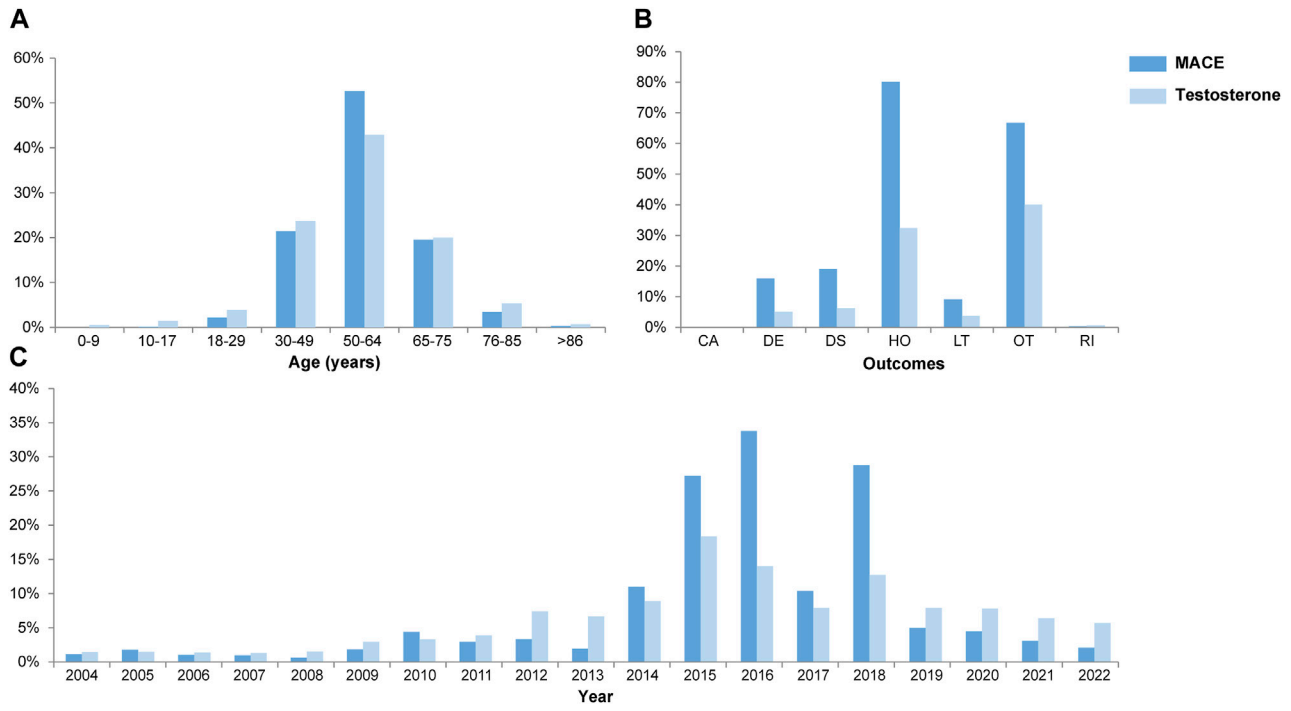

FIGURE 2
Combined box plots of the demography, including age **(A)**, outcomes **(B)**, and yearly report number **(C)**. *x*-axis, variables; *y*-axis, percentage of concerned variables; years, years old; CA, congenital anomaly; DE, death; DS, disability; HO, hospitalization (initial and prolonged); LT, life threatening; OT, other serious conditions; RI, required intervention.

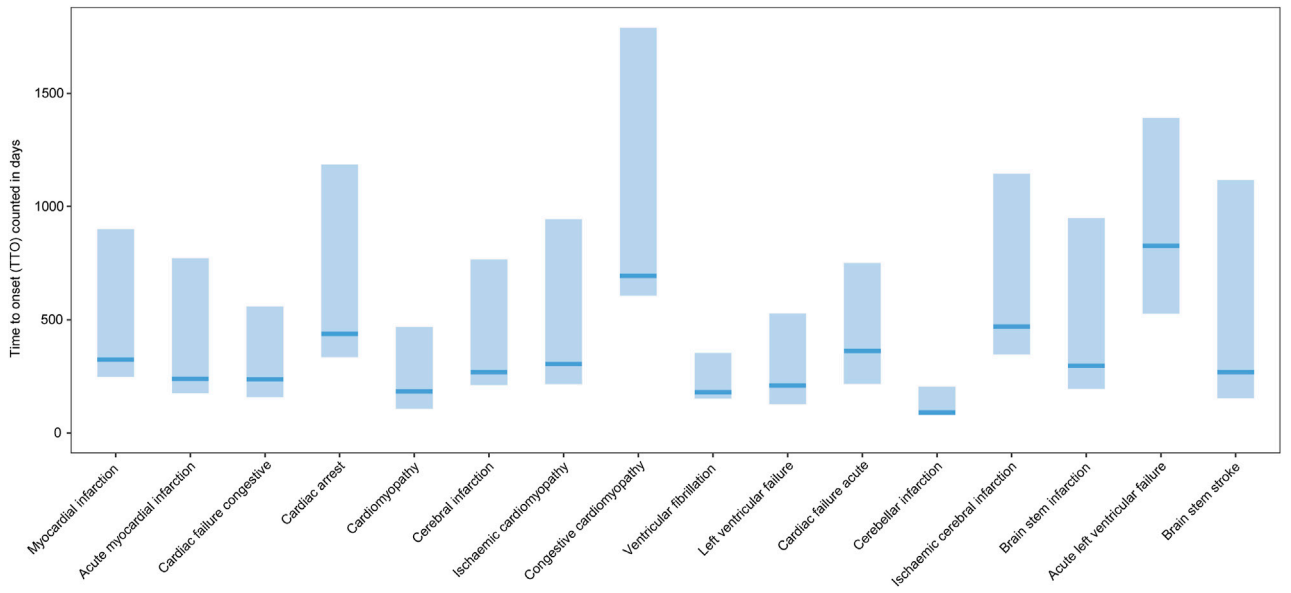

FIGURE 3
Box plot of the time-to-onset of the MACE. *x*-axis: MACEs; *y*-axis: time-to-onset (TTO) counted in days; bold bar within the stick: median TTO of concerned MACEs; lower end of the stick: 1/4 quantile of the TTO; upper end of the stick: 3/4 quantile of the TTO.

3,057 cases (10.57%) referred to MACEs and 19,727 cases (68.30%) referred to the gender as male of age above 50 yo (Supplementary Table S1). The elderly groups with no exposure to exogenous testosterone with ages above 50 yo (NT >50 yo) and 65 yo (NT >65 yo), accounted for 2,393,876 (Figure 1) and 1,350,931 cases in total, respectively. Men accounted for 97.81%

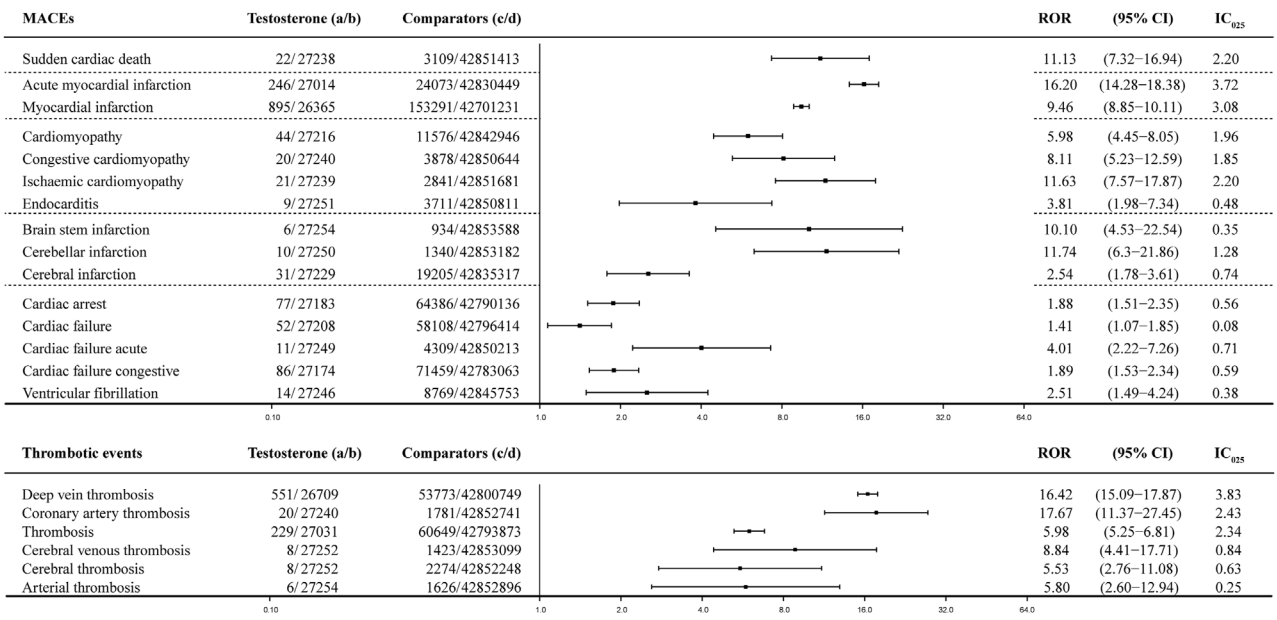

FIGURE 4
Forest plot of the adjusted ROR of testosterone: dataset of testosterone treatment (TT), which was filtered with the gender as male, age above 50 yo, and all AE reports referring to interfering concomitants and morbidities were dropped prior to the calculation. MACE, major adverse cardiovascular event; a: number of reports referring to both the targeted drug and the interested adverse event (testosterone–MACE); b: number of reports referring to the targeted drug paired with all the reported adverse events (AEs) other than MACEs; c: number of reports referring to MACEs concerning all the other drugs other than the targeted drug; d: number of reports referring to all the reported drug–AE pairs other than testosterone–MACE; 95% CI, 95% confidence interval; IC_{025}, lower limit of the information component of the Bayesian confidence propagation neural network.

of MACE-related cases, while 90.97% testosterone recipients were male. About 52.60% subjects referring to MACEs were within the age gap of 50 yo–64 yo, while 42.85% of testosterone users were in the same age group (Figure 2A). Notably, most of the MACE-related reports (3,401) were filed between 2014 and 2018 (Figure 2C), which indicated that there must be follow-up cases, as the sum of the number of reports exceeded the total case number of 3,057 and enabled the calculation of the TTO (Supplementary Table S1; Figure 3). The most recorded MACEs included MI (1,700 cases, 55.61%, with a median TTO of 246 days), AMI (605 cases, 19.79%, with a median TTO of 173 days), and cardiac congestive failure (333 cases, 10.79%, with a median TTO of 156 days). There were indications and concomitant drugs that indicated morbidities other than TD, including hypertension, DM, and increased blood cholesterol as the top three indications, while aspirin, lisinopril, and metformin were the top three concomitant drugs. The outcomes of MACE-related reports tended to be more serious than the reports of testosterone users (Figure 2B). There were 2,451 cases (80.18%) of recorded hospitalization or prolonged hospitalization (HO), 581 cases (19.01%) of recorded disability (DS), 489 cases (16.00%) of recorded deaths (DEs), and 2,039 cases (66.70%) referring to other serious conditions (OT).

3.2 Adjusted ROR of MACEs

Paired with TT, MACEs generated various PV signals that could be roughly categorized into four subgroups: infarctions, cardiac failure, cardiomyopathy, and cardiac arrhythmia, such as VF and cardiac arrest (Figure 4). Infarctions were the most significant PV signals generated when paired with testosterone, including AMI with the ROR value as 16.20 (95% CI: 14.28–18.38) and IC_{025} as 3.72 and MI with the ROR value as 9.46 (95% CI: 8.85–10.11) and IC_{025} as 3.08; both were strong signals generated by the BCPNN. Infarctions related to the brain were relatively weaker, including cerebellar infarction with the ROR value as 11.74 (95% CI: 6.30–21.86) and IC_{025} as 1.28. Cardiac infarctions were considerably more common and more intense in signals on the IC_{025} basis, although the ROR value was roughly at the same level. There were 895 cases of MI and 246 cases of AMI, while cerebral infarctions were counted in dozens. Cardiomyopathy-related AEs and sudden cardiac deaths were the next category, counted in dozens but generated medium signals, including sudden cardiac deaths with the ROR value as 11.13 (95% CI: 7.32–16.94) and IC_{025} as 2.20; cardiomyopathy with the ROR value as 5.98 (95% CI: 4.45–8.05) and IC_{025} as 1.96; congestive cardiomyopathy with the ROR value as 8.11 (95% CI: 5.23–12.59) and IC_{025} as 1.85; and ischemic cardiomyopathy with the ROR value as 11.63 (95% CI: 7.57–17.87) and IC_{025} as 2.20. To interpret the results, we also investigated thrombosis events, due to the reasonable speculation that infarctions and strokes might be rooted in embolic and thrombosis events. Arterial thrombosis and cerebral thrombosis counted less than 10 cases, while coronary arterial thrombosis count 20 cases, with the ROR value as 17.67 (95% CI: 11.37–27.45) and IC_{025} as 2.43. Cardiac failure and cardiac arrhythmia events, such as VF, were rare and weak, among which cardiac failure acute was the strongest signal with the ROR value as 4.01 (95% CI: 2.22–7.26) and IC_{025} as 0.71. Although ventricular arrhythmia, such as VF, in itself

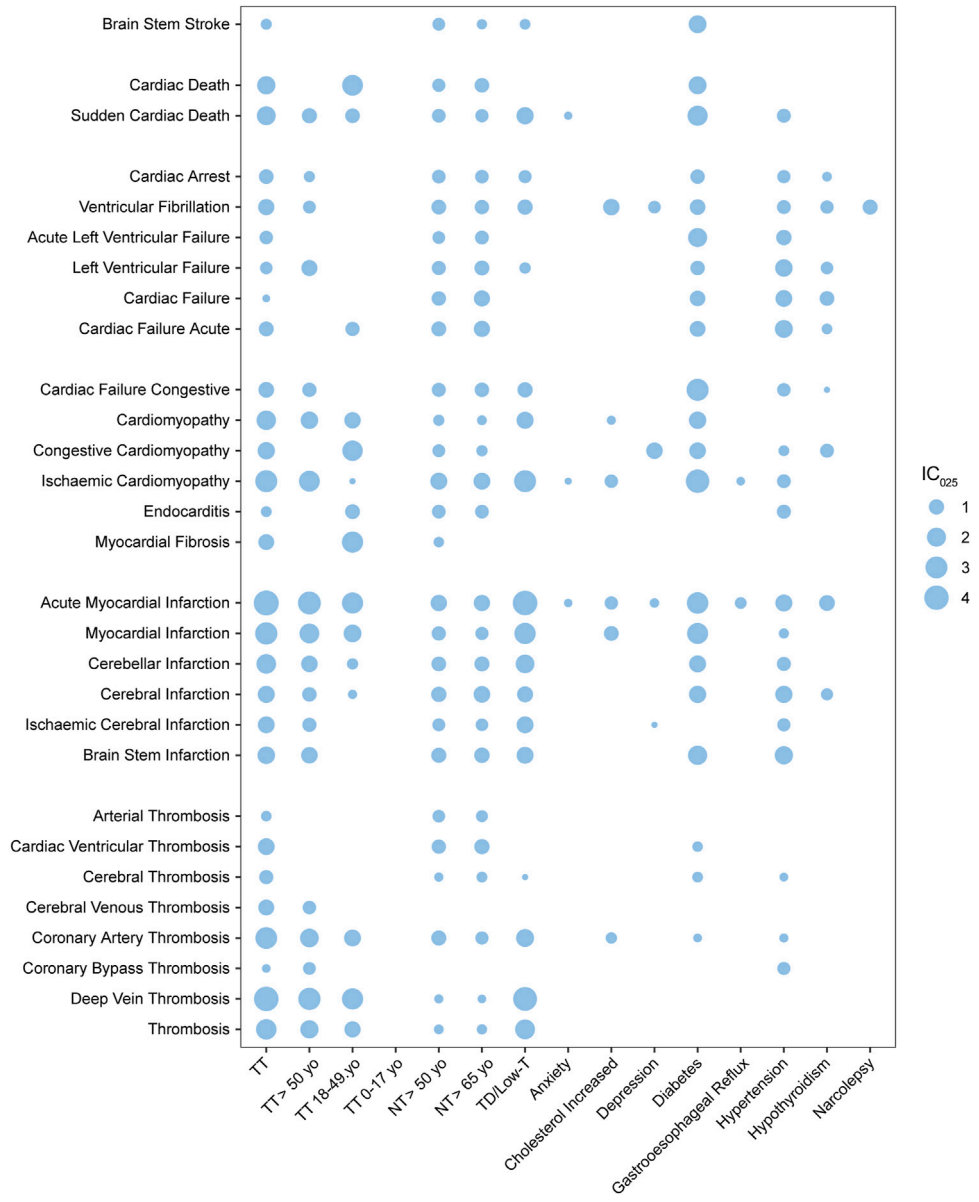

FIGURE 5
Bubble plot of pharmacovigilance signals generated by MACEs paired with various risk factors; TT, testosterone treatment; NT, no record of TT; TD, testosterone deficiency; low-T, low testosterone level; yo, years old; the intensity of the signal is defined using the value of the lower limit of the information component (IC_{025}) and was demonstrated with the size of the bubble.

is not a direct cause of left ventricular cardiac failure, it can lead to it if it is not treated promptly (Packer, 1992), including VF with the ROR value as 2.51 (95% CI: 1.49–4.24) and IC_{025} as 0.38. Cardiac arrest was the most common AE of arrhythmia counting 77 cases, with the ROR value as 1.88 (95% CI: 1.51–2.35) and IC_{025} as 0.56. Compared with crude IC_{025} (Figure 5, detailed in Supplementary Table S2), almost all the signals were weaker for the adjusted ROR, including AMI with the IC_{025} value as 4.25 (crude) vs. 3.72 (adjusted); MI with the IC_{025} value as 3.12 (crude) vs. 3.71 (adjusted); and ischemic cardiomyopathy with the IC_{025} value as 3.02 (crude) vs. 2.20 (adjusted), while weak signals such as cardiac deaths, brain stem strokes, and brain stem infarctions disappeared for the adjusted calculation, due to the casting out of reports referring to indications of MACEs and concomitant drugs that could have generated valid PV signals of MACEs.

3.3 Panorama of risk factors and MACEs

As shown in the bubble map (Figure 5, detailed in Supplementary Table S2), the value of IC_{025} was represented by the size of the bubble, while every bubble for a TT–MACE combination was left unpainted if the combination did not generate valid PV signals. The *x*-axis demonstrated risk factors including TT (alongside the subgroups of TT: 0–17 yo, TT: 18–49 yo, and TT >50 yo), elderly without TT

(including NT >50 yo and NT >65 yo), TD, and top 10 indications alongside TT except "pain," while the *y*-axis listed MACEs with which they were paired. The PTs of MACEs were roughly categorized into five subgroups: infarction and stroke, cardiac death, cardiomyopathy, cardiac arrhythmia, and cardiac failure. The PTs related to embolic and thrombosis events were also analyzed and demonstrated in Figure 5.

3.3.1 Morbidities

Morbidities including TD, DM, and hypertension were generated and shared almost all MACE-related PV signals with TT, while the other eight indications, depression, anxiety, gastroesophageal reflux disease, narcolepsy, and other morbidities, were not so associated with MACEs. Compared with TT, DM as a risk factor demonstrated notable figures when associated with MACE, including brain stem stroke (BSS) with the IC_{025} value as 1.65 (vs. the IC_{025} value as 0.29 for TT–BSS), acute left ventricular failure (LVF) with IC_{025} as 2.00 (vs. 0.65 for TT–LVF), and cardiac failure (CF) with IC_{025} as 3.05 (vs. 1.10 for TT–CF); hypertension–LVF generated the IC_{025} value as 1.5, but DM and hypertension generated little thrombotic PV signals. Cardiac death, endocarditis, and myocardial fibrosis were unique to TT and generated PV signals with the IC_{025} value as 1.77, 0.28, and 1.13, respectively, compared with hypertension and TD.

3.3.2 Thrombotic events

While testosterone was found to increase the risk of venous thrombotic events, the risk of arterial thrombotic events, particularly the events related to the heart or brain did not exhibit a significant increase. In total, when paired with testosterone, thrombosis generated medium signals with IC_{025} as 2.47 (vs. 2.25 for TD–thrombosis), while coronal arterial thrombosis (CAT) generated IC_{025} as 2.92 (vs. 1.68 for TD–CAT) and deep vein thrombosis (DVT) with IC_{025} as 4.04 (*vs.* 3.76 for TD–DVT). When it comes to cardiac- or cerebral-related thrombosis, cardiac ventricular thrombosis has a value of 1.36, while cerebral thrombosis has a value of 0.78 and cerebral venous thrombosis has a value of 1.15. As an endogenous hormone, testosterone is widely used for TT (Baillargeon et al., 2015; Elliott et al., 2017), and there is limited evidence that other medications can deal with low-T. It was unlikely that we could distinguish the differences between the datasets of TD and TT. However, for arterial thrombosis, cardiac ventricular thrombosis, cerebral thrombosis, and coronal artery thrombosis, there were significant differences between TT and TD, which demonstrated almost no association; while for deep vein thrombosis, there was no significant difference between TT and TD.

3.3.3 Age and MACEs

Normal aging is a risk factor for various health hazards, including hypogonadism, CV issues, and MACEs (Nguyen et al., 2015). Compared with morbidities including TD, DM, and hypertension, the risk factor of age is insignificant, based on FAERS data. Weak PV signals could be generated between an elderly group without TT (NT >50 yo and NT >65 yo) and arterial thrombosis events and cardiac failure events, while TD could not (Figure 5). For lethal cases, when associated with NT >50 yo, sudden cardiac death generated the IC_{025} value of 0.75, while the elderly group of TT (TT >50 yo) generated the IC_{025} value of 0.98; meanwhile, the TD–sudden cardiac death pair generated the IC_{025} value of 1.48. Cardiac death associated with TT could generate a medium signal, but it can later be ruled out by the adjusted ROR, mentioned in Section 3.2. For testosterone users, most MACE signals were stronger in the age group above 50 yo (TT >50 yo) than in the age group of 18–49 yo (TT 18–49 yo), especially for ischemic cardiomyopathy (IC_{025} as 2.72) and cerebral-related infarctions, including ischemic cerebral infarction (IC_{025} as 0.78) and brain stem infarction (IC_{025} as 1.31). However, for congestive cardiomyopathy (IC_{025} as 2.45), endocarditis (IC_{025} as 0.92) and myocardial fibrosis (IC_{025} as 2.72), which are unique to testosterone users, have stronger signals when associated with TT 18–49 yo, compared to TT and TT >50 yo. The signals generated by TT subgroups stratified by age were generally weaker than TT. MACEs and thrombosis events generated no valid PV signals in the non-age group (TT: 0–17 yo).

3.3.4 The chi-square test

Chi square (Chi^2) tests were applied to investigate correlations between the patterns of MACEs associated with various risk factors, including TD, with or without TT, and morbidities, using a null hypothesis claiming that the prevalence of any two given series of IC_{025} was the same (Supplementary Table S3). No significant differences were found based on the Chi^2 test, but among all the series, testosterone users aged between 18 and 49 yo (TT: 18–49 yo) exhibited a slight deviation from testosterone users aged above 65 yo (p value = 0.54) and TD (p value = 0.4) and non-TT cases above 50 yo (p value = 0.79) and above 65 yo (p value = 0.75).

3.4 Developing trend of PV signals

Data mining procedures were also applied to investigate the association between TT and MACEs based on the reports of each year separately and on the dataset that accumulated over time by adding yearly data to the previous years. To demonstrate the changing pattern of the yearly tendency (Figure 6, detailed in Supplementary Table S4, taking MI as an example), the natural logarithm value of the ROR (ln ROR) and IC_{025} was used as vertical coordinates and were plotted against each calendar year as horizontal coordinates. For IC_{025}, there was no valid PV signal of MI for both yearly calculations, until 2014; while for ln ROR, there was a valid PV signal in 2008. Since 2014, the value of ln ROR and IC_{025} changed dramatically. For the accumulation calculation, the signal achieved equilibrium since 2019; while for the separate calculation, the plot demonstrated a double peak and then underwent a decrease since 2019.

4 Discussion

It should be noted that the TRAVERSE. (2019) began in 2018, which was the first TT trial designed to fully evaluate testosterone-induced CV events. The results of this trial, which were derived from a double-blind and placebo-controlled study, would provide more conclusive evidence of the CV safety of TT, but the findings might not be available for a decade (Bhasin et al., 2022). Our work is the

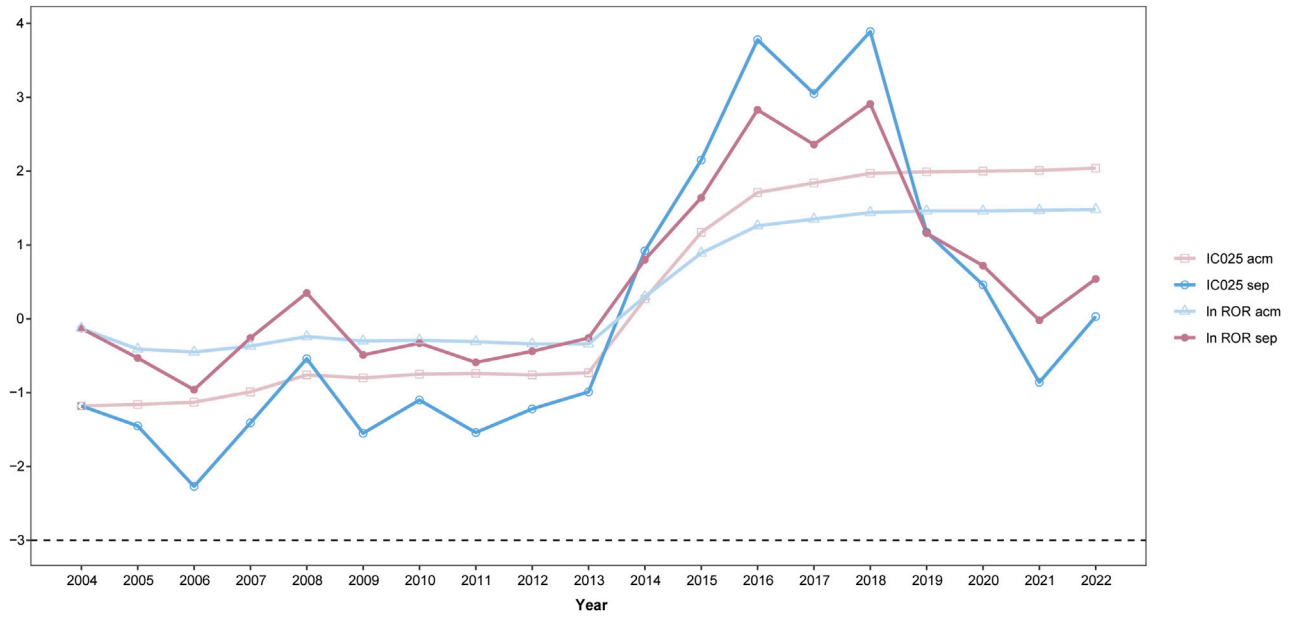

FIGURE 6
Trend of pharmacovigilance signals taking myocardial infarction (MI) as an example; IC_{025}, lower limit of the information component; ln ROR, natural logarithm value of the ROR; acm, calculation based on the accumulated dataset year after year; sep, calculation based on the dataset of every single year; *x*-axis, time in the calendar order; *y*-axis, natural algorithm value of the ROR (ln ROR); IC_{025}, lower limit of the information component.

latest data mining approach used for investigating the association between TT and MACEs based on the FAERS database.

4.1 Control group

The testosterone level is usually not shown by AE reports in the FAERS, although the dosage information might give us some clues about severity of TD, as the therapeutic dosage was intended to maintain the suggested threshold level between 300 and 350 ng/dL according to the guidelines (Salter and Mulhall, 2019). In addition, testosterone is widely used for men with hypogonadism as TRT (Elliott et al., 2017; Bhasin et al., 2018), which meant that the population of testosterone users largely overlapped with the population with TD. Therefore, it was challenging to define a control group with TD and without TT. All the cases referring to men above 50 yo (and above 65 yo), without recording TT and without indications referring to MACEs, who were probably undergoing a decrease in testosterone levels (Petering and Brooks, 2017; Bhasin et al., 2018; Grober et al., 2021) (Supplementary Table S3), were extracted to represent the population of low-T and served as control groups together with the TD group, which was composed of all reports referring to low-T as indications. Signals generated by testosterone paired with MACEs and by control groups paired with MACEs proved that the dataset of TT and TD were largely composed of the same cases, and most of the cases of TT were indeed cases of TRT. Testosterone users aged between 18 and 49 yo demonstrated a slight deviation from control groups including TD, non-TT cases, and testosterone users aged above 50 yo, which indicated that age is a significant risk factor of MACEs, as the low-T status is a risk factor for MACEs (Shores et al., 2012). Previous publications stated that testosterone could improve the blood fibrinolytic activity of patients, thus playing a role in the treatment of occlusive vascular diseases, but its causal relationship was worth considering (Fearnley and Chakrabarti, 1962). If the lower testosterone status was amended by TT, patients aged between 18 and 49 yo achieved benefits for preventing MACEs, especially for congestive cardiomyopathy, endocarditis, and myocardial fibrosis, which were almost unique to patients receiving TT between 18 and 49 yo.

4.2 Interfering

TD could be caused by various conditions, including normal aging, hypogonadism, injury, or dysfunction of testicles, disorders that affect the pituitary gland and cause kidney diseases (Bhasin et al., 2018). Since not all TT was associated with a decreased mortality compared with no TT (Shores et al., 2012) and DM and hypertension also generated valid PV signals referring to MACEs, our findings should be interpreted cautiously, considering that morbidities and concomitant drugs may be a source of bias. To eliminate interfering caused by concomitant drugs and indications, the dataset which was extracted from the FAERS underwent the data mining analysis described in Section 2.5. Reports that referred to concomitant drugs that generated valid PV signals and indications related to MACEs were cast out from the dataset of TT, and the adjusted ROR was calculated (Supplementary Table S1). Although all the values of the adjusted ROR and IC_{025} were lower than the crude calculation, it indicated that lesser cases were taken into consideration, but with more credibility.

TT might be beneficial to TD patients as it reduces cardiac failure and cardiac arrhythmia; however, it increased the risk of infarctions and cardiomyopathy, according to FAERS data. The mechanism might show that androgen exposure increases cardiotoxicity by activating inflammatory mediators (Sessa et al., 2022) and that testosterone increased the risk of thrombosis, and infarctions could be caused by thrombosis, which matched with the result of Luo's study, stating that genetically predicted endogenous testosterone is positively correlated with thromboembolism and heart failure, especially in men (Luo et al., 2019). Another systematic review and meta-analysis of placebo-controlled randomized trials on men, who had been treated with testosterone for more than 12 weeks and who reported CV events, concluded that exogenous testosterone increased the risk of CV events (Xu et al., 2013). We made a comprehensive summary of the association between TT and CV events (Gagliano-Jucá and Basaria, 2019) and mentioned that there were several retrospectives and prescription database studies referring to the increased number of CV events in men who received TRT (Vigen et al., 2013; Finkle et al., 2014; Etminan et al., 2015; Martinez et al., 2016).

In addition, cardiomyopathy-related signals could be generated when associated with TT, and stronger signals than those associated with TD could also be generated, when evaluated by IC_{025}. Cardiomyopathy is usually caused by the long-term use of anabolic steroids, which are synthetic derivatives of testosterone, and due to the toxicity of other medications (Liang et al., 2019), they might cause the irreversible destruction of the heart tissue (Salimi et al., 2020). Our findings indicated that TT notably increases the risk of cardiomyopathy and other types of damage referring to the heart, such as endocarditis and myocardial fibrosis, and this could be supported by a case report that claims that exogenous testosterone is a rare and reversible cause of cardiomyopathy in young and otherwise healthy athletes, and a high index of suspicion is required to prevent potentially fatal side effects (Doleeb et al., 2019). Congestive cardiomyopathy tends to occur among testosterone users aged 18–49 yo, while ischemic cardiomyopathy tends to occur among patients above 50 yo. All cardiomyopathy-related events generated weaker signals among subjects above 50 yo and 65 yo who had no record of TT, compared to their counterparts who accepted TT. Therefore, a conservative use of testosterone is warranted in men with CV diseases, who may be at greater risk for adverse outcomes (Shores and Matsumoto, 2014).

There were several studies that suggested that testosterone therapy was not significantly associated with the occurrence of MACEs or even reduced such risks (Gencer and Mach, 2016; Maggi et al., 2016), which can also be explained by our study, considering the morbidities. Normal aging, TD, DM, and hypertension were morbidities that were associated with MACE; notably, they seemed to have little effect on thrombosis events, except in TD (Figure 5). Brain stem stroke, ischemic cardiomyopathy, sudden cardiac death, and cardiac failure-related events associated with diabetic patients generated stronger signals and were associated with TT, while cardiac failure-related events associated with hypertension generated strong signals than those associated with TT. These findings indicated that TT might benefit the patient with DM and hypertension by preventing cardiac failure, especially cardiac failure events such as left ventricular failure and acute left ventricular failure, which were more related to cardiac arrhythmia, such as VF. Although VF itself is not a direct cause of left ventricular cardiac failure, it can lead to it if it is not treated promptly (Packer, 1992). In general, MACE-related signals generated by TT were stronger than those generated by TD, but were weaker than their counterparts generated by patients with DM and hypertension. These findings indicated that TT may improve the cardiac output, as suggested by previous publications (Pugh et al., 2004; Park et al., 2021), potentially benefiting ischemic myopathy. However, it may have a negative impact on cardiac failure caused by congestive reasons, indicating that the effects of testosterone on the heart are complex and context-dependent; while it seems to have no significant effect on cardiac arrhythmia-related MACEs, although animal models suggest that androgen increases the risk of hydro-electrolytic and autonomic imbalances, but did not alter the vascular or cardiac function or morphology (Salimi et al., 2020). Notably, the PT of cardiac death generated a valid PV signal when associated with TT by a crude calculation, but was ruled out from the results of the adjusted ROR, which indicated that this signal might be contributed by interfering, but is still worthy of demonstration in the bubble map.

4.3 Underreporting

As an endogenous hormone, testosterone was first used for TT in the late 1930s and has become an established treatment for male hypogonadism, since then (Bhasin et al., 2007); however, reports referring to TT-induced MACEs are relatively rare in the FARES, and PV signals of TT-induced MACEs did not emerge until 2015. To make the situation even more precarious, in 2014, the FDA agreed that enough attention should be paid to the potential risk signals of CV risks (Garnick, 2015; Seftel, 2015). Therefore, we should be more cautious when we monitor PV signals in a retrospective study on the signals which were dramatically increased, and then in the next few years, it gradually decreased. Hypothetically, if there is an association that exists between the risk factor and the outcome, the disproportionality caused by it should have presented us with some stable levels on a yearly basis. To fix the biases inherent to PV studies and notices publicized by authorities, AE reports filed to the FAERS in the following several years should be carefully examined and subjected to more restricted inclusion criteria, such as only accepting the reports filed by health professionals. We shall also focus on unreported signals, which were steady and gradually increased for the pharmacosurveillance purpose. These findings also indicated that there might still be a large number of related adverse events that went unrecorded, and the health workers should be reminded to pay more attention to MACEs associated with TT.

4.4 Limitations

There were several concerns that might undermine the credibility of this paper. Although the dataset of TD was largely overlapped with the dataset of TT, there were 5,072 cases (17.54%) of TT referring to indications as the "product used for unknown indication." Therefore, for these cases, the possibility of alternative testosterone treatment other than TRT, for example, using as bodybuilding supplements (Doleeb et al., 2019), cannot be ruled out. However, we cannot cast out these cases either. Spontaneous reporting systems including the FAERS were exposed to the biases inherent to PV studies. The FDA Advisory

Committee agreed that enough attention should be paid to the potential risk signals of CV risks in 2014 (Garnick, 2015; Seftel, 2015), which coincidently matched the gush of MACE-related ADR reports and a surge in the ROR for the TT–MACE pair. Therefore, we should be cautious when we try to interpret the calculations. In addition, since TT is the prevailing treatment for TD, it is unlikely that we could discuss testosterone-induced MACEs without considering that these conditions might be caused by a low testosterone status (Shores and Matsumoto, 2014), and the causal relationships between MACEs and testosterone could not be confirmed by the data mining approach alone.

5 Conclusions

In conclusion, we aimed to address the long-standing controversy shrouding the association between TT and MACEs, based on FARES data. Age turned out to be the most significant risk factor for TT-induced MACEs. Compared with the TD population, TT increased the risk of MACEs, especially for infarction- and cardiomyopathy-related events, while it demonstrated curative effects when paired with cardiac arrhythmia- and cardiac failure-related events and stroke and sudden cardiac death. TT demonstrated benefits in preventing MACEs related to cardiac congestive failure and ischemic events for patients who suffered with DM and hypertension. Endocarditis and myocardial fibrosis were uniquely associated with TT, especially among male adults. Computational studies are crucial in setting up well-designed scientific studies, while micro-RNA molecules have been shown to play various significant roles in many physiological and pathophysiological processes in living organisms (Lukasik and Zielenkiewicz, 2019). We reported that micro-RNAs, including hsa-miR-133a, hsa-miR-21, hsa-miR-499a, hsa-miR-1, and hsa-miR-126, played an active role in the genesis and development of different types of heart damage, using an integrative analysis (Sessa et al., 2018). Further studies focused on identifying molecular markers related to MACEs that could be used for both diagnostic and therapeutic purposes and could have an ambitious goal of revealing the mechanism of TT-induced MACEs. Healthcare workers should be fully aware of the benefits and possible risks of TT to improve the effectiveness and safety of drug treatments and patients' quality of life.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the following: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

X-YQ and M-MY designed the study; J-ML, M-MY, HZ, and Z-RL conducted the study; QZ and HZ analyzed and interpreted the data; QZ and Z-RL contributed to the production of forms, figures, and analytical methods; M-MY, J-ML, and HZ drafted the manuscript; HZ, J-ML, X-YQ, M-KZ, and M-MY revised 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

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1182113/full#supplementary-material

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Infections associated with clozapine: a pharmacovigilance study using VigiBase®

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Introduction: Clozapine is primarily reserved for treatment-resistant schizophrenia due to safety concerns associated with its use. Infections have been reported with clozapine, which may lead to elevated serum levels of the drug. However, the existing literature on this topic is limited. Therefore, we conducted a study using VigiBase® to investigate the potential over-reporting of infections associated with clozapine, to explore the presence of dose-dependency, and to investigate the underlying mechanism.

Methods: Disproportionality analyses were performed using VigiBase to assess the association between clozapine and all types of infections, the association between clozapine-associated infections and neutropenia, the association between clozapine-associated infections and agranulocytosis, the dose–effect relationship between clozapine and infections, and the interaction between clozapine and the main strong CYP450 inhibitors using reports carried out until 11 April 2023.

Results: A statistically significant signal of infections was observed with clozapine, as indicated by an information component of 0.43 [95% CI: (0.41–0.45)]. The most commonly reported infections were respiratory and gastrointestinal in nature. Neutropenia showed weaker association with clozapine-associated reports of infections compared to other clozapine-associated reports [X2 (1, N = 204,073) = 454; $p < 0.005$], while agranulocytosis demonstrated a stronger association with clozapine-associated reports of infections [X2 (1, N = 204,073) = 56; $p < 0.005$]. No evidence of dose-dependency was observed. Among the 17 tested CYP inhibitors, significant drug–drug interactions were found with clarithromycin, metronidazole, valproic acid, lansoprazole, omeprazole, amiodarone, and esomeprazole.

Discussion: Our study revealed a significant safety signal between clozapine use and infections, predominantly respiratory and gastrointestinal infections. The co-administration of clozapine with valproic acid or proton pump inhibitors may potentially contribute to an increased risk of infection. Further vigilance is warranted in clinical practice, and consideration of therapeutic drug monitoring of clozapine in cases involving concomitant use of these drugs or in the presence of infections may be beneficial.

KEYWORDS
clozapine, infection, overdose, interaction, pharmacovigilance

Introduction

Clozapine is an atypical antipsychotic drug mostly used in patients with treatment-resistant schizophrenia. Over the years, its use has increased in many countries, with the prevalence of clozapine consumption in 2014 ranging from 0.9 to 173.2 per 100,000 persons, depending on the country (Bachmann et al., 2017; Remington et al., 2017). Safety issues associated with clozapine are common and include agranulocytosis (occurring in approximately 1.0% of patients) and neutropenia (occurring in approximately 3.0% of patients) (Rajagopal, 2005). Due to these safety concerns, clozapine is usually reserved for treatment-resistant schizophrenia despite its demonstrated efficacy in managing positive, negative, and overall symptoms and relapse rates in schizophrenia, compared to first-generation antipsychotics and pooled first-/second-generation antipsychotics (Wagner et al., 2021).

Infections have also been reported with clozapine, potentially leading to the elevation of serum levels of the drug. A systematic review identified 40 cases of infections with demonstrated elevated clozapine levels (Clark et al., 2018). In a Chinese cohort of patients undergoing therapeutic drug monitoring during infection and non-infection periods, the median levels of clozapine were significantly higher in the infection period compared to those in the non-infection period (n = 42; p < 0.001) (Zhang et al., 2021). Elevation of clozapine levels with infection may be due to downregulation of metabolizing enzymes such as cytochrome P450 (Clark et al., 2018). Additionally, a retrospective study from the UK found an increased risk of COVID-19 infection in clozapine-treated patients compared to those on other antipsychotic drugs (adjusted hazard ratio = 1.76; 95% CI 1.14–2.72) (Govind et al., 2021).

Clozapine might be more strongly associated with pneumonia than with other infections. A study on a Taiwanese registry with 33,024 inpatients with schizophrenia found that the current use of clozapine was associated with a dose-dependent increase in the risk of pneumonia (adjusted risk ratio = 3.18; 95% CI: 2.62–3.86) (Kuo et al., 2013). A study using VigiBase®, the WHO global safety report database, supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions (De Leon et al., 2020).

Patients with schizophrenia often receive polypharmacotherapy, exposing them to potential drug–drug interactions (DDIs). A cross-sectional observational study in a psychiatric hospital found a high prevalence (88.7%) of potential DDI in this population (Bačar Bole et al., 2023). Clozapine is metabolized by various CYP450 enzymes, including CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 (Chetty and Murray, 2007; Pardiñas et al., 2019). Therefore, the association of clozapine with CYP450 inhibitors could lead to clozapine overdose and increase the risk of infection.

Sex-related differences in clozapine tolerability have also been described in 147 treatment-resistant patients treated with clozapine (Martini et al., 2021). Age onset incidence of schizophrenia also differs by sex (Jauhar et al., 2022). As sex-specific differences in the susceptibility to infections and immune response to infection have been reported (McClelland and Smith, 2011), it is also possible that sex differences in clozapine-associated infections exist.

However, until now, studies about clozapine-associated infections remain scarce and are poorly described. Except for clozapine-induced pneumonia, which has been widely described (De Leon et al., 2020), it is unclear what kind of other infection clozapine exposure might lead to. The mechanism behind these infections also needs to be understood as it could be hypothesized that clozapine-induced infections are caused by clozapine-associated neutropenia. Dose-dependency, patient-associated risk factors, and potential DDIs leading to infections also need to be explored to improve preventive measures. Thus, for a better understanding of clozapine-associated infections, a study was conducted using VigiBase®. The objectives were to assess if clozapine was associated with an over-reporting of infections, to characterize these infections, to evaluate dose-dependency and sex differences, and to investigate potential DDIs associated with infections. The study also explored if clozapine-associated infections were more associated with neutropenia.

Materials and methods

Study design

We conducted a retrospective pharmacovigilance cohort study using VigiBase®, the WHO global individual case safety report (ICSR) database. Access to the data was granted by the WHO Uppsala Monitoring Centre. The database contains suspected drugs, suspected adverse drug reactions (ADRs), patient demographics, and other variables, with over 32 million ICSRs received from 130 countries, since 1967 and previously described elsewhere (Chrétien et al., 2021). The study protocol was registered on ClinicalTrials.gov with the identifier NCT05919550.

Setting and participants

We utilized all the reports from the de-duplicated VigiBase® dataset from the 11th of April 2023 version. The suspected duplicates were identified using vigiMatch, an algorithm developed by the Uppsala Monitoring Centre, and excluded. The scope of the dataset was limited to drugs; vaccines were excluded due to their distinct usage profile, potential for higher infection reporting, and reporting bias associated with the COVID-19 pandemic.

Variables

Infections were identified using the Medical Dictionary for Regulatory Activities (MedDRA v25.1) System Organ Class infections and infestations (Supplementary Table S1). The analysis included preferred terms of infection, as shown in Supplementary Table S1. Some terms were overly general,

making it challenging to comprehensively understand the nature of the ongoing infection (e.g., the term "Infection"). Neutropenia and agranulocytosis were defined using their associated preferred terms. Clozapine was identified using the Anatomical and Therapeutic Chemical classification and/or its international non-proprietary name. The daily dose of clozapine was extracted from clozapine reports and divided into quartiles to perform the dose-dependency analysis (reports with the available daily dose were attributed to their corresponding quartile).

Outcomes

The primary outcome was the association between clozapine and all types of infections. Secondary outcomes included the following:

- The association between clozapine and all types of infections over time (cumulative).
- The association between clozapine and all types of infections:
  - In women population
  - In men population
  - In people aged 44 or lower
  - In people aged 45 or higher
- The association of clozapine with more detailed terms of infection (all MedDRA preferred terms included in the infection and infestation System Organ Class groups), for which at least five cases were reported with clozapine.
- The association between clozapine-associated infection and neutropenia, and the association between clozapine-associated infection and agranulocytosis.
- The dose–effect relationship between clozapine and infections.
- The interaction between clozapine and various strong CYP450 inhibitors [amiodarone, atazanavir, cannabidiol, ciclosporin, clarithromycin, clobazam, esomeprazole, felbamate, fluconazole, fluvoxamine, itraconazole, lansoprazole, metronidazole, omeprazole, ritonavir, voriconazole, and valproic acid (VPA)] and the reporting of infection. CYP450 inhibitors were defined using WHODrug Insight (Uppsala Center, 2023) and the interaction table from Geneva University Hospitals (Geneva University Hospital, 2020) (Supplementary Table S3).

Statistical analyses

To assess the association of clozapine with the reporting of infections, a disproportionality analysis was used to evaluate the associations between drugs and reactions using VigiBase® (Faillie, 2019). This type of study was previously described (Chrétien et al., 2021). In the present study, the information component (IC) and its 95% credibility interval (CI) were used to evaluate disproportionality. The IC is a Bayesian measure of the disproportionality between the observed and the expected reporting of a drug–ADR pair, developed by members of the WHO Uppsala Monitoring Centre (Bate et al., 1998). We chose to compute the analysis only for drugs that reported at least five cases of infections as IC was found to be more reliable when at least three to five cases of an ADR were reported for a drug (Evans et al., 2001). A lower end of the 95% CI of the IC > 0 was deemed significant.

- A disproportionality analysis was used to evaluate the association between clozapine and all MedDRA preferred terms included in the infection and infestation System Organ Class groups using the same method as described previously.
- A disproportionality analysis was used to evaluate the association between each quartile of the dose of clozapine and the reporting of infections using the same method as described previously.
- A disproportionality analysis was used to evaluate the association between clozapine and various CYP450 inhibitors (amiodarone, atazanavir, cannabidiol, ciclosporin, clarithromycin, clobazam, esomeprazole, felbamate, fluconazole, fluvoxamine, itraconazole, lansoprazole, metronidazole, omeprazole, ritonavir, voriconazole, and VPA) and the reporting of infection. IC was also used for this analysis.
- A chi-squared test was used to assess the association between clozapine-associated infection and neutropenias by comparing the reporting of neutropenia in clozapine-associated infection reports to the reporting of neutropenia in other clozapine-associated reports. The same test was used with agranulocytosis.

Descriptive study using VigiBase®

We described the clinical features of clozapine-related infections, reporting the reports' completeness score, demographic parameters (age and sex), dose, seriousness, and percentage of death. The percentage of seriousness and death with other drugs associated with infections was also evaluated for comparison.

Results

Statistical analysis to assess the association of clozapine with the reporting of infections

Out of the 204,073 reports of clozapine-associated suspected ADRs, 19,404 were related to infections. A statistically significant signal of infections was found with clozapine, with an IC of 0.43 [95% CI: (0.41–0.45)] (Table 1). This signal was of similar magnitude among genders and tested age classes (Table 1). It was also consistent over time (Figure 1).

Descriptive study using VigiBase®

Table 2 presents the features of clozapine-associated reports of infections. Among these reports, 94.3% were considered serious and 9.8% of cases resulted in death. This is compared with reports of infection associated with other drugs, where 62.6% were considered serious and 6.8% resulted in death.

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TABLE 1 Disproportionality analysis in VigiBase: reports of association of clozapine with infections.

	N	IC	95% CI
Clozapine	19,404	0.43	[0.41; 0.45]
Clozapine (men)[a]	11,585	0.54	[0.51; 0.56]
Clozapine (women)[a]	7,534	0.44	[0.40; 0.47]
Clozapine (<45 yo)[a]	6,102	0.25	[0.21; 0.28]
Clozapine (≥45 yo)[a]	9,577	0.71	[0.68; 0.73]

N, number of reports; IC, information component; 95% CI, 95% credibility interval; yo, year old.
[a]Age was unknown in 19.8%, and sex was unknown un 2.6%.

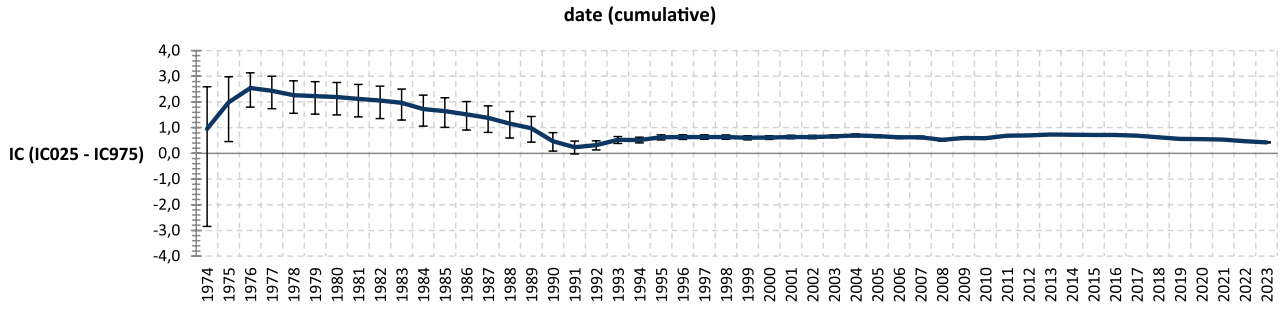

FIGURE 1
Disproportionality analysis of clozapine-associated infection over time (cumulative*). *Cumulative: previous data are used at the current date. For example, for the year 1977, data from 1974–1977 are used to compute the disproportionality analysis. Thus, at each point of the figure, cases and non-cases reported until this point are used to compute the information component.

TABLE 2 Description of clozapine-associated reports of infection.

Age	N available	15,549
	Median (IQR) in years	50 (38–62)
Sex	N available	18,906
	Sex ratio (male/female individuals)	1.57
Dose (in mg)	N available	2,319
	Median (IQR)	250 (100–400)
Completeness score (median with IQR)	0.42 (0.28–0.62)	
Seriousness	N available	15,421
	%	94.3%
Death (%)	9.8%	

Statistical analysis to assess the association of clozapine with all MedDRA preferred terms included in the infection and infestation System Organ Class groups

A total of 60 terms of infection were significantly associated with clozapine. The four most reported terms were pneumonia (5,751 reports), lower respiratory tract infection (2,268 reports), urinary tract infection (1,628 reports), and infections (1,564 reports). The 10 most significant signals were pneumonia aspiration [N = 850; IC: 3.28 (3.17–3.37)], viral myocarditis [N = 25; IC: 3.64 (2.97–4.11)], empyema [N = 75; IC = 3.22 (2.83–3.49)], lower respiratory tract infection [N = 2,268; IC: 2.79 (2.72–2.84)], infective exacerbation of chronic obstructive airways disease [N = 30; IC: 3.24 (2.63–3.67)], appendicitis perforated [N = 93; IC: 2.81 (2.46–3.05)], appendicitis [N = 261; IC: 2.61 (2.41–2.76)], abdominal sepsis [N = 24; IC: 3.01 (2.32–3.49)], lung abscess [N = 58; IC: 2.69

TABLE 3 Terms of infection associated with a significant over-reporting with clozapine (more than 15 reports per term).

Term	N	IC	IC025[a]	IC975
Pneumonia aspiration	850	3.28	3.17	3.37
Viral myocarditis	25	3.64	2.97	4.11
Empyema	75	3.22	2.83	3.49
Lower respiratory tract infection	2,268	2.79	2.72	2.84
Infective exacerbation of chronic obstructive airways disease	30	3.24	2.63	3.67
Appendicitis perforated	93	2.81	2.46	3.05
Appendicitis	261	2.61	2.41	2.76
Abdominal sepsis	24	3.01	2.32	3.49
Lung abscess	58	2.69	2.25	3.00
Parotitis	41	2.36	1.84	2.73
Coronavirus infection	178	2.07	1.82	2.25
Chronic hepatitis C	15	2.55	1.68	3.15
Pneumonia	5,751	1.67	1.62	1.70
Hepatitis C	302	1.73	1.54	1.87
Sialadenitis	43	2.05	1.54	2.41
Urosepsis	149	1.80	1.53	2.00
H1N1 influenza	30	2.02	1.41	2.45
Sepsis	1,521	1.43	1.35	1.49
Infectious pleural effusion	23	2.02	1.32	2.51
Viral infection	489	1.29	1.14	1.4
Suspected COVID-19	62	1.53	1.11	1.83
Gastroenteritis	225	1.25	1.03	1.41
Pulmonary sepsis	16	1.74	0.90	2.33
Infection	1,564	0.96	0.88	1.02
Respiratory tract infection	257	1.07	0.87	1.22
Stoma site infection	25	1.46	0.79	1.93
Neutropenic sepsis	65	1.19	0.78	1.49
Urinary tract infection	1,628	0.76	0.68	0.82
Endocarditis	51	1.14	0.67	1.47
Pyelonephritis	83	0.87	0.51	1.13
Hepatitis viral	15	1.35	0.48	1.95
Brain abscess	19	1.24	0.47	1.78
COVID-19	1,155	0.54	0.45	0.61
Pharyngitis	256	0.64	0.43	0.79
Abscess oral	22	1.11	0.39	1.61
Atypical pneumonia	34	0.91	0.34	1.32
Infectious mononucleosis	26	1.00	0.34	1.46
Septic shock	187	0.43	0.19	0.6

(Continued on following page)

TABLE 3 (*Continued*) Terms of infection associated with a significant over-reporting with clozapine (more than 15 reports per term).

Term	N	IC	IC025[a]	IC975
Encephalitis	42	0.67	0.16	1.03
Abscess	142	0.37	0.09	0.57

N, number of reports; IC, information component; IC025, lower end of the credibility interval; IC975, upper end of the credibility interval.
[a]The lower end of the credibility interval (IC025) is traditionally used as the threshold for generating a safety signal in pharmacovigilance databases and was used here to order the table.

TABLE 4 Disproportionality analysis for the drug–drug interaction between clozapine and a list of CYP450 inhibitors on the reporting of infections.

CYP inhibitor	N	IC	IC025	IC975	CYP1A2		CYP3A4		CYP2D6		CYP2C9		CYP2C19	
					WHO	HUG	WHO	HUG	WHO	HUG	WHO	HUG	WHO	HUG
Clarithromycin[a]	65	1.99	1.58	2.29	—	—	—	ST	—	—	—	—	—	—
Metronidazole[a]	53	1.68	1.22	2.01	—	—	—	—	—	—	WE	ST	—	—
Valproic acid[a]	1944	0.96	0.89	1.02	—	—	—	—	—	—	UN	ST	—	—
Lansoprazole[a]	453	0.95	0.8	1.07	—	—	—	—	—	—	—	—	UN	ST
Omeprazole[a]	598	0.49	0.36	0.59	—	—	—	—	—	—	—	—	MO	ST
Amiodarone[a]	15	1.18	0.31	1.78	UN	MO	WE	MO	WE	ST	MO	ST	—	—
Esomeprazole[a]	136	0.49	0.2	0.69	—	—	—	—	—	—	—	—	MO	ST
Clobazam	18	0.78	−0.01	1.33	—	—	—	MO	WE	—	—	—	—	MO
Fluvoxamine	45	0.43	−0.07	0.78	ST	ST	MO	MO	UN	—	WE	MO	ST	ST
Fluconazole	30	0.28	−0.33	0.71	—	—	MO	ST	—	—	MO	ST	ST	ST
Ciclosporin	8	−0.25	−1.46	0.55	—	—	MO	ST	—	—	—	—	—	—
Voriconazole	3	NA	NA	NA	—	—	ST	ST	—	—	WE	ST	MO	ST
Itraconazole	3	NA	NA	NA	—	—	ST	ST	—	—	—	—	—	—
Ritonavir	2	NA	NA	NA	UN	—	ST	ST	WE	ST	UN	—	—	—
Cannabidiol	1	NA	NA	NA	—	MO	—	ST	—	—	—	—	—	—
Felbamate	0	NA	NA	NA	—	—	—	—	—	—	—	—	WE	ST
Atazanavir	0	NA	NA	NA	UN	MO	—	ST	—	—	UN	MO	—	—

CYP, cytochrome; FDA, Food and Drug Administration; HUG, Hôpital Universitaire de Genève (Geneva University Hospitals); MO, moderate inhibitor; N, number of reports; NA, not applicable (not enough reports to compute the analysis); IC, information component; IC025, lower end of the credibility interval, IC975, upper end of the credibility interval; ST, strong inhibitor; UN, unclassified inhibitor; WE, weak inhibitor; WHO, World Health Organization classification.
HUG, classification contains two levels: MO and ST.
WHO, classification contains four levels: UN, WE, MO, and ST.
[a]Statistically significant signal of the drug–drug interaction.

(2.25–3.00)], and complicated appendicitis [N = 9; IC: 3.18 (2.04–3.94)] (Table 3; Supplementary Table S5).

Statistical analysis to assess the association of clozapine-associated reports of infections with neutropenia or agranulocytosis

Neutropenia was reported in 6.13% of the reports of clozapine-associated infections. It was less associated with clozapine-associated reports of infections compared to other clozapine-associated reports: X2 (1, N = 204,073) = 454; $p < 0.0005$). However, agranulocytosis was more associated with clozapine-associated reports of infections compared to other clozapine-associated reports: X2 (1, N = 204,073) = 56; $p < 0.0005$. However, agranulocytosis was reported in only 3.33% of the reports of clozapine-associated infection.

Statistical analysis to assess the dose–effect relationship between the dose of clozapine and infections

The dose was rarely reported as only 2,319 (1.14%) reports included this information. When using the dose to perform the

disproportionality analysis, no signal of dose-dependency could be found (Supplementary Table S4). The quartiles of doses found in our study were as follows: 100 mg/day, 250 mg/day, and 400 mg/day.

Statistical analysis to assess the DDI between clozapine and various CYP450 inhibitors on the reporting of infections

Among the 17 tested CYP inhibitors, a significant drug–drug interaction was found with clarithromycin, metronidazole, VPA, lansoprazole, omeprazole, amiodarone, and esomeprazole (Table 4).

Discussion

In our study, conducted under real-life conditions using the largest pharmacovigilance database worldwide, we identified a significant association between clozapine and reported infections. This signal was consistent over time (Figure 1). Various types of infections were linked to clozapine use in our study, with 94.3% of them considered serious and 9.8% resulting in death at the time of reporting. Although serious adverse effects tend to be more reported than non-serious effects, our findings imply that people treated with clozapine should be carefully followed in the case of symptoms of infection.

The most frequently reported infections were respiratory and gastrointestinal in nature. Patients and families should be educated about the risk of infections, particularly respiratory and gastrointestinal infections.

Clozapine may be particularly associated with pneumonia compared to other infections. A Taiwanese registry study involving a nationwide cohort of 33,024 inpatients with schizophrenia found that the current use of clozapine (adjusted RR = 3.18; 95% CI: 2.62–3.86, $p < 0.001$) was linked to a dose-dependent increase in the risk of pneumonia. On the other hand, quetiapine, olanzapine, zotepine, and risperidone showed a lesser extent of association with an increased risk of pneumonia. Unlike clozapine, no clear dose-dependent relationship was observed for these antipsychotics. The risk of pneumonia with clozapine was found to be strongest within the first 30 days of treatment (Kuo et al., 2013).

A retrospective study based on clinical records from the UK also reported an increased risk of COVID-19 infection in clozapine-treated patients compared to those on other antipsychotic medications (adjusted HR = 1.76; 95% CI 1.14–2.72) (Govind et al., 2021). However, a register-based cohort study from the Stockholm region did not find an association between clozapine treatment and severe COVID-19 infection. The adjusted HR for the exposed group compared to the unexposed group was 0.96 (95% CI: 0.54 and 1.70) for inpatient care, 1.69 (0.48 and 5.93) for care in an intensive care unit (ICU), and 0.86 (0.26 and 2.80) for death (Ohlis et al., 2022). This study might have lacked statistical power due to the low number of clozapine-treated patients suffering from COVID-19 during the study period. In another English retrospective 1-year cohort study, the incidence of infection was compared between 64 patients starting clozapine and 120 patients starting paliperidone palmitate long-acting injection (PPLAI). The incidence of infection was greater in clozapine starters than in PPLAI starters (28% vs. 6%; $p = 0.001$; adjusted odds ratio 5.82 (95% CI = 2.15–15.76). Similar to our findings, infectious episodes in clozapine patients were not statistically related to changes in neutrophil counts. According to the authors' classification, the most commonly reported infection in the clozapine group was respiratory infection; however, the majority of infections were non-respiratory-related (Mace et al., 2022).

Regarding the risk of gastrointestinal infection, particularly appendicitis, a retrospective study including 465 patients, of whom 65 were on clozapine, showed that the clozapine exposure group exhibited a higher incidence of appendicitis during the observation period than the non-exposure group (863 cases vs. 124 cases per 100,000 person-years) (Kawakita et al., 2022). Additionally, a case series of six patients with perforated appendicitis during clozapine treatment reported a 20-fold increase in appendicitis incidence compared to the general population in male subjects of the same age group (Steinert and Jans, 2021). The authors also suspected a dose-dependency as they observed high clozapine serum levels in three of those patients during the course of appendicitis.

Possible indirect mechanisms of clozapine predisposition to infection, particularly aspiration pneumonia, include sialorrhea and impairment of swallowing function with esophageal dilatation and hypomotility (Abdelmawla and Ahmed, 2009). A systematic review during the first month of clozapine treatment indicated that up to 50% of patients develop fever and flu-like symptoms, seemingly driven by increased cytokines (Røge et al., 2012). A recent study comparing the levels of secondary antibodies of clozapine users with those of the users of antipsychotics other than clozapine (control group) noted lower secondary antibodies among clozapine users. Total serum immunoglobulins [immunoglobulin (Ig)G, IgA, and IgM] and specific immunoglobulin antibodies to *Haemophilus influenzae* and pneumococcus were decreased (Ponsford et al., 2019). Lower immunoglobulin levels might contribute to the onset of infections.

In our study, neutropenia was less associated with clozapine-associated reports of infections compared to other clozapine-associated reports (p-value < 0.005), indicating that most of these infections were probably not linked to clozapine-associated neutropenia. However, agranulocytosis was more associated with clozapine-associated reports of infections compared to other clozapine-associated reports (p-value < 0.005), which is expected as infection is very common in agranulocytosis patients. Indeed, a retrospective Finn study on 163 patients with clozapine-induced agranulocytosis found that 78.6% of the patients presented with an infection (Lahdelma and Appelberg, 2012). The median age of the patients in this study was 49 years, which is very close to the median age in our study (50 years), but the sex ratio was lower in their study (1.09 vs. 1.57 in our study). However, since agranulocytosis was reported in only 3.33% of the reports of clozapine-associated infections, it is not the main cause of the signal of infections observed in our study.

Although men and women have a similar prevalence of schizophrenia (Li et al., 2016), research indicates that men often experience the onset of severe schizophrenia symptoms at an earlier age compared to women. Specifically, men tend to encounter the peak period of initial pronounced psychotic symptoms between

20 and 24 years of age, whereas women tend to experience these symptoms 5 or more years later (Kahn et al., 2015). This might be the reason why there are important gender differences in clozapine prescription. Indeed, several studies, including ours, have reported that men represented between 63.1% and 78.6% of patients treated with clozapine (Taylor, 2004; Silveira et al., 2015). Consequently, sex is probably not a risk factor for clozapine-induced infections.

The median dose in our study was 250 mg (IQR = 100–400). This aligns with the typical dose found in the clozapine-treated population as Caucasians are usually prescribed 300–600 mg/day to reach the therapeutic range, while in Asian countries, average clozapine doses are lower than 300 mg/day (de Leon et al., 2020). However, it is essential to consider that dose reporting was unavailable in more than 98% of the reports in the database. The results of the tests performed in this study to explore a dose-dependency effect do not allow us to draw a conclusion.

The results of the disproportionality analysis for drug–drug interactions (DDI) between clozapine and CYP450 inhibitors on the reporting of infections are more challenging to interpret. Except for ciclosporin (an inhibitor of CYP3A4), a trend toward a DDI was found with all CYP inhibitors, for which a disproportionality analysis could be computed. However, it is unclear which specific CYP450 enzymes may be involved. The associations observed with certain CYP inhibitors, such as clarithromycin and metronidazole, may be influenced by an indication bias since these drugs are commonly prescribed in the context of infections. VPA, one of the most co-reported drugs in the DDI analysis, has been associated with an increase in oxidative stress. Given the potential for clozapine to induce oxidative stress as well, the combination of VPA and clozapine may potentially favor the onset of certain types of infections (Gai et al., 2020; Salimi et al., 2022).

Some authors suspect that the association of clozapine with proton pump inhibitors (PPI) might increase the formation of reactive metabolites and contribute to the increase in hematological adverse drug reactions (ADRs) (Wiciński et al., 2017). However, the oxidative stress hypothesis is inconclusive with PPIs as these drugs usually alleviate oxidative stress (Gao et al., 2019; Gandhi et al., 2021). PPIs have been associated with respiratory infections in different retrospective studies, suggesting a potential pharmacodynamic interaction (Ho et al., 2017; Wang et al., 2019). In a retrospective chart review, aiming to explore the potential effect of polypharmacy on the hematologic profiles of clozapine patients, 24 out of 26 (96%) of the subset of patients who were prescribed a PPI or ranitidine concomitantly with clozapine experienced hematological ADRs (Shuman et al., 2014). A case of infection during PPI treatment with elevated plasma clozapine levels was reported in a 51-year-old woman and could potentially be linked to the switch from omeprazole to esomeprazole (Wagner et al., 2011). The authors speculated that this might be due to the removal of induction of clozapine metabolism by omeprazole. However, the delay was not in favor of this hypothesis. Omeprazole and lansoprazole, in addition to being CYP2C19 inhibitors, are also CYP1A2 inducers. In a case series involving two patients, the prescription of omeprazole was associated with a reduction in clozapine plasma concentrations of 41.9% and 44.7% (Frick et al., 2003). Another retrospective study in 13 psychiatric patients found that the switch from omeprazole to pantoprazole led to an increase in clozapine levels in non-smoking patients and to a decrease in clozapine levels in smoking patients. This was probably caused by the discontinuation of enzyme induction in the cytochrome P450 enzyme 1A2 by omeprazole in non-smokers, whereas CYP1A2 remained induced in smokers (Mookhoek and Loonen, 2004). As the prevalence of cigarette smoking is high in schizophrenia patients (around 70%–80%) and probably even higher in treatment-resistant schizophrenia patients (Ding and Hu, 2021), we believe that the DDI observed in our study between PPIs and clozapine is probably more linked to the CYP2C19 inhibition by PPIs.

Regardless of the cause of infection, several reports showed that infection leads to an increase in the toxicity levels of clozapine and its metabolites in the serum (Darling and Huthwaite, 2011; Espnes et al., 2012; Zhang et al., 2021; Chengappa et al., 2022). This is likely to be mediated by cytokine suppression of cytochrome P450 1A2 (CYP1A2), the main hepatic microsomal system involved in clozapine metabolism, which is also involved in the metabolism of several antibiotics commonly used to treat infections. This further enhances the potential for clozapine toxicity (Røge et al., 2012). However, despite sex being a factor of cytochrome P450 expression (Zanger and Schwab, 2013), we did not find any sex-related significant differences in clozapine-associated infections.

Limitations

Our study was subject to various inherent limitations stemming from the utilization of a pharmacovigilance database. Of paramount importance among these limitations is the issue of under-reporting. Nevertheless, it is reassuring that despite this limitation, the results and significance of the disproportionality analysis remained unaffected (Montastruc et al., 2011).

However, it is crucial to recognize that the likelihood of a suspected ADR being drug-related may not be uniform across all cases. Although disproportionality analysis of spontaneous reports is a valuable tool for detecting safety signals, it possesses certain intrinsic limitations as well. One such limitation is the potential presence of low-quality data due to missing information. Additionally, the causal relationship between the reported drug and the ADR remains unproven (Egberts et al., 2002; Garbe and Suissa, 2014).

Moreover, it is worth noting that the reporting pattern of ADRs may vary between new and old drugs, with more rigorous monitoring typically occurring during the period of drug marketing and shortly thereafter.

It is vital to emphasize that, due to under-reporting of ADRs, pharmacovigilance data cannot be utilized to determine the incidence rates of ADRs (Sharrar and Dieck, 2013). Furthermore, our study lacked information on the smoking history of participants despite its significant impact on the pharmacokinetics of clozapine and the risk of respiratory infection.

Conclusion

This study has revealed a significant safety signal concerning the association between clozapine and reported infections. Respiratory infections, as well as gastrointestinal infections, including

appendicitis, were the most commonly reported infections. The co-administration of clozapine with valproic acid (VPA) or proton pump inhibitors (PPIs) may potentially increase the risk of infection. However, as this study was based on pharmacovigilance data, a definitive causal relationship between clozapine exposure and the occurrence of infections cannot be established with certainty. Nevertheless, in clinical practice, psychiatrists should remain vigilant for signs of infections when prescribing clozapine and ensure that mandatory vaccines, including pneumococcal vaccination, have been administered. Conducting a study to evaluate the relevance of therapeutic drug monitoring of clozapine when the patient's treatment regimen is altered (especially with VPA or PPIs) or when an infection occurs would be of considerable interest.

Data availability statement

The datasets presented in this article are not readily available because data are owned by the WHO Uppsala Monitoring Center. Requests to access the datasets should be directed to https://who-umc.org/vigibase/.

Ethics statement

The studies involving humans were approved by the Comité d'éthique du CHU de Caen. 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

BC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Writing–original draft. PB: Writing–review and editing. AS: Writing–review and editing. MS: Writing–review and editing. CD: Writing–review and editing. VL-B: Writing–review and editing. JA: Supervision, Writing–review and editing. SF: 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1260915/full#supplementary-material

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A pharmacovigilance study of etoposide in the FDA adverse event reporting system (FAERS) database, what does the real world say?

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Introduction: Etoposide is a broad-spectrum antitumor drug that has been extensively studied in clinical trials. However, limited information is available regarding its real-world adverse reactions. Therefore, this study aimed to assess and evaluate etoposide-related adverse events in a real-world setting by using data mining method on the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: Through the analysis of 16,134,686 reports in the FAERS database, a total of 9,892 reports of etoposide-related adverse drug events (ADEs) were identified. To determine the significance of these ADEs, various disproportionality analysis algorithms were applied, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) algorithms.

Results: As a result, 478 significant disproportionality preferred terms (PTs) that were identified by all four algorithms were retained. These PTs included commonly reported adverse events such as thrombocytopenia, leukopenia, anemia, stomatitis, and pneumonitis, which align with those documented in the drug's instructions and previous clinical trials. However, our analysis also uncovered unexpected and significant ADEs, including thrombotic microangiopathy, ototoxicity, second primary malignancy, nephropathy toxic, and ovarian failure. Furthermore, we examined the time-to-onset (TTO) of these ADEs using the Weibull distribution test and found that the median TTO for etoposide-associated ADEs was 10 days (interquartile range [IQR] 2–32 days). The majority of cases occurred within the first month (73.8%) after etoposide administration. Additionally, our analysis revealed specific high-risk signals for males, such as pneumonia and cardiac infarction, while females showed signals for drug resistance and ototoxicity.

Discussion: These findings provide valuable insight into the occurrence of ADEs following etoposide initiation, which can potentially support clinical monitoring and risk identification efforts.

KEYWORDS

etoposide, real-word analysis, pharmacovigilance, adverse drug event, FAERS

1 Introduction

Etoposide (VP-16) is a semi-synthetic derivative of the natural antibiotic podophyllotoxin, acting as a potent inhibitor of topoisomerase-II (Cheema et al., 2011). This inhibition leads to DNA strand breaks and the induction of apoptosis, triggering mutagenic and cell death pathways (Meresse et al., 2004; Le and Wang, 2023). Upon entry into the human body, etoposide predominantly binds to serum albumin (93%–98%) and undergoes elimination via the kidneys and biliary tract following glucuronidation (Le and Wang, 2023). The recommended oral dose of etoposide for monotherapy or combination therapy is 100–200 mg/m2/day on days 1–5, or 200 mg/m2/day on days 1, 3, and 5 every 3–4 weeks. Since its approval by the FDA in 1983, etoposide has been widely utilized in the treatment of various solid and hematologic tumors, such as small cell lung cancer, germ cell tumors, and lymphoma (McHugh et al., 2020; Rudin et al., 2020; Jeha et al., 2021; Torka et al., 2023). When combined with other chemotherapeutic agents, it has achieved a remission rate of over 80% (Meresse et al., 2004). In a clinical study involving patients with nonseminomatous germ cell tumors, adjuvant etoposide plus cisplatin for 2 cycles demonstrated prolonged disease-specific and relapse-free survival, along with acceptable toxicity and lower drug costs (McHugh et al., 2020).

Adverse drug events (ADEs) are crucial concerns in modern healthcare as they have a significant impact on patient safety, treatment outcomes, and overall public health (Montané and Santesmases, 2020). Given the outstanding efficacy and widespread use of etoposide in the treatment of tumors, it is important to understand its adverse effects to improve patient care (Edwards and Aronson, 2000). Common adverse reactions reported in association with etoposide dosing include myelosuppression, gastrointestinal toxicity, and hypersensitivity reactions (Henwood and Brogden, 1990; Zhu et al., 2016). However, unknown adverse reactions of etoposide are expected to be identified in post-marketing studies due to the limitations of clinical trials, such as restricted populations, limited follow-up time, and complications (Yan et al., 2022; Javed and Kumar, 2023). Therefore, searching for potential ADEs of etoposide through post-marketing surveillance using data mining algorithms is highly warranted.

The pharmacovigilance of drugs relies on the identification of statistical signals derived from diverse data sources (Vogel et al., 2020). Signals in pharmacovigilance refer to novel or known connections between adverse events and drugs (Javed and Kumar, 2023). Disproportionality analysis, a widely utilized method, is employed to detect signals using pharmacovigilance databases (Jain et al., 2023). This type of analysis considers the distribution of all drugs and events in the database, calculates statistical associations between drugs and ADEs, and is frequently employed in post-market safety assessments of drugs (Almenoff et al., 2007; Vogel et al., 2020; Sharma et al., 2023). The FDA Adverse Event Reporting System (FAERS) is a publicly accessible database that collects reports of ADEs from healthcare professionals, patients, and drug manufacturers. It serves as a crucial tool for the FDA's post-marketing safety monitoring of drugs and medical products, and it is one of the largest pharmacovigilance databases worldwide (Meng et al., 2019). Additionally, due to the large sample size of the FAERS database, data mining techniques possess sufficient statistical power to detect rare adverse reactions that are challenging to identify in traditional epidemiological studies (Duggirala et al., 2016; Jiao et al., 2020; Sharma and Kumar, 2022). Given that etoposide-related adverse reaction reports primarily originate from clinical trials, with a focus on specific organ systems, we utilized the FAERS database to conduct disproportionality analyses. This assessment aimed to evaluate the long-term safety of etoposide through post-marketing surveillance, providing a comprehensive and valuable reference for its real-world safety.

2 Material and methods

2.1 Data source and pre-processing

To systematically evaluate the safety of etoposide in the post-marketing period, we conducted a retrospective pharmacovigilance study using data obtained from the FAERS database. The FAERS database covers data from the first quarter of 2004 to the fourth quarter of 2022 and can be accessed at (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS data consists of seven datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse drug reaction information (REAC), patient outcomes information (OUCT), reported sources (RPSR), drug therapy start dates and end dates (THER), and indications for drug administration (INDI) (Shu et al., 2022b). We imported all the downloaded data from the FAERS database into SAS software (version 9.4) for further collation and analysis. We acquired a total of 19,494,698 reports. Since the database is updated on a quarterly basis, there will unavoidably be duplication of previous public reports. According to the FDA's recommendations, we operated deduplication process before statistical analyses, following the criteria: (1) If the CASEIDs were the same, the latest FDA_DT were selected. (2) If the CASEIDs and the FDA_DT were the same, the higher PRIMARYIDs were selected (Shu et al., 2022b). The removing the duplicate records led to a decrease in the number of reports to 16,134,686 (Figure 1). The 3D structure of etoposide is derived from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Kim et al., 2023).

2.2 Drug identification and adverse events

As FAERS had two variables including DRUGNAME and PROD_AI, both the brand names and common names were employed to recognize records related to etoposide. In this study, "ETOPOSIDE", "VP-16," "LASTET," "TOPOSAR," "VEPESID," and "CELLTOP" were used to search. The reported drugs in FAERS were classified into four modalities: PS (primary suspect), SS (second suspect), C (concomitant), and I (interacting). To enhance accuracy, the role code of ADEs was retained only as the PS drug (Zhang et al., 2023). During the period of this research, we identified totally 9892 ADEs reports of etoposide as the PS drug. System Organ Class (SOC) was the highest level of the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0. Available from https://www.meddra.org/) terminology, by which all ADEs in reports were coded of Preferred Terms (PTs) (Tieu and

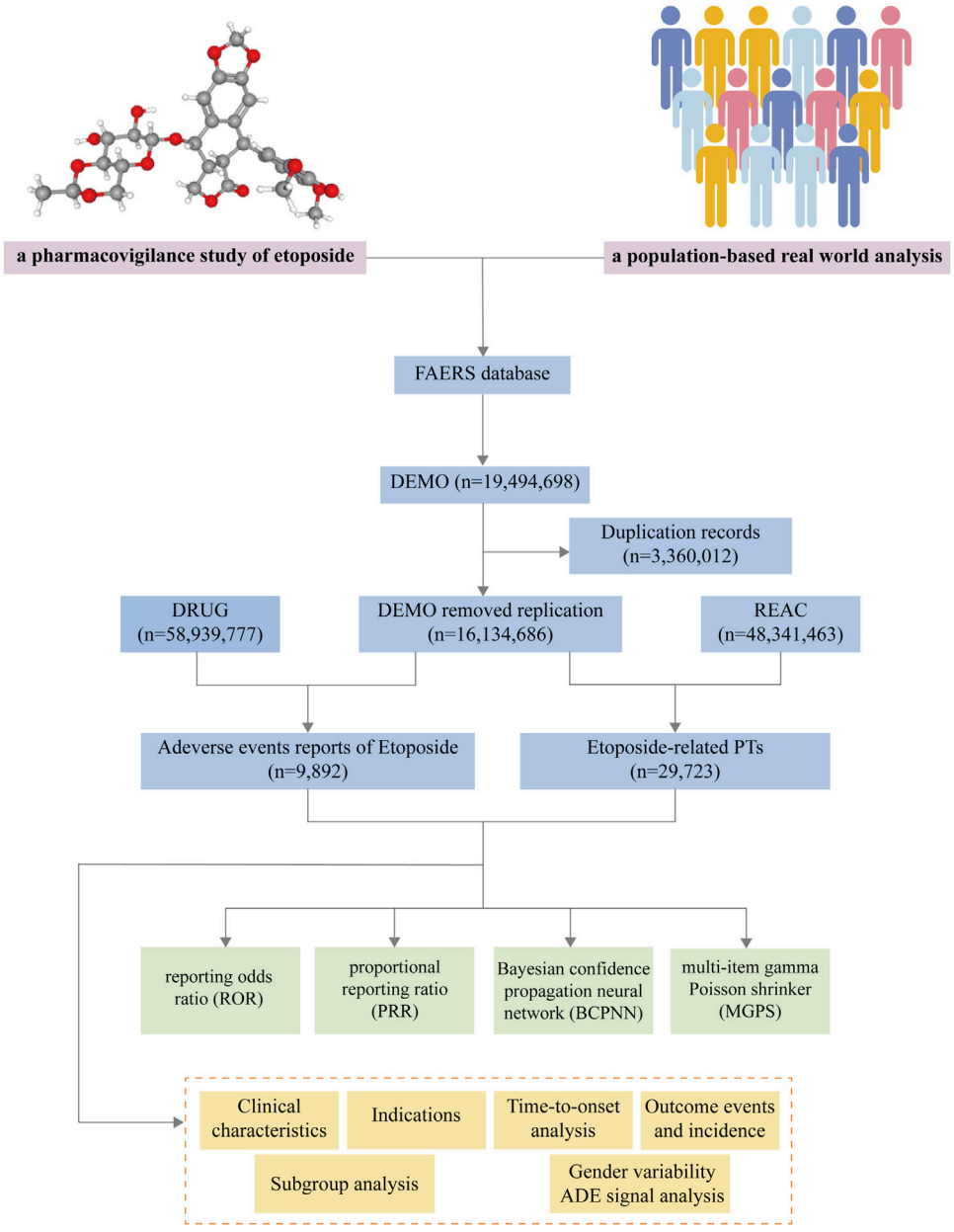

FIGURE 1
The flow diagram of selecting etoposide-related ADEs from FAERS database.

Breder, 2018). Then, 29,723 etoposide-related PTs were screened out (Figure 1). We performed case/non-case analyses to determine whether the ADEs reported for etoposide were statistically significant at the PT and SOC levels compared to other drugs in the complete FAERS database.

Furthermore, the time-to-onset (TTO) of ADEs caused by etoposide were defined as the interval between EVENT_DT (ADEs onset date, in DEMO file) and START_DT (start date of etoposide use, in THER file). Input errors including inaccurate or missing date entries and EVENT_DT earlier than START_DT were eliminated. For exhaustively evaluating the TTO, we incorporated median, quartile, and Weibull shape parameter test in our research (Kinoshita et al., 2020; Shu et al., 2022d). The varying risk incidence increase or decrease of the ADEs over time could be determined and predicted by the Weibull distribution, with scale (α) and shape (β) being two parameters used to describe the Weibull distribution shape (Mazhar et al., 2021).

2.3 Subgroup analysis

Subgroup analyses were conducted to investigate the association between etoposide dosing and adverse effects in subgroups based on age (<18 [child and adolescent], 18–64 [adult], and >64 [elder]), gender (male and female), weight (<80 kg, 80–100 kg, and >100 kg), and reporting person (consumer and health professional).

TABLE 1 Four major algorithms used to assess potential associations between etoposide and ADEs. a, Number of reports that contain both targeted drug and targeted drug adverse reactions; b, Number of reports of other drug adverse reactions that contain the targeted drug; c, Number of reports of targeted drug adverse reactions that contain other drugs; d, Number of reports that contain other drugs and other drug adverse reactions. 95% CI, 95% confidence interval; N, the number of reports; $\chi 2$, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E (IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

Algorithms	Equation	Criteria
ROR	ROR = (ad/bc)	lower limit of 95% CI > 1
	95%CI = eln (ROR)±1.96 (1/a+1/b+1/c+1/d)^0.5	
PRR	PRR = a (c+d)/c/(a+b)	N ≥ 3 PRR≥2, $\chi 2$≥4, N ≥ 3
	$\chi 2$ = [(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	
BCPNN	IC = log2a (a+b+c+d)/((a+c)(a+b))	IC025 > 0
	95%CI = E (IC) ± 2V(IC)^0.5	
MGPS	EBGM = a (a+b+c+d)/(a+c)/(a+b)	EBGM05 > 2
	95%CI = eln (EBGM)±1.96 (1/a+1/b+1/c+1/d)^0.5	

2.4 Data mining algorithm and statistical analysis

Disproportionality analysis is primarily used as a tool for hypothesizing possible causal relationships between drugs and adverse events. It is based on comparing the observed and expected number of reports for each specific combination of drug and adverse event (Montastruc et al., 2011; Caster et al., 2020; Hu et al., 2020; Sharma et al., 2023). Consequently, in our research, we conducted a disproportionality analysis to determine the potential correlation between etoposide and all ADEs. Considering that separate methods of detecting signals may be insufficient, the four algorithms including 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 implied (Lindquist et al., 2000; van Puijenbroek et al., 2002; Shao et al., 2021; Zhou et al., 2021). PRR and ROR are frequencyist (non-Bayesian), while BCPNN and MGPS are Bayesian (Sakaeda et al., 2013). Information Components (IC) are used in the tool BCPNN to measure disproportionality (Hauben and Zhou, 2003; Bate, 2007). MGPS analysis is a well-established technique for reducing the rate of false-positive reports by applying a Bayesian shrinkage estimator to the observed/expected ratio to give smaller risk estimates with narrower confidence intervals, even if the event counts are small (Napoli et al., 2014; Trippe et al., 2017). The two Bayesian methods (BCPNN and MGPS) were considered useful because each detected unique signal even when there were few reports of ADE for a particular drug (Nomura et al., 2015). Overall, the higher the value of the four parameters, the stronger the signal value. The specific formulas and the criteria of positive safety signal detection of the four algorithms were shown in Table 1. Only the signals that had at a minimum of three targeted drug ADEs records were counted. To assure the reliability of the results, we selected ADEs signals that satisfy the above four algorithm criteria simultaneously for the study (Sakaeda et al., 2013; Yin et al., 2022). We also excluded the indications for etoposide from the ADEs to avoid unclear presentation (Tang et al., 2022). The drug label of etoposide was obtained from the DailyMed (https://dailymed.nlm.nih.gov/dailymed/index.cfm)(Yao et al., 2017), and Summary of Product Characteristics (SmPC) (https://www.ema.europa.eu/en/glossary/summary-product-characteristics) (Nezvalova-Henriksen et al., 2023). Novelty/unexpectedness signal is defined as any significant ADEs detected without being outlined in the drug label (Shu et al., 2022a). All processing of data and statistical analyses were carried out using SAS 9.4, Microsoft EXCEL 2019, and R (version 4.2.1).

3 Results

3.1 Annual distribution of etoposide-related ADE reports

According to the data from the FAERS database, there were a total of 9892 ADEs reports for etoposide between January 2004 and December 2022. From an overall perspective, the number of ADE reports has been increasing over the years, as depicted in Figure 2. The lowest and highest number of reports were observed in 2005 (114 reports) and 2020 (1230 reports), respectively. Notably, there was a substantial increase in the number of reports in 2015. More detailed information on the annual distribution can be found in Figure 2.

3.2 General characteristics in the real-world population

Table 2 displayed the population characteristics of the ADEs reports associated with etoposide. It is notable that there were more male patients reported (49.6%) compared to female patients (34.3%), potentially due to specific indications of the drug such as testicular cancer. The reported proportions of body weight in the categories of <80 kg, 80–100 kg, and >100 kg was 15.7%, 4.5%, and 1.3%, respectively. A higher occurrence of etoposide-related ADEs was observed in young (22.5%) and middle-aged patients (39.4%) compared to elderly patients (14.1%).

The majority of ADE reports were from the United States (27.2%), followed by France (11.1%), Japan (9.2%), Canada (8.7%), and Italy (5.0%). Interestingly, health professionals accounted for the highest proportion (88.7%) of these reports.

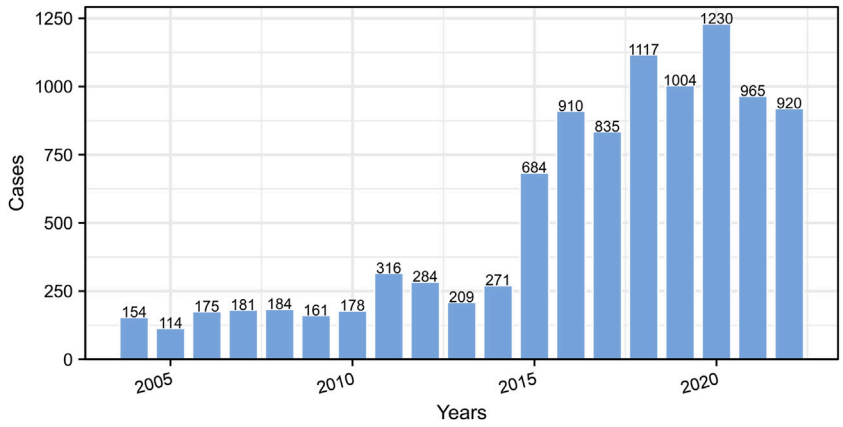

FIGURE2
The annual distribution of etoposide-related ADE reports from 2004 to 2022.

Among the serious outcomes reported, 50.5% were classified as "other serious outcomes," while the most frequently reported serious outcome was hospitalization (24.6%). Additionally, the percentages of death and life-threatening outcomes were 15.5% and 8.3%, respectively. These outcomes may be more closely associated with the progression of the underlying tumor.

The top five indications for etoposide use included cases where the product was used for an unknown indication (6.7%), acute myeloid leukemia (4.6%), small cell lung cancer (3.7%), Hodgkin's disease (3.6%), and acute lymphocytic leukemia (3.5%).

3.3 Signals detection at the system organ class level

Table 3 presented the signal strength and number of reports for etoposide at the System Organ Class (SOC) level. Our statistical analysis identified a total of 27 organ systems that were implicated in etoposide-induced ADEs. The SOC that met all four criteria simultaneously and showed significant association with etoposide ADEs was blood and lymphatic system disorders (SOC code: 10005329, 3745 reports).

Additionally, other significant SOCs that met three criteria at the same time included infections and infestations (SOC code: 10021881, 3641 reports), and neoplasms benign, malignant, and unspecified (including cysts and polyps) (SOC code: 10029104, 1852 reports). Furthermore, there were several other significant SOCs that met at least one of the criteria. These included respiratory, thoracic, and mediastinal disorders (SOC code: 10038738, 2075 reports), cardiac disorders (SOC code: 10007541, 995 reports), vascular disorders (SOC code: 10047065, 976 reports), renal and urinary disorders (SOC code: 10038359, 854 reports), metabolism and nutrition disorders (SOC code: 10027433, 808 reports), hepatobiliary disorders (SOC code: 10019805, 566 reports), immune system disorders (SOC code: 10021428, 441 reports), ear and labyrinth disorders (SOC code: 10013993, 184 reports), congenital, familial, genetic disorders (SOC code: 10010331, 143 reports), and endocrine disorders (SOC code: 10014698, 114 reports).

3.4 Signals detection at the preferred terms level

A total of 478 etoposide-induced ADEs that covering 26 SOCs at the PT level were detected after compliance with all four algorithms simultaneously. The full results were listed in Supplementary Table S1. We then ranked all the PTs with ADEs case number exceeding 30 (a>30) according to the value of EBGM05 (the most stringent algorithm) from largest to smallest, and selected a total of 68 ADEs that met the screening criteria (Sakaeda et al., 2013). They were grouped by SOC and the result was shown in Table 4.

In our study, some PTs including thrombocytopenia (PT: 10043555, case number 417), leukopenia (PT:10024384, case number 176), myelosuppression (PT:10028584, n = 47), febrile neutropenia (PT:10016288, n = 874), anaemia (PT:10002034, case number 345), oesophagitis (PT:10030216, n = 45), stomatitis (PT: 10042128, n = 109), hepatotoxicity (PT:10019851, n = 41), peripheral sensory neuropathy (PT:10034620, n = 33), neurotoxicity (PT:10029350, n = 32), and pneumonitis (PT: 10035742, n = 67) were complied with warnings in instructions and drug labels. Of particular note, more than 40 unexpected significant ADEs were uncovered in drug labels, including disseminated intravascular coagulation (PT:10013442, n = 62), thrombotic microangiopathy (PT:10043645, n = 35), cardiotoxicity (PT:10048610, n = 73), ototoxicity (PT:10033109, n = 37), deafness (PT:10011878, n = 51), multiple organ dysfunction syndrome (PT:10077361, n = 165), drug resistance (PT:10059866, n = 46), hepatic failure (PT:10019663, n = 52), bacteraemia (PT:10003997, n = 69), sepsis (PT:10040047, n = 379), *clostridium difficile* infection (PT:10054236, n = 32), second primary malignancy (PT:10039801, n = 43), malignant neoplasm progression (PT:10051398, n = 203), encephalopathy (PT:10014625, n = 102), nephropathy toxic (PT:10029155, n = 72), ovarian failure (PT:10033165, n = 43), acute respiratory distress syndrome (PT: 10001052, n = 77), respiratory failure (PT:10038695, n = 183), hypoxia (PT:10021143, n = 68), and so on. Furthermore, although there were some PTs with a small number of cases, the signal value intensity was high, such as Erythema ab igne (n = 4, EBGM 722.84 [240.57]), primary hypogonadism (n = 16, EBGM

TABLE 2 Clinical characteristics of reports with etoposide from the FAERS Database (January 2004–December 2022).

Characteristics	Case number, n	Case proportion, %
Number of events	9892	
Gender		
Female	3392	34.3
Male	4903	49.6
Unknown	1597	16.1
Weight (kg)		
<80	1553	15.7
80–100	449	4.5
>100	127	1.3
Unknown	7763	78.5
Age (years)		
<18	2228	22.5
18–64	3893	39.4
>64	1399	14.1
Unknown	2372	24.0
Reported Countries (top five)		
America	2694	27.2
France	1100	11.1
Japan	912	9.2
Canada	858	8.7
Italy	494	5.0
Reported Person		
Health professional	8779	88.7
Consumer	608	6.2
Unknown	505	5.1
Serious Outcomes		
Death (DE)	1937	15.5
Life-threatening (LF)	1041	8.3
Hospitalization (HO)	3065	24.6
Disability (DS)	133	1.1
Other serious outcomes	6308	50.5
Indications (top five)		
Product used for unknown indication	661	6.7
Acute myeloid leukaemia	456	4.6
Small cell lung cancer	370	3.7
Hodgkin's disease	360	3.6
Acute lymphocytic leukaemia	344	3.5

TABLE 3 Signal strength of ADEs of etoposide at the System Organ Class (SOC) level in FAERS database. An asterisk indicates a positive signal value under this algorithm. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

SOC name	Case number	ROR (95%CI)	PRR (χ2)	IC(IC025)	EBGM(EBGM05)
Blood and lymphatic system disorders	3745	8.53 (8.24–8.83)*	7.58 (21665.64)*	2.92 (1.25)*	7.55 (7.34)*
Infections and infestations	3641	2.57 (2.48–2.66)*	2.37 (3050.51)*	1.25 (-0.42)	2.37 (2.30)*
General disorders and administration site conditions	3106	0.56 (0.54–0.58)	0.60 (985.15)	−0.73 (-2.40)	0.60 (0.58)
Injury, poisoning and procedural complications	2500	0.85 (0.82–0.89)	0.86 (60.59)	−0.21 (-1.88)	0.86 (0.83)
Gastrointestinal disorders	2249	0.87 (0.84–0.91)	0.88 (38.71)	−0.18 (-1.85)	0.88 (0.85)
Respiratory, thoracic and mediastinal disorders	2075	1.51 (1.44–1.58)*	1.47 (328.26)	0.56 (-1.11)	1.47 (1.42)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1852	2.34 (2.23–2.45)*	2.25 (1327.28)*	1.17 (-0.49)	2.25 (2.17)*
Nervous system disorders	1724	0.65 (0.62–0.68)	0.67 (305.59)	−0.58 (-2.24)	0.67 (0.64)
Investigations	1406	0.74 (0.70–0.78)	0.75 (119.71)	−0.41 (-2.07)	0.75 (0.72)
Cardiac disorders	995	1.24 (1.16–1.32)*	1.23 (43.13)	0.30 (-1.37)	1.23 (1.16)
Vascular disorders	976	1.52 (1.43–1.62)*	1.50 (167.46)	0.59 (-1.08)	1.50 (1.42)
Skin and subcutaneous tissue disorders	856	0.52 (0.49–0.56)	0.54 (361.48)	−0.90 (-2.56)	0.54 (0.51)
Renal and urinary disorders	854	1.47 (1.37–1.57)*	1.46 (124.1)	0.54 (-1.12)	1.46 (1.37)
Metabolism and nutrition disorders	808	1.25 (1.16–1.34)*	1.24 (38.53)	0.31 (-1.36)	1.24 (1.17)
Hepatobiliary disorders	566	2.10 (1.93–2.28)*	2.08 (318.85)*	1.05 (-0.61)	2.08 (1.94)
Musculoskeletal and connective tissue disorders	441	0.27 (0.25–0.30)	0.28 (855.40)	−1.83 (-3.50)	0.28 (0.26)
Immune system disorders	441	1.36 (1.24–1.50)*	1.36 (41.95)	0.44 (-1.23)	1.36 (1.25)
Psychiatric disorders	292	0.16 (0.14–0.18)	0.17 (1246.38)	−2.55 (-4.21)	0.17 (0.16)
Surgical and medical procedures	231	0.61 (0.53–0.69)	0.61 (58.82)	−0.72 (-2.38)	0.61 (0.55)
Eye disorders	217	0.37 (0.32–0.42)	0.37 (235.75)	−1.43 (-3.10)	0.37 (0.33)
Ear and labyrinth disorders	184	1.42 (1.23–1.64)*	1.42 (22.70)	0.50 (-1.16)	1.42 (1.26)
Reproductive system and breast disorders	149	0.54 (0.46–0.63)	0.54 (59.52)	−0.89 (-2.56)	0.54 (0.47)
Congenital, familial and genetic disorders	143	1.53 (1.29–1.80)*	1.52 (25.73)	0.61 (-1.06)	1.52 (1.33)
Endocrine disorders	114	1.54 (1.28–1.85)*	1.54 (21.63)	0.62 (-1.04)	1.54 (1.32)
Pregnancy, puerperium and perinatal conditions	96	0.72 (0.59–0.89)	0.73 (10.00)	−0.46 (-2.13)	0.73 (0.61)
Product issues	48	0.11 (0.08–0.14)	0.11 (363.25)	−3.22 (-4.89)	0.11 (0.08)
Social circumstances	14	0.10 (0.06–0.17)	0.10 (112.74)	−3.31 (-4.97)	0.10 (0.07)

194.20 [125.44]), hypertensive hydrocephalus (n = 3, EBGM 232.34 [88.55]), genotoxicity (n = 4, EBGM 191.34 [79.92]), renal salt-wasting syndrome (n = 19, EBGM 105.11 [71.23]). This suggested that the occurrence of these ADEs and etoposide administration were also closely related and deserved clinical attention. Supplementary Table S1 provided the EGBM 05 rankings of all the 478 PTs. Supplementary Table S2 summarizes all the adverse reactions mentioned in the DailyMed and SmPC instructions. Supplementary Figures S1A, S1B intersects the positive signals found in this study with the adverse drug reactions mentioned in DailyMed and SmPC. To sum up, the ADEs analysis of real-world data based on the FAERS database could also provide a great reference for the revision of etoposide instructions.

3.5 Time-to-onset analysis of etoposide-related ADEs

The onset times of etoposide-related ADEs were extracted and analyzed from the FAERS database. After removing any missing or incorrect onset time reports, a total of 2138 ADEs with available onset times were included in the analysis. The median onset time was found to be 10 days, with an interquartile range (IQR) of 2–32 days.

Regarding the distribution of ADEs over time, Figure 3 illustrates that the majority of ADEs occurred within the first month after etoposide administration (n = 1579, 73.8%). The number of ADEs decreased with a time delay, with 196 ADEs (9.2%) occurring in the second month and 137 ADEs (6.4%)

TABLE 4 Signal strength of ADEs of etoposide at the Preferred terms (PTs) level in FAERS database. Asterisks indicate new and significant signals of etoposide-associated ADEs from FAERS database. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

SOC name	Preferred terms (PTs)	Case numbers	ROR(95%CI)	PRR	χ2	IC (IC025)	EBGM (EBGM05)
Blood and lymphatic system disorders	Febrile bone marrow aplasia*	80	42.49 (34.03–53.07)	42.38	3150.61	5.37 (3.70)	41.33 (34.32)
Blood and lymphatic system disorders	Febrile neutropenia	874	30.34 (28.35–32.47)	29.48	23639.47	4.86 (3.19)	28.97 (27.37)
Blood and lymphatic system disorders	Bone marrow failure*	248	22.15 (19.53–25.12)	21.98	4901.18	4.44 (2.77)	21.70 (19.53)
Blood and lymphatic system disorders	Haematotoxicity	87	23.16 (18.74–28.63)	23.10	1813.81	4.51 (2.84)	22.79 (19.09)
Blood and lymphatic system disorders	Aplastic anaemia	60	23.97 (18.57–30.94)	23.93	1299.08	4.56 (2.89)	23.59 (19.06)
Blood and lymphatic system disorders	Pancytopenia	386	14.89 (13.46–16.47)	14.71	4893.66	3.87 (2.20)	14.59 (13.41)
Blood and lymphatic system disorders	Neutropenia	561	9.43 (8.67–10.25)	9.27	4123.11	3.21 (1.54)	9.22 (8.60)
Blood and lymphatic system disorders	Thrombocytopenia	417	7.96 (7.23–8.77)	7.86	2490.27	2.97 (1.30)	7.83 (7.22)
Blood and lymphatic system disorders	Disseminated intravascular coagulation*	62	8.42 (6.56–10.80)	8.40	402.2	3.06 (1.40)	8.36 (6.78)
Blood and lymphatic system disorders	Leukopenia	176	7.36 (6.34–8.54)	7.32	957.31	2.87 (1.20)	7.29 (6.44)
Blood and lymphatic system disorders	Thrombotic microangiopathy*	35	8.41 (6.04–11.73)	8.41	227.22	3.06 (1.40)	8.37 (6.34)
Blood and lymphatic system disorders	Lymphopenia	50	7.66 (5.80–10.11)	7.64	287.48	2.93 (1.26)	7.61 (6.03)
Blood and lymphatic system disorders	Cytopenia	34	7.84 (5.59–10.98)	7.83	201.58	2.96 (1.30)	7.80 (5.88)
Blood and lymphatic system disorders	Myelosuppression	47	6.32 (4.74–8.41)	6.31	209.16	2.65 (0.99)	6.29 (4.95)
Blood and lymphatic system disorders	Agranulocytosis	45	5.60 (4.18–7.51)	5.59	169.21	2.48 (0.81)	5.58 (4.37)
Blood and lymphatic system disorders	Anaemia	345	3.64 (3.27–4.04)	3.61	650.42	1.85 (0.18)	3.60 (3.29)
Cardiac disorders	Cardiotoxicity*	73	19.62 (15.57–24.71)	19.57	1271.21	4.27 (2.61)	19.35 (15.95)
Cardiac disorders	Acute myocardial infarction	53	3.37 (2.58–4.42)	3.37	88.13	1.75 (0.08)	3.36 (2.68)
Congenital, familial and genetic disorders	Aplasia	61	52.62 (40.77–67.92)	52.52	2986.25	5.67 (4.00)	50.90 (41.11)
Ear and labyrinth disorders	Ototoxicity*	37	44.18 (31.86–61.25)	44.12	1518.22	5.43 (3.76)	42.98 (32.70)
Ear and labyrinth disorders	Deafness*	51	4.10 (3.12–5.40)	4.10	119.16	2.03 (0.37)	4.09 (3.25)
Gastrointestinal disorders	Neutropenic colitis*	42	51.05 (37.54–69.42)	50.98	1995.59	5.63 (3.96)	49.46 (38.25)
Gastrointestinal disorders	Oesophagitis	45	8.31 (6.20–11.14)	8.30	287.4	3.05 (1.38)	8.26 (6.46)
Gastrointestinal disorders	Colitis*	72	4.23 (3.36–5.34)	4.23	176.96	2.08 (0.41)	4.22 (3.47)
Gastrointestinal disorders	Stomatitis	109	3.83 (3.17–4.62)	3.82	226.59	1.93 (0.27)	3.81 (3.26)
General disorders and administration site conditions	Mucosal inflammation	256	20.84 (18.41–23.58)	20.67	4732.89	4.35 (2.69)	20.42 (18.41)
General disorders and administration site conditions	Multiple organ dysfunction syndrome*	165	7.53 (6.46–8.78)	7.50	925.24	2.90 (1.23)	7.47 (6.57)
General disorders and administration site conditions	Drug resistance*	46	3.92 (2.94–5.24)	3.92	99.84	1.97 (0.30)	3.91 (3.07)
Hepatobiliary disorders	Venoocclusive liver disease*	107	48.75 (40.21–59.11)	48.58	4841.96	5.56 (3.89)	47.20 (40.17)

(Continued on following page)

TABLE 4 (*Continued*) Signal strength of ADEs of etoposide at the Preferred terms (PTs) level in FAERS database. Asterisks indicate new and significant signals of etoposide-associated ADEs from FAERS database. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

SOC name	Preferred terms (PTs)	Case numbers	ROR(95%CI)	PRR	χ2	IC (IC025)	EBGM (EBGM05)
Hepatobiliary disorders	Hepatotoxicity	41	4.00 (2.94–5.44)	4.00	91.88	2.00 (0.33)	3.99 (3.09)
Hepatobiliary disorders	Hepatic failure*	52	3.39 (2.58–4.46)	3.39	87.43	1.76 (0.09)	3.38 (2.69)
Immune system disorders	Haemophagocytic lymphohistiocytosis*	80	19.91 (15.97–24.83)	19.86	1415.83	4.30 (2.63)	19.63 (16.32)
Immune system disorders	Anaphylactic reaction	94	3.83 (3.13–4.70)	3.82	195.81	1.93 (0.27)	3.82 (3.22)
Infections and infestations	Neutropenic sepsis*	104	28.74 (23.67–34.90)	28.65	2727.12	4.82 (3.15)	28.17 (23.94)
Infections and infestations	Aspergillus infection*	57	15.77 (12.14–20.47)	15.74	779.22	3.96 (2.30)	15.60 (12.54)
Infections and infestations	Bacteraemia*	69	12.95 (10.21–16.41)	12.92	753.03	3.68 (2.01)	12.83 (10.52)
Infections and infestations	Septic shock*	216	10.82 (9.46–12.38)	10.75	1899.2	3.42 (1.75)	10.69 (9.55)
Infections and infestations	Bronchopulmonary aspergillosis*	36	10.13 (7.30–14.06)	10.12	294.15	3.33 (1.66)	10.07 (7.65)
Infections and infestations	Cytomegalovirus infection*	71	8.98 (7.11–11.35)	8.96	499.8	3.16 (1.49)	8.92 (7.34)
Infections and infestations	Pneumocystis jirovecii pneumonia*	51	8.85 (6.72–11.66)	8.84	352.82	3.14 (1.47)	8.80 (6.99)
Infections and infestations	Sepsis*	379	6.97 (6.29–7.71)	6.89	1904.02	2.78 (1.11)	6.87 (6.31)
Infections and infestations	*Clostridium difficile* colitis*	38	7.41 (5.38–10.19)	7.40	209.34	2.88 (1.22)	7.37 (5.64)
Infections and infestations	*Candida* infection*	49	4.94 (3.73–6.54)	4.93	153.24	2.30 (0.63)	4.92 (3.89)
Infections and infestations	Bacterial infection*	39	4.60 (3.36–6.30)	4.59	109.38	2.20 (0.53)	4.58 (3.52)
Infections and infestations	Fungal infection*	62	3.86 (3.01–4.96)	3.86	131.03	1.95 (0.28)	3.85 (3.13)
Infections and infestations	*Clostridium difficile* infection*	32	3.24 (2.29–4.58)	3.24	49.34	1.69 (0.03)	3.23 (2.42)
Injury, poisoning and procedural complications	Infusion related reaction*	161	5.53 (4.74–6.46)	5.51	592.5	2.46 (0.79)	5.49 (4.82)
Injury, poisoning and procedural complications	Off label use	1143	3.47 (3.27–3.69)	3.38	1932.16	1.75 (0.09)	3.37 (3.21)
Investigations	Ejection fraction decreased*	31	4.07 (2.86–5.79)	4.06	71.48	2.02 (0.35)	4.06 (3.02)
Metabolism and nutrition disorders	Tumour lysis syndrome	145	37.61 (31.89–44.36)	37.43	5026.69	5.19 (3.53)	36.61 (31.89)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome*	189	26.49 (22.94–30.60)	26.33	4533.37	4.70 (3.03)	25.93 (22.98)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy*	43	10.32 (7.64–13.93)	10.30	358.96	3.36 (1.69)	10.24 (7.97)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression*	203	4.45 (3.87–5.11)	4.42	537.25	2.14 (0.48)	4.41 (3.93)
Nervous system disorders	Posterior reversible encephalopathy syndrome*	102	21.69 (17.84–26.38)	21.62	1980.34	4.42 (2.75)	21.35 (18.13)
Nervous system disorders	Peripheral sensory neuropathy	33	12.22 (8.67–17.21)	12.20	336.95	3.60 (1.93)	12.12 (9.10)
Nervous system disorders	Encephalopathy*	102	8.98 (7.39–10.91)	8.95	716.68	3.15 (1.49)	8.91 (7.57)
Nervous system disorders	Neurotoxicity	32	4.23 (2.99–5.99)	4.23	78.76	2.08 (0.41)	4.22 (3.16)
Renal and urinary disorders	Nephropathy toxic*	72	14.88 (11.79–18.77)	14.84	921.35	3.88 (2.21)	14.72 (12.12)

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TABLE 4 (*Continued*) Signal strength of ADEs of etoposide at the Preferred terms (PTs) level in FAERS database. Asterisks indicate new and significant signals of etoposide-associated ADEs from FAERS database. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; EBGM, empirical Bayesian geometric mean.

SOC name	Preferred terms (PTs)	Case numbers	ROR(95%CI)	PRR	χ2	IC (IC025)	EBGM (EBGM05)
Reproductive system and breast disorders	Ovarian failure*	43	179.93 (131.29–246.60)	179.67	6879.7	7.34 (5.67)	161.89 (124.36)
Respiratory, thoracic and mediastinal disorders	Pulmonary toxicity	37	12.61 (9.12–17.43)	12.59	391.94	3.64 (1.98)	12.51 (9.54)
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome*	77	8.88 (7.10–11.11)	8.86	534.06	3.14 (1.47)	8.82 (7.31)
Respiratory, thoracic and mediastinal disorders	Pulmonary haemorrhage*	34	8.32 (5.94–11.66)	8.32	217.77	3.05 (1.38)	8.28 (6.24)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	67	5.61 (4.41–7.13)	5.60	252.21	2.48 (0.81)	5.58 (4.57)
Respiratory, thoracic and mediastinal disorders	Respiratory failure*	183	5.02 (4.34–5.80)	4.99	583.1	2.32 (0.65)	4.98 (4.41)
Respiratory, thoracic and mediastinal disorders	Respiratory distress*	70	5.05 (3.99–6.39)	5.04	226.08	2.33 (0.66)	5.03 (4.13)
Respiratory, thoracic and mediastinal disorders	Hypoxia*	68	4.09 (3.22–5.19)	4.08	157.79	2.03 (0.36)	4.07 (3.34)
Surgical and medical procedures	Stem cell transplant	33	28.65 (20.31–40.43)	28.62	864.50	4.81 (3.15)	28.14 (21.10)
Vascular disorders	Venoocclusive disease	41	34.97 (25.66–47.66)	34.93	1322.82	5.10 (3.43)	34.21 (26.41)
Vascular disorders	Flushing	196	3.69 (3.20–4.24)	3.67	380.31	1.87 (0.21)	3.66 (3.26)
Vascular disorders	Cyanosis	34	4.26 (3.04–5.97)	4.26	84.58	2.09 (0.42)	4.25 (3.21)

occurring in the third month. Notably, our data showed that adverse events may still occur after 1 year of etoposide treatment, accounting for 3.2% of cases.

In the evaluation of the Weibull Shape Parameter analysis (Table 5), the shape parameter (β) was calculated to be 0.55, and the upper limit of its 95% confidence interval (CI) was 0.57. The value of $\beta < 1$ suggested that the incidence of ADEs was considered to decrease over time, indicating an early failure type.

3.6 Subgroup analysis

Figure 4 illustrates the findings of the disproportionate analysis stratified by patient age. Among the two subgroups aged <18 and 18–64 years, the highest number of cases were associated with the positive signal of "off-label use." Conversely, in the >64 age subgroup, "febrile neutropenia" had the highest number of cases. Furthermore, when analyzing the number of top 10 ADEs in each subgroup, it was found that cough and flushing signals were only reported in the subgroup of age <18. On the other hand, acute kidney injury and pneumonia were found to be more common in the other two age subgroups (18–64, and >64).

Likewise, this subgroup disparity in ADEs was also evaluated across weight (Supplementary Figure S2), gender (Supplementary Figure S3), and reporting person (Supplementary Figure S4). These subgroup analyses provide a way to compare signal values between different subgroups, allowing for the identification of similarities and differences. This information is crucial for more detailed clinical management and can help healthcare professionals tailor their approach based on specific subgroup characteristics.

3.7 Gender differences in etoposide-related ADEs

At the PT level, using the ROR algorithm, we identified 58 signals that showed disproportionality in the occurrence of ADEs between males and females. Some of the major ADEs that were more likely to occur in women included cardiac failure congestive, primary hypogonadism, nausea, oesophagitis, death, disease progression, drug resistance, fatigue, multiple organ dysfunction syndrome, hepatic function abnormality, haemophagocytic lymphohistiocytosis, staphylococcal infection, and urinary tract infection. On the other hand, high-risk ADEs in males included leukopenia, thrombocytopenia, pneumonia, hyponatremia, neoplasm progression, peripheral neuropathy, confusional state, acute kidney injury, and pulmonary embolism (Figure 5). You could find all the detailed results in Supplementary Table S3.

To further differentiate etoposide-related ADEs in terms of gender, we generated a "volcano plot" in Figure 6 to visualize the results. Each point in the plot represented an etoposide-related ADE, and ADEs with significant Log2ROR and -log10 (adjusted *p*-value)

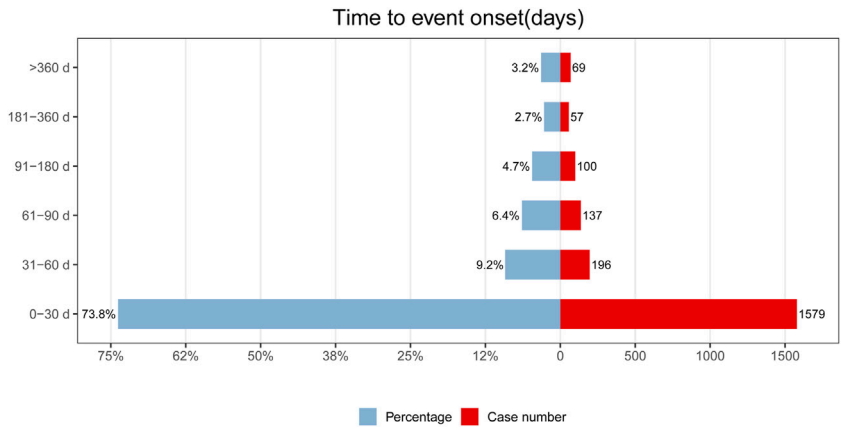

FIGURE 3
Time-to-onset of etoposide-related ADEs.

TABLE 5 Time-to-onset analysis for etoposide-related signals using the Weibull distribution test. n, number of cases with available time-to-onset; IQR, interquartile range; TTO, Time-to-onset. A TTO of 0 days means that the adverse event happens within the day of treatment.

Cases	TTO (days)		Weibull distribution				Failure type
n			Scale parameter		Shape parameter		
	Media (IQR)	Min-Max	α	95% CI	β	95% CI	
2138	10 (2–32)	0–4900	38.56	35.05–42.07	0.55	0.53–0.57	Early failure

were labeled. In males, three significant signals were observed, including pneumonia, myocardial infarction, and atrial fibrillation. In females, five significant signals were found including drug resistance, cardiac failure congestive, fatigue, ototoxicity, and multiple organ dysfunction syndrome (Figure 6).

4 Discussion

We conducted a post-marketing pharmacovigilance analysis of etoposide by collecting and evaluating real-world data from the largest sample, with the aim of identifying potential, new adverse reactions to etoposide and analyzing the onset time of adverse reactions as well as gender differences. These findings may help guide updates to the SmPC and provide new evidence for the rational use of etoposide in clinical practice.

4.1 Baseline data description

Our study uncovered a yearly increase in the number of reported adverse event reports associated with etoposide, beginning in 2004 and maintaining a relatively high level since 2016. This upward trend suggests not only the effectiveness of etoposide treatment, leading to its increased use in various indications and patient populations, but also emphasizes the importance of analyzing these adverse reactions. Another significant finding was that etoposide-related adverse events occurred more commonly in males (49.6%) compared to females (34.3%). This observation aligns with the higher incidence of etoposide usage in men for major indications such as acute myeloid leukemia (AML), acute lymphocytic leukemia, Hodgkin's lymphoma, small cell lung cancer, and specific indications like testicular cancer (Sant et al., 2010; Townsend and Linch, 2012; Hellesøy et al., 2021; Rudin et al., 2021; Chovanec et al., 2023). Furthermore, our study highlighted that approximately 90% (88.7%) of adverse event reports were provided by health professionals, which adds credibility to the results of our analysis.

4.2 Blood and infection-related adverse reactions

Based on disproportionality analysis, we found that the most common and significant ADEs at the SOC levels included "blood and lymphatic system disorders," and "infections and infestations". One of the most frequent dose-limiting adverse reactions in cancer therapy is hematotoxicity (n = 87, ROR 23.16 [18.74–28.63]). The fast blood cell turnover renders them a potential target for conventional chemotherapy, and such toxicity can contribute to a range of blood disorders (Haglund et al., 2010). Furthermore, there were many previous clinical studies that also confirmed the hematological toxicity of etoposide. Tonder's research suggested that 8 of 12 high-grade glioma patients occurred hematotoxicity of World Health Organization (WHO) grade 3 or 4 after administration of carboplatin and etoposide (Tonder et al., 2014).

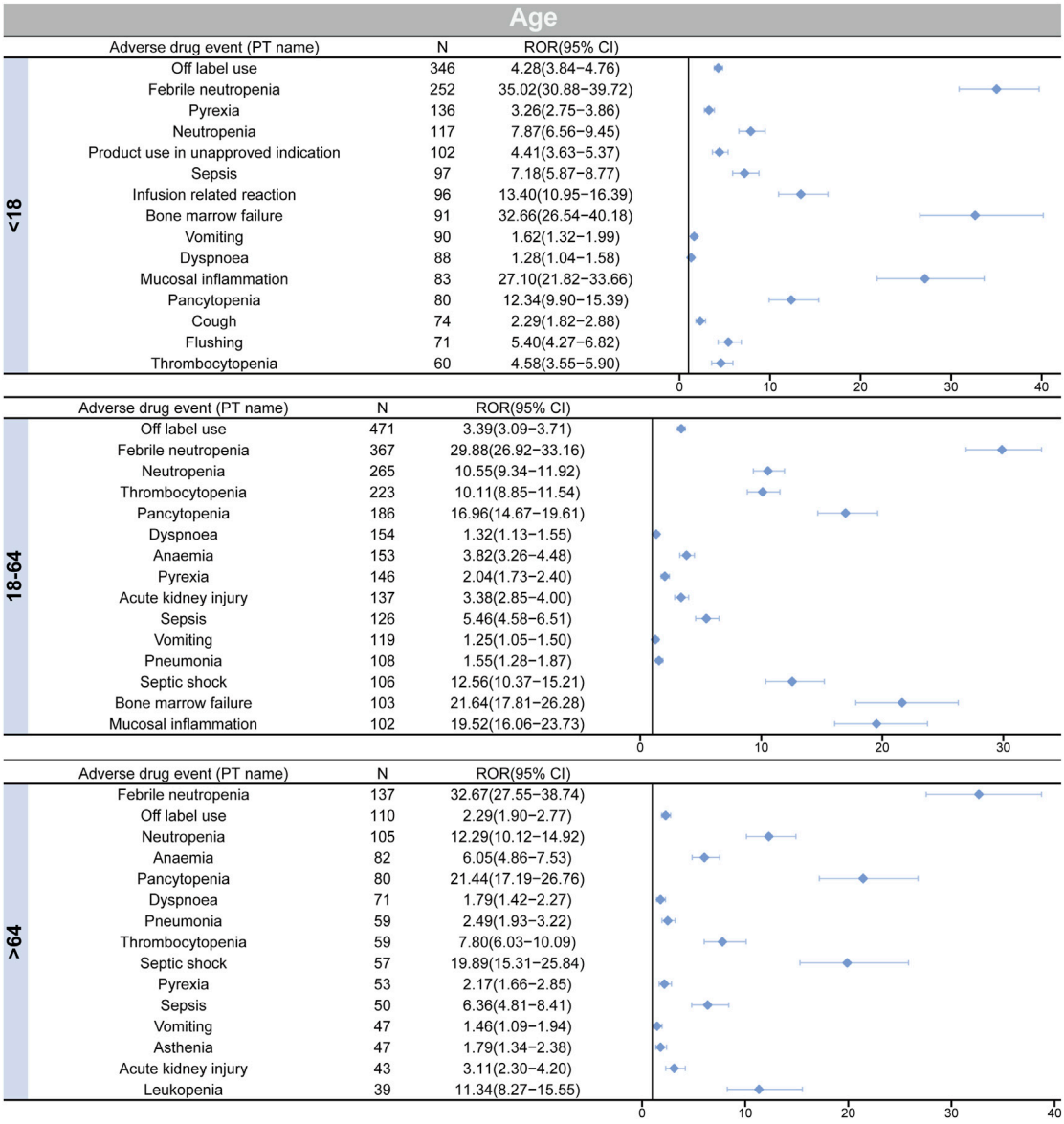

FIGURE 4
Age-based subgroup analysis of etoposide-related ADEs.

In another multicenter phase II trial in small cell lung cancer (SCLC), treatment with etoposide resulted in grade 3 to 4 leukopenia and grade 3 thrombocytopenia in 74% and 10% of patients, respectively (Bremnes et al., 2001). A meta-analysis bringing together the results of three randomized controlled trail in SCLC showed that etoposide/cisplatin was more likely to have blood-related side effects than irinotecan/cisplatin (Jeremić and Milićić, 2007). Through a real-world analysis of etoposide, we had also identified a number of significant hematologic adverse signals including anemia (n = 345, ROR 3.64 [3.27–4.04]), leukopenia (n = 176, ROR 7.36 [6.34–8.54]), thrombocytopenia (n = 417, ROR 7.96 [7.23–8.77]), and myelosuppression (n = 47, ROR 6.32 [4.74–8.41]), which were consistent with the results of previous clinical trials and the drug's instructions. Furthermore, we have identified novel, unlabeled signals in the instructions, such as thrombotic microangiopathy (n = 35, ROR 8.41 [6.04–11.73]). Although the risk of thrombotic microangiopathy has been reported to increase significantly with etoposide after autologous stem cell transplantation in neuroblastoma patients, the specific role of etoposide in causing vascular endothelial injury requires further investigation (Vantelon et al., 2001; Jodele et al., 2018).

In addition to hematologic toxicity, various opportunistic infections are considered to be strongly associated with increased patient mortality, reduced chemotherapy doses, treatment delays, and increased healthcare costs (Peretz et al., 2016; Nordvig et al., 2018; Abdel-Azim et al., 2019). The reported incidence of infections associated with etoposide use in different clinical trials of SCLC ranged from 6% to 33% (Saito et al., 2006; Morabito et al., 2017;

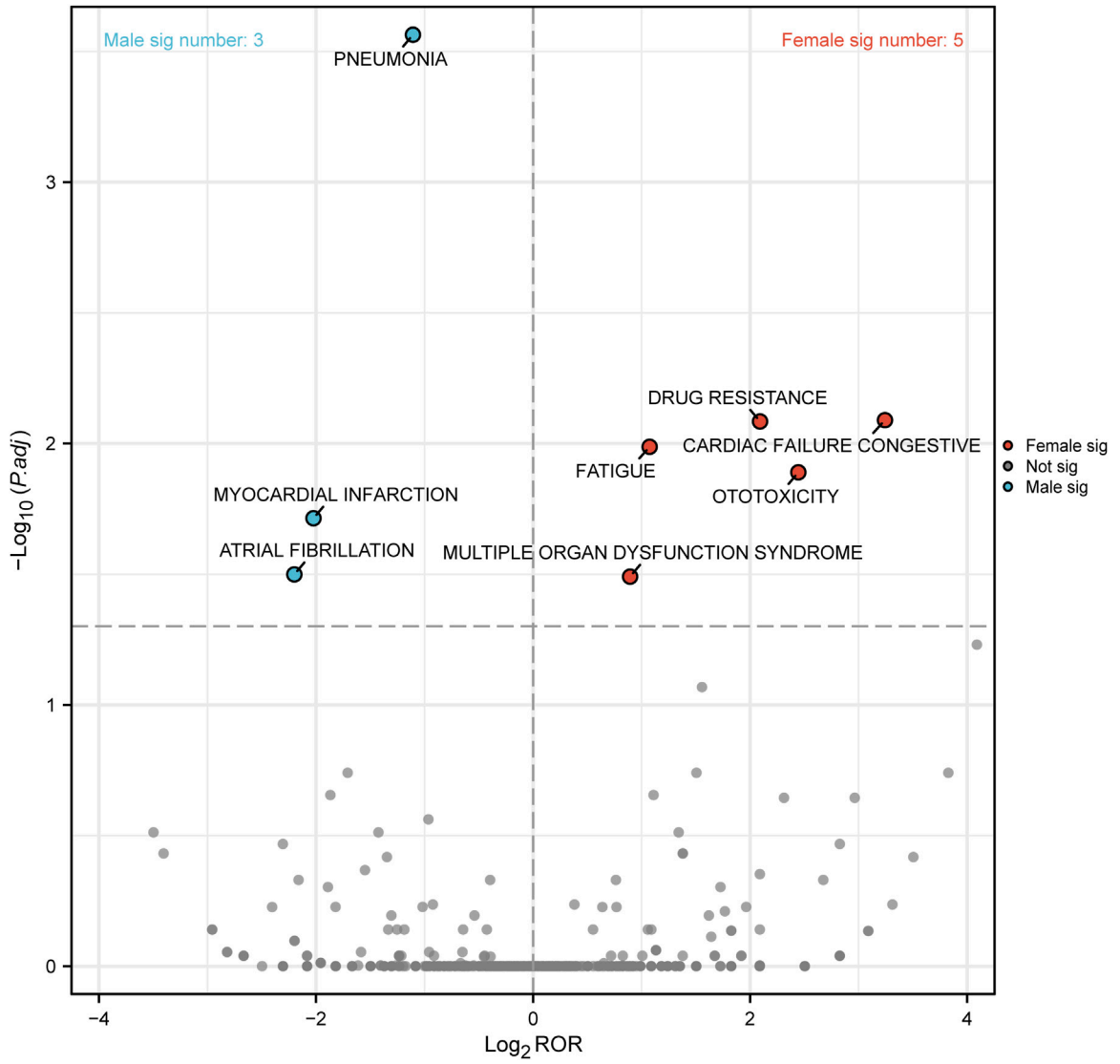

FIGURE 5
Reporting odds ratios (ROR) with 95% CI for all positive gender-related ADEs. CI, confidence interval; ROR, Reporting odds ratio.

Socinski et al., 2017; Shimokawa et al., 2023). Additionally, similar infections have been reported in the treatment of tumors of blood, ovarian, prostate and breast origin (Dahl et al., 2000; Papandreou et al., 2002; Lu et al., 2015; Matsumoto et al., 2015). The myelosuppressive effect of etoposide, particularly its impact on neutrophil production, is likely the main contributing factor to the development of various aggressive infections. These infections, in turn, can further impair neutrophil production and hasten their depletion. Therefore, prophylactic administration of colony-stimulating factor injections is necessary (Urban et al., 1996; Kuderer et al., 2007; Mhaskar et al., 2014; Wang et al., 2015). In conclusion, it is imperative for clinicians to closely monitor patients' coagulation function following the administration of etoposide. Antiplatelet agents should be used with caution, particularly in patients identified as high-risk for thrombosis during pre-treatment evaluation. Furthermore, timely intervention is crucial for managing various potential infections.

4.3 Neoplasms-related adverse reactions

At the neoplasm level, we also identified a number of ADEs with strong signal values. Second primary malignancy (SPM) (n = 43, ROR 10.32 [7.64–13.93]) is defined as a second, distinct pathological diagnosis of the same or different origin as the first primary malignancy, and chemotherapy also increases the risk of secondary hematologic or solid malignancies (Lenzi et al., 2020; Geng et al., 2023). The mechanism of etoposide-induced second primary malignancy (SPM) can be attributed to two possible explanations. Firstly, it can cause translocation rearrangement of the MLL gene on chromosome 11q23 (Ezoe, 2012). Secondly, the formation of catechol during drug metabolism can contribute to SPM development (Hartmann and Lipp, 2006; Zahnreich and Schmidberger, 2021). In addition, our study revealed that tumor lysis syndrome (TLS) also has strong signal value (n = 145, ROR 37.61). TLS occurs due to the rapid breakdown of malignant cells,

FIGURE 6
Volcano map of gender difference risk signal for etoposide. ROR, reporting odds ratios; *P*.adj, the *p*-value is adjusted with false discovery rate (FDR) method.

leading to the release of cellular contents, such as electrolytes, nucleic acids, and metabolites, into the bloodstream. This phenomenon typically happens spontaneously or after treatment in patients with malignancies (Durani and Hogan, 2020; Grewal et al., 2023). TLS is characterized by its high lethality and is often associated with the administration of cytotoxic chemotherapy. Clinical manifestations of TLS primarily include hyperuricemia, hyperkalemia, and hyperphosphatemia, which can result in acute respiratory distress, disseminated intravascular coagulation, and renal failure (Calvo Villas, 2019; Tambaro and Wierda, 2020). We came across a case report which described a patient with testicular cancer who developed TLS and eventually succumbed to an infection and respiratory distress syndrome after receiving etoposide chemotherapy (Kobatake et al., 2015). It is therefore essential to assess the risk before chemotherapy and closely monitor electrolyte levels after treatment in patients with high-risk factors for TLS, such as those with highly proliferative hematologic tumors or pre-existing renal dysfunction (Durani and Hogan, 2020). In conclusion, our

study alerts clinical decision makers that they should be aware of these lethal tumor-related signals during etoposide administration.

4.4 Adverse reactions at other SOC level

ADEs associated with etoposide administration may also involve other organs or tissues based on our disproportionality analysis. The observed cardiac disorders of etoposide use in our research included cardiotoxicity (n = 73, ROR 319.62 [15.57–24.71]) and acute myocardial infarction (n = 53, ROR 3.37 [2.58–4.42]).The metabolic disturbances caused by chemotherapy drugs and the oxidative damage by the oxygen radicals they produce might be reasonable explanations for its cardiotoxicity (Pai and Nahata, 2000; Simbre et al., 2005). As for the nephropathy toxic (n = 72, ROR 14.88 [11.79–18.77]) associated with etoposide administration, in addition to the above-mentioned TLS that might trigger renal failure, other possible explanations include delayed clearance of the drug in the kidney or an increased burden on the kidney from microthrombosis. Other than the more common adverse reactions listed above, there are a number of less commonly reported toxicities involving the ear and reproductive system that require caution. Ear and labyrinth disorders associated with etoposide administration were identified in our study including ototoxicity (n = 37, ROR 44.18 [31.86–61.25]) and deafness (n = 51, ROR 4.10 [3.12–5.40]), which may be related to drug-induced damage to cochlear hair cells (Kushner et al., 2006). Notably, an analysis of adverse drug reaction (ADR) reports describing drug-induced ototoxicity from the Italian spontaneous reporting system also identified a potential role for etoposide in the development of tinnitus, which is also in agreement with our results (Barbieri et al., 2019). Regarding the relationship between etoposide and ovarian failure (n = 43, ROR 179.93 [131.29–246.60]), it was reported that Anti-Muller hormone (an indicator of ovarian reserve function) was significantly lower in patients receiving etoposide-containing chemotherapy compared to the general population, and reduced ovarian function was difficult to restore after discontinuation of the drug (Meissner et al., 2015; Anderson et al., 2018). Prior to chemotherapy with etoposide, female patients should be informed of the potential gonadal toxicity. Age-specific discussions and fertility preservation procedures should also be considered, such as the use of gonadotropin-releasing hormone agonist prior to chemotherapy to reduce the number of primordial follicles entering the differentiation phase and to reduce follicular apoptosis, thereby protecting ovarian reserve function (Blumenfeld, 2007; Moore et al., 2015). In conclusion, the above newly identified signals in different organs may need to be specified in subsequent updates of the drug specification.

4.5 Time-to-onset and gender difference of ADEs

The findings of our study indicate that the majority of ADEs following etoposide treatment occur within 3 months, with the highest incidence observed in the first month (73.8%). In total, 89.4% of ADEs were reported within the first 3 months. Given this information, it is crucial to pay close attention to ADEs within the first month following etoposide administration. Timely identification and management of adverse events caused by etoposide therapy at an early stage are essential. It is noteworthy that there is a lack of comprehensive studies focusing on the specific timing of adverse reactions after etoposide administration, making our study a valuable contribution in this area. Gender differences have been shown to affect the bioavailability, distribution, metabolism, and elimination of drugs, leading to variations in ADEs between males and females (Zopf et al., 2009; de Vries et al., 2020; Farkouh et al., 2020). However, there is a lack of reported gender-specific ADEs associated with etoposide treatment. In our study, we observed that females had a higher number of positive signal values for ADEs compared to males. This finding aligns with previous research indicating that females are more prone to experiencing ADEs (Tran et al., 1998; Anderson, 2005). Interestingly, in males, we identified pneumonia as a high-risk signal, which may be attributed to their longer airways compared to females (Talaminos Barroso et al., 2018). Enhancing our understanding of gender-related ADEs will contribute to improving drug safety, efficacy, and optimizing drug therapy for both males and females (Sharifi et al., 2021). Subsequent clinical trials and mechanistic studies are necessary to validate and provide explanations for these ADEs with gender differences. This will guide better drug regimens for both males and females.

The present research, although suggesting a potentially significant relationship between the use of etoposide and the likelihood of reporting ADEs in FAERS, is not without limitations. First, it is important to acknowledge that FAERS is a spontaneous reporting system, and information collected from various countries and professionals may be incomplete or inaccurate, which can introduce bias into the analysis results. Second, despite our detailed explanation in the discussion section, FAERS alone cannot provide sufficient evidence to establish a causal relationship between drug use and ADEs (Shu et al., 2022c). Therefore, our findings should be viewed more as a warning to clinicians and pharmacists to remain vigilant regarding potential adverse events. Third, it is worth noting that monotherapy is uncommon in cancer treatment. Although etoposide was identified as the primary suspect in the reported adverse events in our analysis, it is challenging to determine the adverse effects solely caused by etoposide (Ezoe, 2012). Finally, it is also worth exploring how these ADEs impact across races, or across regions (Sabblah et al., 2017)? It is crucial to consider these limitations when interpreting the findings of our research and to encourage further investigations, including clinical trials and self-testing cohort data of clinical dosing information, to validate and expand upon our observations.

5 Conclusion

In conclusion, this study conducted a scientific and systematic analysis of adverse reactions linked to etoposide dosing, including their onset times and potential gender differences using the FAERS database. It is crucial that clinicians maintain a high level of vigilance regarding these potentially serious ADEs. Additionally, considering the potential gender differences is important for optimizing drug selection and closely monitoring patients. Further prospective clinical studies are required to confirm and enhance our understanding of the association between etoposide and these ADEs.

Data availability statement

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

Author contributions

ZC: Conceptualization, Visualization, Writing–original draft. FC: Conceptualization, Writing–original draft. LW: Formal Analysis, Writing–original draft. FZ: Formal Analysis, Writing–original draft. RP: Visualization, Writing–original draf. YT: Visualization, Writing–original draf. XZ: Writing–review and editing. JZ: Writing–review and editing. YZ: Writing–review and editing. XY: Funding acquisition, Supervision, Writing–original draft, 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.2023.1259908/full#supplementary-material

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Cardiovascular risk of Janus kinase inhibitors compared with biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis without underlying cardiovascular diseases: a nationwide cohort study

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Objectives: Despite the ethnic differences in cardiovascular (CV) risks and recent increase in the prescription of Janus kinase (JAK) inhibitors, limited evidence is available for their CV outcomes in Asian patients with rheumatoid arthritis (RA). We aimed to compare the major adverse CV events (MACEs) of JAK inhibitors to those of biologic disease-modifying antirheumatic drugs (bDMARDs) in Korean patients with RA without baseline CV disease (CVD).

Methods: In a nationwide retrospective cohort study, patients newly diagnosed with RA without a history of CVD between 2013 and 2018 were identified using the National Health Insurance Service database. The cohort was followed up until the end of 2019 for the development of MACEs. Hazard ratios (HRs) for MACEs such as myocardial infarction, stroke, coronary revascularization, or all-cause death, were estimated using Cox proportional hazard regression in a propensity score-matched cohort.

Results: In total, 4,230 matched patients with RA were included (846 JAK inhibitor users and 3,384 bDMARD users). The crude incidence rate (95% confidence intervals, CI) per 100 patient-years for MACEs was 0.83 (0.31–1.81) and 0.74 (0.53–1.02) in the JAK inhibitor and bDMARD groups, respectively. The risk of MACEs was not significantly different between JAK inhibitor and bDMARD users with an adjusted HR (95% CI) of 1.28 (0.53–3.11). There were no significant differences in the risk of MACEs between JAK inhibitors and bDMARDs in each subgroup according to the types of bDMARDs, age, sex, Charlson comorbidity index score, and comorbidities.

Conclusion: Compared to bDMARDs, JAK inhibitors were not associated with the occurrence of MACEs in Korean patients with RA without a history of CVD.

KEYWORDS

janus kinase inhibitors, biologic DMARDs, cardiovascular risk, asian, rheumatoid arthritis

1 Introduction

Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular (CV)-related morbidity and mortality, possibly due to the chronic, systemic immune-mediated inflammation (Avina-Zubieta et al., 2012; Smolen et al., 2018). Disease-modifying antirheumatic drugs (DMARDs), including conventional, biologic or targeted synthetic DMARDs, are mainly used for lifetime management of RA, among which Janus kinase (JAK) inhibitors targeting JAK family kinases offer an important alternative to biologic DMARDs (bDMARDs) (Smolen et al., 2018; Takabayashi et al., 2021). The recent European League Against Rheumatism (EULAR) guideline recommends JAK inhibitors for patients with poor prognostic factors who fail to achieve the treatment target with initial treatment with conventional synthetic DMARDs (csDMARDs) along with bDMARDs (Smolen et al., 2020). Three JAK inhibitors are currently available for the clinical management of RA since the first approval of tofacitinib approximately 10 years ago, and then baricitinib and upadacitinib approximately 3–4 years ago in the United States (US) and Korea (US Food & Drug Administration; Korean Ministry of Food and Drug Safety).

However, increasing evidence suggests that JAK inhibitors are unsuitable for patients at risk for thromboembolic or CV events because they may negatively impact thrombopoietin signaling and platelet homeostasis by blocking the intracellular signaling pathways of inflammatory cytokines (Gadina et al., 2019; Baldini et al., 2021; Song et al., 2022; Ytterberg et al., 2022). Nevertheless, the association between JAK inhibitors and CV outcomes is unclear. Several studies, including randomized controlled trials (RCTs) and large population-based cohorts, have shown that JAK inhibitors do not have a significant impact on the risk of major adverse CV events (MACEs) in patients with RA regardless of their underlying CV risk (Xie et al., 2019b; Khosrow-Khavar et al., 2022; Taylor et al., 2022). However, a recent large-scale RCT reported an increased risk of MACEs with tofacitinib compared to that with a tumor necrosis factor (TNF) inhibitor in patients aged ≥50 years with RA and CV risk factors (Ytterberg et al., 2022). Therefore, the regulatory authorities recommend restricting the use of JAK inhibitors in patients with risk factors for CV disease (CVD) and those with a history of smoking (US Food and Drug Administration, 2021a; European Medicines Agency, 2022; Korean Ministry of Food and Drug Safety, 2022). However, this recommendation cannot be directly applied to patients aged <50 years and those without underlying CVD (Singh, 2022). Moreover, most studies on the impact of JAK inhibitors on MACEs have included Western populations. Despite the ethnic differences in CV risks and mortality between the Asian and Western populations and recent increase in the prevalence of RA and prescription of JAK inhibitors in Korea, limited evidence is available for the CV outcomes of JAK inhibitors in the Asian population (Won et al., 2018; Health Insurance Review and Assessment Service, 2022; Tsao et al., 2022). Very recently, a cohort study was conducted in the Asian patients with RA to assess the CV risks of JAK inhibitors and showed no difference in the risk compared to TNF inhibitors (Tong et al., 2023). Nevertheless, to the best of our knowledge, there is a lack of studies comparing CVD risk between JAK inhibitors and bDMARDs in Asian RA patients without a history of CVDs.

Successful control of RA with JAK inhibitors while minimizing its negative effects on CVD is clinically important. Therefore, this study aimed to compare the CV risk of JAK inhibitors and bDMARDs in Korean patients newly diagnosed with RA without baseline CVD.

2 Materials and methods

2.1 Study design and data source

This cohort study was performed using national insurance reimbursement claims data from 2011 to 2019, which were officially provided by the Health Insurance Review and Assessment Service (HIRA) of Korea. The HIRA is an independent and public insurance agency that reviews medical fees, evaluates whether the prescribed drugs are medically necessary on the basis of drug labels, and provides national insurance coverage to 97.1% Korean citizens (Health Insurance Review and Assessment Service, 2021a; Health Insurance Review and Assessment Service, 2021b). The data included information on demographics, diagnosis, procedure, and prescription, with an unidentifiable code representing each individual. This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University (IRB No. CUIRB-2019-E012, 25 September 2019), which waived the requirement for informed consent because all patient data were anonymized and de-identified by a randomized identification number prior to retrospective analysis.

2.2 Study population

Adult patients who were first diagnosed with RA using the diagnostic codes of M05 or M06 in accordance with the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) between 1 January 2013 and 31 December 2018 and were prescribed at least one csDMARD (hydroxychloroquine, methotrexate, sulfasalazine or leflunomide) on the first day of RA diagnosis according to claims data were eligible for inclusion (World Health Organization, 2019). As shown in Figure 1, the index date was defined as the first prescription date of bDMARDs (including TNF inhibitors [such as infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol] and non-TNF inhibitors [such as rituximab, abatacept, anakinra,

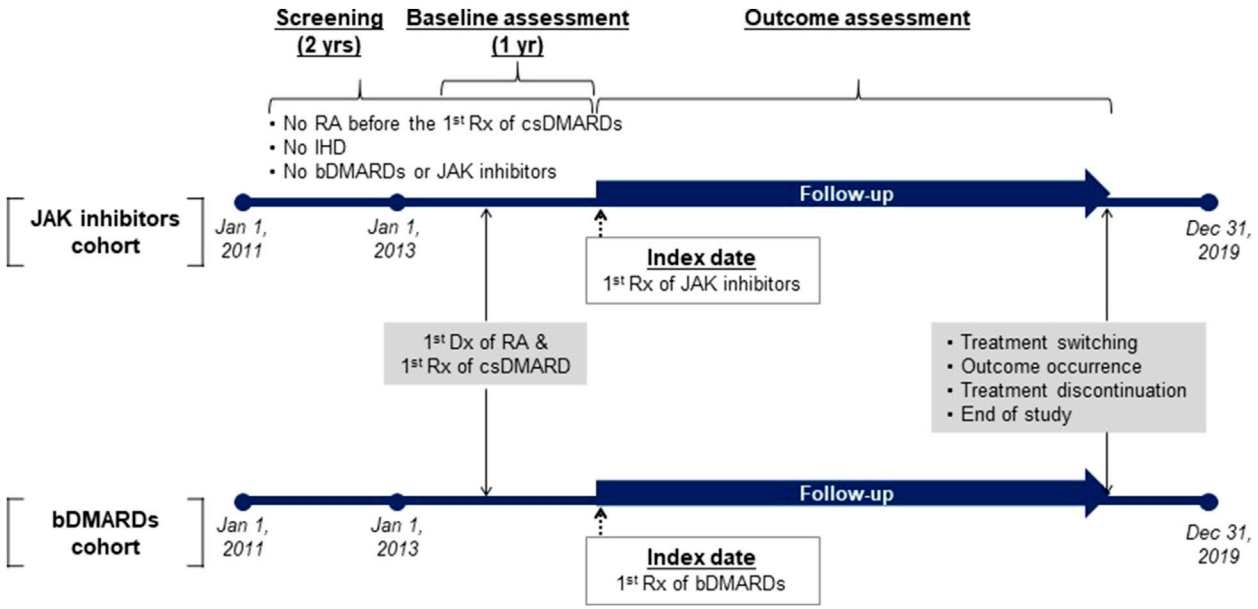


FIGURE 1
Study timeline. Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; Dx, diagnosis; IHD, ischemic heart disease; JAK, Janus kinase; RA, rheumatoid arthritis; Rx, prescription.

and tocilizumab]) or JAK inhibitors (including tofacitinib and baricitinib). Upadacitinib, which was first used in Korea in 2020, could not be included in this study considering the study design. Users who had not received bDMARDs or JAK inhibitors within the last 2 years were defined as new users of bDMARDs or JAK inhibitors. Patients were excluded if they were (1) <20 years old on the index date; (2) diagnosed with RA 2 years before the first prescription of csDMARDs; (3) diagnosed with rheumatic heart disease (ICD-10 codes: I00–I09), ischemic heart disease (ICD-10 codes: I20–I25), valve disorders (ICD-10 codes: I34–I36), heart failure (ICD-10 codes: I50), or stroke (ICD-10 codes: I60–I69) within 2 years before the index date; (4) prescribed csDMARDs only once before the index date considering eligible patients for the use of JAK inhibitors or bDMARDs based on the EULAR guideline or Korean insurance coverage criteria; (5) diagnosed with only adult-onset Still disease (ICD-10 codes: M06.1) or inflammatory polyarthropathy (ICD-10 codes: M06.4) to include only patients with a diagnostic code for RA; (6) diagnosed with cancer (ICD-10 codes: C00–C99) during the study period which might affect the study outcomes; and (7) diagnosed with ankylosing spondylitis (ICD-10 codes: M45), Crohn's disease (ICD-10 codes: K50), ulcerative colitis (ICD-10 codes: K51), psoriatic arthritis (ICD-10 codes: M07.0–M07.3), or psoriasis (ICD-10 codes: L40) for which JAK inhibitors or bDMARDs could be used (Kim et al., 2011; Health Insurance Review and Assessment Service, 2019; Smolen et al., 2020). For the latter two exclusions, all available data between 2011 and 2019 were used to clearly evaluate the study outcomes (Kim et al., 2011). Ultimately, our intention was to include naïve users for JAK inhibitors or bDMARDs among newly diagnosed patients with RA who had no history of CVDs. The baseline period was used for assessing comorbidities, comedications, and confirming new use of bDMARDs or JAK inhibitors.

2.3 Exposure data

Exposure was determined by the prescription date and number of days of drug supply. The dosing intervals for bDMARDs administered via infusion was determined based on the drug label (Korean Ministry of Food and Drug Safety, 2022). Patients were grouped into JAK inhibitor and bDMARD groups according to initial prescription and followed up thereafter. Patients were followed-up from the day after the index date and to the date of the following censoring events, whichever occurred first: 1) index drug discontinuation defined as treatment gap >365 days between its prescriptions, 2) switching to a JAK inhibitor in the bDMARD group or a bDMARD in the JAK inhibitor group, 3) outcome occurrence, and 4) end of the study (31 December 2019). The follow-up period for each patient varied depending on the patient's entry date. Switching to a different JAK inhibitor or bDMARD was permitted in the JAK inhibitor and bDMARD groups, respectively.

2.4 Study outcomes

The primary outcome was a composite MACE of myocardial infarction (MI, ICD-10 codes: I21), ischemic stroke (ICD-10 code: I63), coronary revascularization such as angioplasty or bypass surgery (procedure codes: M6551–M6554, M6561–M6567, M6571, M6572, M6620, M6634, M6638, O1640–O1642, O1647–O1649, OA640–OA642, and OA647–OA649) or all-cause death (claims related to death as a medical result) (Kip et al., 2008). The secondary outcomes included each component of the MACEs. The date of the first occurrence of any of the above four components was defined as the date of composite CV outcomes. In addition, we

considered hospitalization for MI, stroke, or coronary revascularization and diagnosis of stroke based on brain imaging including computed tomography (CT) or magnetic resonance imaging (MRI) to validate the clinical outcomes (Yeom et al., 2015; Park et al., 2019).

2.5 Confounding variables

During the 365-day baseline period prior to the index date, the following baseline characteristics, which were considered to be potentially associated with the study outcomes and RA severity, were assessed: age at the index date, sex, index year, type of insurance, Charlson comorbidity index (CCI) score, comorbidities (e.g., dyslipidemia, diabetes mellitus, hypertension, osteoporosis, anemia and eye disorders), medications for RA (e.g., csDMARDs, corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], and tramadol), and comedications (e.g., statins, antidiabetics and antihypertensives). The adjusted model included covariates such as age, sex, index year, type of insurance, CCI score, and comorbidities (except diabetes mellitus). Age was included as the categorical variable in the final model.

2.6 Statistical analysis

Propensity score (PS) matching was performed to adjust for the effect of confounding variables between the JAK inhibitor and bDMARD groups. The PS was estimated using logistic regression with variables including age, sex, index year, type of insurance, medications for RA, CCI score, comorbidities, and comedications. JAK inhibitor users were matched 1:4 to bDMARD users using the greedy 5-to-1 digit matching algorithm (Parsons, 2001). Distribution of propensity score before and after matching was examined using a standardized difference, with a value exceeding 0.1 considered indicative of an imbalance.

Data are shown as numbers and percentages for categorical variables and medians and ranges for continuous data. Fisher's exact test and the chi-square test were used to compare categorical data, while the unpaired *t*-test and Mann-Whitney U test were used to compare continuous data. Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated for primary and secondary outcomes in the PS-matched study cohort. Cox proportional hazard regression was used to estimate hazard ratios (HRs) and 95% CI for study outcomes according to the use of JAK inhibitors or bDMARDs. The proportionality assumption in the Cox proportional hazard model was examined using the goodness-of-fit test.

Subgroup analysis was performed according to the type of bDMARD (TNF inhibitors only and others), age (<65 and ≥65 years), sex, CCI score, and presence of CVD-related comorbidities (such as hypertension or dyslipidemia) or RA-related comorbidities (such as eye disorders, osteoporosis, or anemia). Sensitivity analyses were performed to evaluate the robustness of the primary analysis results under the modifications of the permissible treatment gap of 90 and 180 days (US Food and Drug Administration, 2013). Statistical significance was set at a two-sided *p*-value of <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States of America).

3 Results

3.1 Demographic characteristics

Among the 354,728 patients with RA who were prescribed at least one csDMARD between 2013 and 2018, 334,708 patients were excluded according to the predefined exclusion criteria. The eligible study cohort included 20,020 patients newly diagnosed with RA, without underlying CVD, and with no recent prescription of bDMARDs and JAK inhibitors (846 JAK inhibitor users and 19,174 bDMARD users before PS matching, Figure 2).

As shown in Table 1, the proportion of methotrexate (81.3% vs. 78.0%) or tramadol (82.1% vs. 79.3%) users was higher in the bDMARD group than in the JAK inhibitor group during a year prior to the first prescription of bDMARDs or JAK inhibitors. Furthermore, more bDMARD users were compared to JAK inhibitor users with the increasing order of the index year. After 1:4 PS matching, 846 JAK inhibitor users were matched with 3,384 bDMARD users, and both groups were well balanced. The mean age of JAK inhibitor and bDMARD users was 48.1 ± 12.7 and 48.5 ± 12.6 years, respectively, and 91.2% patients were <65-year-old. Women accounted for approximately 71% of the study cohort. From 2014 to 2015, approximately 65% patients were first prescribed bDMARD or JAK inhibitors. The CCI score was ≤1 point in 94.6% patients, and more than 50% patients had a history of hypertension or dyslipidemia within a year of the first use of the study drugs. During the baseline assessment period, approximately 79% patients received methotrexate or hydroxychloroquine as csDMARDs, while NSAIDs or corticosteroids were prescribed to more than 90% patients. The average period from the first diagnosis of RA with a csDMARD to the commencement of a JAK inhibitor or a bDMARD was 6.5 months in both groups.

3.2 MACEs associated with the use of JAK inhibitors

As shown in Table 2, the overall IR (95% CI) per 100 patient-years (PY) for composite MACEs after PS matching was 0.83 (0.31–1.81; 6/846 events) and 0.74 (0.53–1.02; 38/3,384 events) in the JAK inhibitor and bDMARD groups, respectively. The median time to onset of the first MACE was 9.14 and 60.71 weeks in the JAK inhibitor and bDMARD groups, respectively. Compared to the risk of MACEs in the bDMARD group, that in the JAK inhibitor group was 28% higher, but the difference was not statistically significant (adjusted HR: 1.28, 95% CI: 0.53–3.11).

None of the patient in the JAK inhibitor group experienced MI or ischemic stroke, while eight patients in the bDMARD group experienced MI only. The IRs (95% CI) of coronary revascularization were 0.28 (0.03–1.00) and 0.35 (0.21–0.55) per 100 PY, in the JAK inhibitor group and bDMARD groups, respectively. The IR (95% CI) of all-cause death was 2.4-fold higher in patients prescribed JAK inhibitors [0.56 (0.15–1.42)]

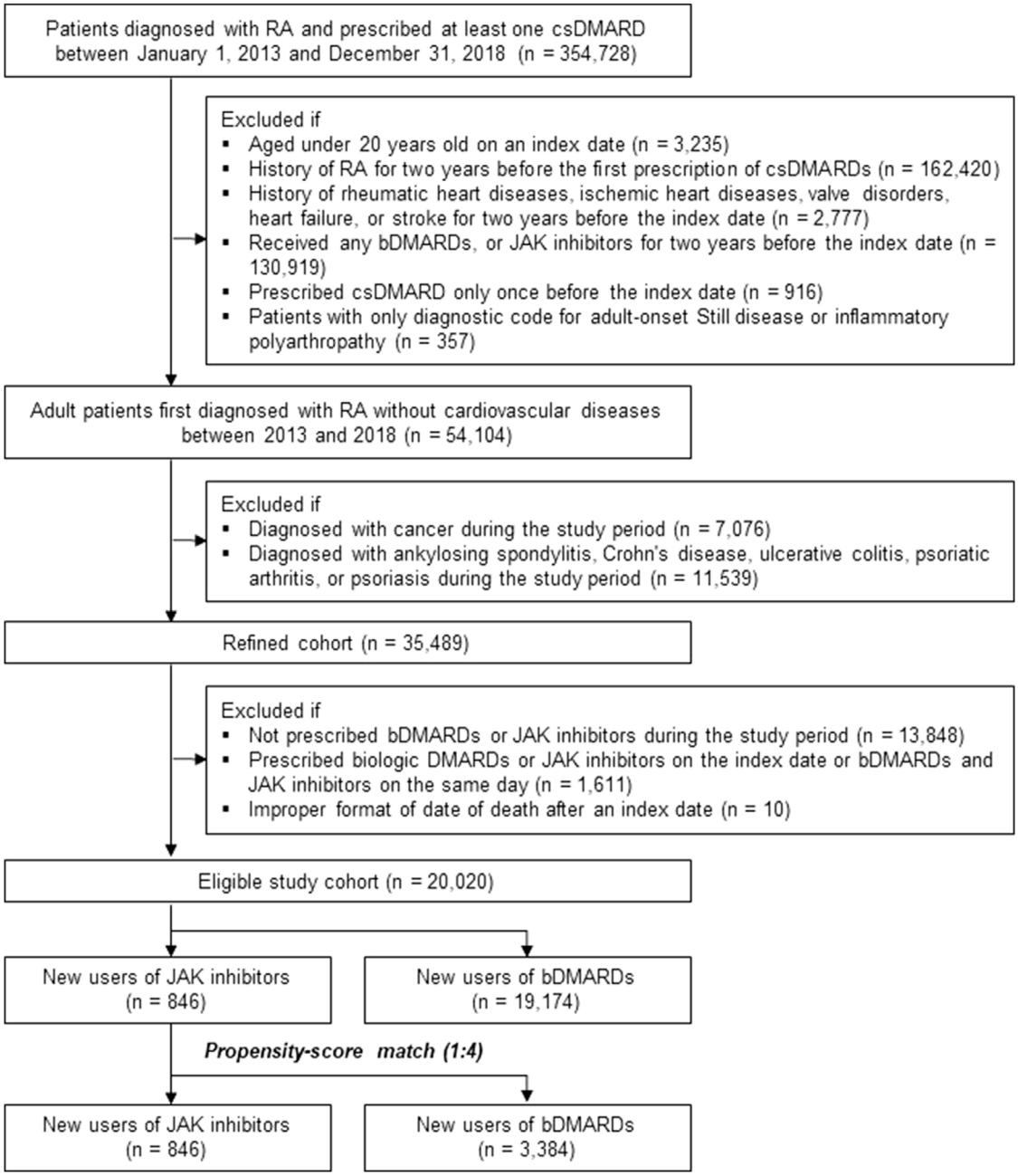


FIGURE 2
Study cohort selection process. Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IHD, ischemic heart disease; JAK, Janus kinase; RA, rheumatoid arthritis.

than in those prescribed bDMARDs [0.23 (0.12–0.41)]. Regarding each component of MACEs, JAK inhibitors did not increase the HR of coronary revascularization and all-cause death compared to bDMARDs (adjusted HR [95% CI]: 0.95 [0.21–4.21] and 2.38 [0.72–7.90], respectively). The proportional hazard assumption was appropriate, as the *p*-value was greater than 0.05 in the goodness-of-fit test.

Figure 3 summarizes the results of subgroup analyses according to the types of bDMARDs, age, sex, CCI score, and comorbidities. Overall, there were no significant differences in the risk of MACEs between JAK inhibitors and bDMARDs in each subgroup. However, the risk of CVD associated with JAK inhibitors tended to increase compared to that with bDMARDs in patients aged ≥65 years (adjusted HR: 1.83, 95% CI: 0.36–9.31). Women who were prescribed JAK inhibitors had higher risks than those who were prescribed bDMARDs (adjusted HR: 2.38, 95% CI: 0.84–6.69); however, the adjusted HR (95% CI) for men was only 0.34 (0.04–2.63). The HRs were higher in patients with comorbidities, such as hypertension, or eye disorder, in comparison to those without the comorbidities.

As shown in Table 3, the risk of MACEs with JAK inhibitors compared to that with bDMARDs did not significantly differ according to the different permissible treatment gaps. When we

TABLE 1 Baseline characteristics before and after 1:4 propensity-score matching, number of patients (%).

Characteristics	Before propensity score matching			After propensity score matching (1:4)			
	JAK inhibitors (n = 846)	bDMARDs (n = 19,174)	*p*-value	JAK inhibitors (n = 846)	bDMARDs (n = 3,384)	*p*-value	SMD
Age, year, mean ± SD	48.1 ± 12.7	48.5 ± 12.6	0.377	48.1 ± 12.7	48.5 ± 12.6	0.352	0.033
<65 years	765 (90.4)	17,246 (89.9)	0.649	765 (90.4)	3,093 (91.4)	0.370	0.034
≥65 years	81 (9.6)	1,928 (10.1)		81 (9.6)	291 (8.6)		
Sex							
Male	249 (29.4)	5,159 (26.9)	0.105	249 (29.4)	991 (29.3)	0.933	0.003
Female	597 (70.6)	14,015 (73.1)		597 (70.6)	2,393 (70.7)		
Index year							
2014	279 (33.0)	8,216 (42.9)	<.001	279 (33.0)	1,103 (32.6)	0.963	0.008
2015	266 (31.4)	6,021 (31.4)		266 (31.4)	1,108 (32.7)		0.028
2016	159 (18.8)	3,119 (16.3)		159 (18.8)	598 (17.7)		0.029
2017	91 (10.8)	1,226 (6.4)		91 (10.8)	364 (10.8)		0
2018	51 (6.0)	592 (4.1)		51 (6.0)	211 (6.2)		0.009
Type of insurance							
Health insurance	828 (97.9)	18,773 (97.9)	0.943	828 (97.9)	3,311 (97.8)	0.958	0.002
Medical aid	18 (2.1)	401 (2.1)		18 (2.1)	73 (2.2)		
CCI score							
0	561(66.3)	12,262 (64.0)	0.153	561(66.3)	2,287 (67.6)	0.337	0.027
1	228 (27.0)	5,232 (27.3)		228 (27.0)	922 (27.3)		0.007
2	47 (5.6)	1,295 (6.8)		47 (5.6)	148 (4.4)		0.055
≥3	10 (1.2)	385 (2.0)		10 (1.2)	27 (0.8)		0.038
Comorbidities							
Hypertension	485 (57.3)	11,255 (58.7)	0.428	485 (57.3)	1,917 (56.7)	0.721	0.014
Dyslipidemia	437 (51.7)	9,981 (52.1)	0.820	437 (51.7)	1,715 (50.7)	0.612	0.019
Diabetes mellitus	189 (22.3)	4,595 (24.0)	0.278	189 (22.3)	718 (21.2)	0.477	0.027
Eye disorders	205 (24.2)	4,903 (25.6)	0.382	205 (24.2)	750 (22.2)	0.198	0.049
Osteoporosis	151 (17.9)	3,737 (19.5)	0.238	151 (17.9)	540 (16.0)	0.183	0.050
Anemia	47 (5.6)	1,107 (5.8)	0.790	47 (5.6)	167 (4.9)	0.461	0.028
Medications for RA							
csDMARDs							
Methotrexate	660 (78.0)	15,592 (81.3)	0.016	660 (78.0)	2,685 (79.3)	0.395	0.032
Hydroxy-chloroquine	668 (79.0)	15,227 (79.4)	0.749	668 (79.0)	2,665 (78.8)	0.895	0.005
Sulfasalazine	389 (46.0)	8,787 (45.8)	0.930	389 (46.0)	1,510 (44.6)	0.477	0.027
Leflunomide	328 (38.8)	8,065 (42.1)	0.058	328 (38.8)	1,311 (38.7)	0.987	0.001
Corticoste-roids	786 (92.9)	18,101 (94.4)	0.065	786 (92.9)	3,159 (93.4)	0.646	0.017
Cumulative dose,[a] mean ± SD	33.2 ± 63.3	28.3 ± 74.1	0.070	31.5 ± 75.5	28.3 ± 74.1	0.311	0.043
NSAIDs	819 (96.8)	18,757 (97.8)	0.050	819 (96.8)	3,298 (97.5)	0.294	0.039

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics before and after 1:4 propensity-score matching, number of patients (%).

Characteristics	Before propensity score matching			After propensity score matching (1:4)			
	JAK inhibitors (n = 846)	bDMARDs (n = 19,174)	*p*-value	JAK inhibitors (n = 846)	bDMARDs (n = 3,384)	*p*-value	SMD
Tramadol	671 (79.3)	15,735 (82.1)	0.042	671 (79.3)	2,760 (81.6)	0.136	0.057
Other comedications							
Statins	249 (29.4)	5,690 (29.7)	0.880	249 (29.4)	1,012 (29.9)	0.788	0.011
Antidiabetics	189 (22.3)	4,595 (24.0)	0.278	189 (22.3)	718 (21.2)	0.477	0.027
Antihyper-tensives	401 (47.4)	9,398 (49.0)	0.358	401 (47.4)	1,613 (47.7)	0.890	0.005

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; CCI, charlson comorbidity index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JAK, janus kinase; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SD, standard deviation; SMD, standardized mean difference.
[a]Prednisolone equivalent dose in milligrams.

TABLE 2 Risks of cardiovascular events in patients with RA treated with JAK inhibitors versus biologic DMARDs for the propensity score matched cohort.

	No. of patients	No. of events (%)	Time to onset (weeks), median (range)	PY	IR per 100 PY (95% CI)	Cardiovascular events	
						Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Primary outcome							
MACE							
JAK inhibitors	846	6 (0.71)	9.14 (4.71–45.43)	720	0.83 (0.31–1.81)	1.27 (0.52–3.08)	1.28 (0.53–3.11)
Biologic DMARDs	3,384	38 (1.12)	60.71 (4.29–221.14)	5,126	0.74 (0.53–1.02)	References	
Secondary outcomes							
Myocardial infarction							
JAK inhibitors	846	0	NA	724	NA	NA	NA
Biologic DMARDs	3,384	8 (0.24)	57.93 (17.43–173.71)	5,148	0.16 (0.07–0.31)	References	
Ischemic stroke							
JAK inhibitors	846	0	NA	724	NA	NA	NA
Biologic DMARDs	3,384	0	NA	5,156	NA	References	
Coronary revascularization							
JAK inhibitors	846	2 (0.24)	13.64 (4.71–22.57)	722	0.28 (0.03–1.00)	0.96 (0.22–4.28)	0.95 (0.21–4.21)
Biologic DMARDs	3,384	18 (0.53)	94.71 (20.14–217.29)	5,142	0.35 (0.21–0.55)	References	
All-cause death							
JAK inhibitors	846	4 (0.47)	9.14 (6.43–45.43)	721	0.56 (0.15–1.42)	2.42 (0.73–7.99)	2.38 (0.72–7.90)
Biologic DMARDs	3,384	12 (0.53)	61.29 (4.29–196.00)	5,149	0.23 (0.12–0.41)	References	

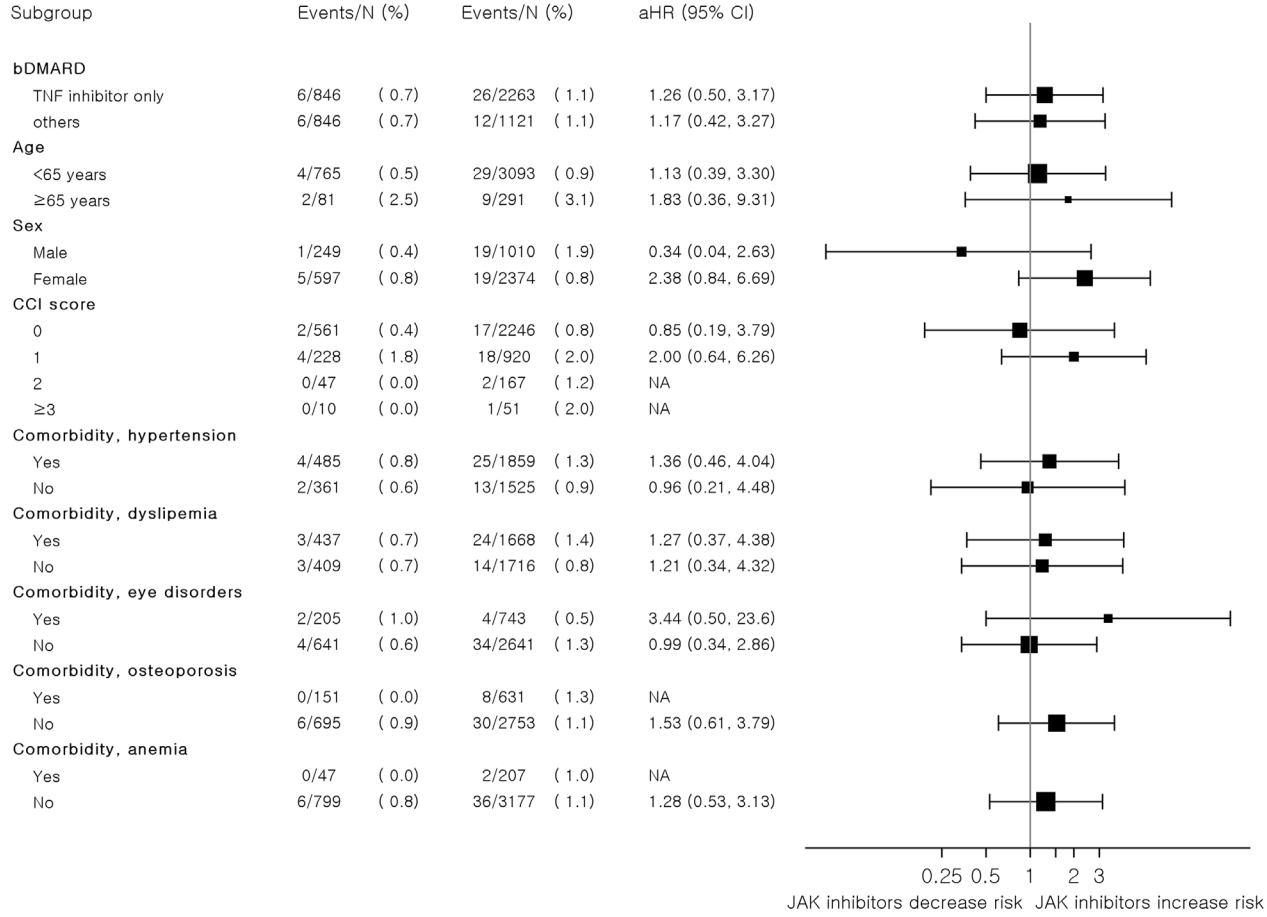
Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; IR, incidence rate; JAK, janus kinase; MACE, major adverse cardiovascular event; NA, not applicable; PY, patient-years; RA, rheumatoid arthritis.

defined the treatment gap as 180 and 90 days, the adjusted HRs (95% CI) were 1.59 (0.52–4.91) and 1.45 (0.54–3.94), respectively.

4 Discussion

To the best of our knowledge, this is the first large population-based cohort study to evaluate the impact of JAK inhibitors on MACEs compared to that of bDMARDs in routine care patients with early diagnosed RA and no underlying CVD in Asia.

Overall, JAK inhibitors, compared to bDMARDs, were not associated with the risk of MACEs in this real-world setting (adjusted HR: 1.28, 95% CI: 0.53–3.11) in newly diagnosed patients with RA with an average disease duration of 6.5 months. Among Asian patients with an average RA duration of 3.2 years, the CV risk was not significantly increased compared to TNF inhibitors



* P−Value is the test of interaction between treatment and each subgroup unadjusted for multiplicity. The adjusted p−value for multiple testing is 0.94 for all subgroups.

FIGURE 3
Subgroup analysis of hazard ratios for major adverse cardiovascular events associated with JAK inhibitors and bDMARDs in a 1:4 variable ratio propensity score-matched cohort of patients with RA. Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IHD, ischemic heart disease; JAK, Janus kinase; RA, rheumatoid arthritis.

TABLE 3 Sensitivity analysis in the propensity-score matched cohort.

	No. of subjects	No. of events (%)	Time to onset (weeks), median (range)	PY	IR per 100 PY (95% CI)	MACEs	
						Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Treatment gap, 180 days							
JAK inhibitors	846	5 (0.59)	7.00 (4.71–22.57)	545	0.92 (0.30–2.14)	1.61 (0.52–4.93)	1.59 (0.52–4.91)
Biologic DMARDs	3,384	22 (0.65)	31.14 (4.29–221.14)	3,811	0.58 (0.36–0.87)	References	
Treatment gap, 90 days							
JAK inhibitors	846	4 (0.47)	6.71 (4.71–11.29)	435	0.92 (0.25–2.35)	1.43 (0.53–3.85)	1.45 (0.54–3.94)
Biologic DMARDs	3,384	16 (0.47)	38.36 (4.29–173.71)	3,087	0.52 (0.30–0.84)	References	

Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; IR, incidence rate; JAK, janus kinase; MACE, major adverse cardiovascular event; PY, patient-years.

[i.e., risk ratio (95% CI), 1.12 (0.64–1.95); Tong et al., 2023]. In American patients with RA and no previous history of CVD, the risk of CVD was not significantly different between tofacitinib and TNF inhibitor users although a decreased risk was reported (pooled weighted HR: 0.81, 95% CI: 0.61–1.07) (Khosrow-Khavar et al., 2022). This might be due to the different definition of the composite CV outcomes, which included hospitalization for MI or stroke in the previous study (Kip et al., 2008); however, coronary revascularization and all-cause death were additionally considered in our study. We defined MACEs considering the most common components of MACEs used in RCTs and observational studies (Kip et al., 2008; Bosco et al., 2021). The results of subgroup analyses showed that the risks of composite CV events associated with JAK inhibitors tended to increase in patients aged ≥65 years and those with a CV-related comorbidities such as hypertension, although the difference was statistically non-significant. This is concordant with the findings of previous studies (Khosrow-Khavar et al., 2022; Ytterberg et al., 2022).

Several RCTs and observational studies have reported inconsistent results. The prospective ORAL surveillance trial revealed that MACEs occurred more often with tofacitinib than with a TNF inhibitor in aged patients with RA and underlying CV risk factors; thus, it might not capture the real-world risk for MACEs in patients without underlying CVDs at treatment initiation (Ytterberg et al., 2022). This was in contrast to the conclusion of previous studies in which JAK inhibitors did not significantly change the CV outcomes and their IRs were unchanged for up to 9.5 years (Xie W. et al., 2019; Cohen et al., 2020). Moreover, several observational studies found no increased CV risks with JAK inhibitors in patients with RA treated regardless of the presence of CV risk factors (Kremer et al., 2021; Khosrow-Khavar et al., 2022). Therefore, continuing research to better understand the CV risks of this important treatment option is recommended in a wide range of patients with RA.

The IRs of MACEs in Asian patients without underlying CVDs (0.83 and 0.74 per 100 PY with JAK inhibitors and bDMARDs, respectively) were similar to those reported in Western patients without underlying CVDs (0.87 and 0.79 per 100 PY with tofacitinib and TNF inhibitors, respectively) (Khosrow-Khavar et al., 2022). However, considering the differences in the definition of MACEs between the studies, as mentioned above, the incidence of MACEs associated with the use of JAK inhibitors or bDMARDs was relatively low in Korean patients with RA compared to that in Westerner patients; this is consistent with the findings of previous studies reporting a low risk of CVDs in Asians (Meadows et al., 2011; Post et al., 2022). The incidences of death from any cause was higher with JAK inhibitors than with bDMARDs in our study (IR of 0.56 and 0.23 with JAK inhibitor and bDMARD, respectively), similar to the findings reported by Khosrow-Khavar et al. (IR of 1.95 and 1.41 with tofacitinib and a TNF inhibitor, respectively) (Khosrow-Khavar et al., 2022). In the ORAL surveillance trial, the HR (95% CI) for all-cause death was significantly high with tofacitinib compared to that with a TNF inhibitor (2.37 [1.34–4.18]) (Ytterberg et al., 2022). It has been reported that bDMARDs may reduce the risk of MACEs, particularly mortality related to coronary heart diseases, in patients with RA (Myasoedova et al., 2017; Xie F. et al., 2019; Provan et al., 2020; Singh et al., 2020). This may be due to a positive impact of these modern treatment strategies on the RA severity and mortality. The causal relationship between the use of JAK inhibitors and CV risk, including death, is unknown. Considering the relatively high mortality rate from any cause in JAK inhibitors, close monitoring and further research into the causal relationship are required.

The time to onset in the bDMARD group was longer in Korean patients without CVDs (12.1 months after the use of bDMARDs) than in American patients (6.1 months); this was likely because the analysis of Western patients included patients with and without CVDs, and the East Asian population exhibited a relatively lower CV risk than the Western population (Meadows et al., 2011; Khosrow-Khavar et al., 2022; Post et al., 2022). While CVD risk has been associated with various factors such as age, sex and chronic diseases, RA diagnosis itself has also been linked to an increased likelihood of developing CVDs. Previous study indicated that the risk of CVD increased shortly after the diagnosis of RA, mostly within a year of the clinical onset of RA (Kerola et al., 2012). In consideration of the recommended initiation time of the bDMARDs or JAK inhibitors after the diagnosis of RA (i.e., at least 6 months), the timeframe for CVD onset associated with these medications may align with the natural history of CVDs in RA patients (Smolen et al., 2020) In JAK inhibitor users, the median time to onset (range) of MACEs was short (1.8 [0.9–9.1] months). In contrast, it was reported that the median time to CV events after tofacitinib use was 5.1 months in Western patients (Khosrow-Khavar et al., 2022). Studies on ethnic differences in the time to drug-induced CV events are limited. Since it is the first study to demonstrate the relatively reduced onset time to the event in Asian users of JAK inhibitors, it is necessary to monitor continuously and expand the related research in Asian patients.

As there was no significant difference among JAK inhibitors regarding the occurrence of CV or thromboembolic events, we analyzed all JAK inhibitors approved for the treatment of RA in Korea until 2018 (i.e., tofacitinib and baricitinib) (Alves et al., 2021). Additionally, we used the bDMARD group as a control group because a bDMARD or a JAK inhibitor was recommended as a second-line agent for patients with poor RA prognostic factors who failed with the first treatment with csDMARD based on the EULAR guideline (Smolen et al., 2020). There was no significant difference in the risk of MACEs associated with the use of TNF and non-TNF inhibitors in patients with RA (Singh et al., 2020). In the subgroup analysis of this study, the HR of JAK inhibitors compared with patients received only TNF inhibitors was similar to that of patients prescribed non-TNF inhibitors.

Although our results highlight a potentially insightful relationship between the use of JAK inhibitors and CV risks in the real world using large-scale administrative data, our study has several limitations. First, there were no clinical laboratory results to evaluate the disease severity of RA at the index date, which might affect the CV risk (Crowson et al., 2013; Health Insurance Review and Assessment Service, 2021a). Therefore, we included patients who were first administered a JAK inhibitor or bDMARD after being newly diagnosed with RA to balance the RA severity and duration. The period from the first diagnosis of RA to the first prescription of the study drug was similar in both groups. It has been reported that the development of CVD in Asian patients with RA might be influenced more by high-grade systemic inflammation compared to individual CVD risk factors, which tend to have a greater impact in non-Asian populations (You et al., 2011) Therefore, further

studies are needed to evaluate the risk of JAK inhibitors in RA patients with advanced disease. Second, coronary artery calcium scores, a known predictive factor for coronary heart disease, could not be assessed due to the nature of the administrative data (Polonsky et al., 2010). Further research is needed using clinical data, including electronic medical records. Third, we used all-cause death, not CV-related death, as a component of MACEs. The balance between the use of all-cause mortality and cardiac-only mortality was approximately equal (Kip et al., 2008; Bosco et al., 2021). However, as it has not been validated to confirm CVD-related death using the ICD-10 code of the claim data from the HIRA, we used all-cause death instead of CVD-related death for the definition of MACEs (Bosco et al., 2021). Lastly, the interpretation of this study results had some caution for RA patients who had longer duration because enrolled patients in 2014 (earliest index date) had maximum follow-up period of 5 years.

Taken together, this large population-based study revealed that, compared to the use of bDMARDs, the use of JAK inhibitors was not significantly associated with the occurrence of MACEs in Asian patients with RA and no underlying CVDs. The results remained robust across various sensitive analyses.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Institutional Review Board of Daegu Catholic University. 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

Y-KS conceptualization, data curation, formal analysis, funding acquisition, methodology, project administration, visualization, writing-original draft; GL data curation, formal analysis, investigation, software, validation, visualization; JH methodology, supervision, writing–review and editing; J-WK validation, writing–review and editing; JK conceptualization, funding acquisition, methodology, supervision, validation, writing–review and editing. 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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Associated adverse health outcomes of polypharmacy and potentially inappropriate medications in community-dwelling older adults with diabetes

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Aim: This study aimed to identify the association of chronic polypharmacy and potentially inappropriate medications (PIMs) with adverse health outcomes (AHOs) in community-dwelling older adults with diabetes in China.

Methods: A 2-year retrospective cohort study was conducted using 11,829 community-followed older adults with diabetes and medical records from 83 hospitals and 702 primary care centers in Shenzhen, China. Chronic polypharmacy and PIMs were identified from prescription records using Beers' criteria, and their associated AHO was analyzed using multivariable logistic regression analysis.

Results: The prevalence of chronic polypharmacy and at least one PIM exposure was 46.37% and 55.09%, respectively. The top five PIMs were diuretics, benzodiazepines, first-generation antihistamines, sulfonylureas, and insulin (sliding scale). Chronic polypharmacy was positively associated with all-cause hospital admission, admission for coronary heart disease, admission for stroke, admission for dementia, and emergency department visits. Exposure to PIMs was positively associated with all-cause hospital admission, admission for heart failure (PIMs ≥2), admission for stroke (PIMs ≥3), emergency department visits, bone fracture, constipation, and diarrhea.

Conclusion: Chronic polypharmacy and PIMs were prevalent in older adults with diabetes in Chinese communities. Iatrogenic exposure to chronic polypharmacy and PIMs is associated with a higher incidence of different AHOs. This observational evidence highlights the necessity of patient-centered medication reviews for chronic polypharmacy and PIMs use in older patients with diabetes in primary care facilities in China and draws attention to the caution of polypharmacy, especially PIM use in older adults with diabetes in clinical practice.

KEYWORDS

polypharmacy, potentially inappropriate medications, adverse health outcome, older, diabetes, clinical practice

1 Introduction

According to research conducted in 138 countries with 255 high-quality data sources, China has the highest prevalence of diabetes among people aged over 65 years in the world with 34.1 million patients, accounting for 25.1% of the 135.6 million older adults with diabetes (Sinclair et al., 2020).

Older adults with diabetes often have at least one other chronic disease, such as hypertension, hyperlipidemia, cardiovascular disease, cerebrovascular disease, chronic liver disease, tumors, or chronic respiratory diseases (Wang et al., 2020; Federation, 2022; Ioakeim-Skoufa et al., 2022). Polypharmacy—the use of multiple medications to treat multiple chronic health conditions—is common in older adults with diabetes when clinicians prescribe medications according to the clinical practice guidelines for each chronic comorbidity (Qato et al., 2008; Su et al., 2020; Remelli et al., 2022). According to a systematic review of 173,838 participants, the pooled prevalence of polypharmacy in older patients with type 2 diabetes was 64% (Remelli et al., 2022). In our previous study conducted in outpatient departments in 52 hospitals in Shenzhen, China, we found that the chronic polypharmacy exposure rate ranged from 51% to 55% (Lu et al., 2022).

The risk of potentially inappropriate medication (PIM) exposure in older adults increases by 5.2% with each additional medication added to their medication list (Miller et al., 2017). PIMs are medications that should be avoided in older adults due to the risk of adverse reactions or insufficient evidence of their benefits, especially when safer and equally or more effective therapeutic alternatives are available for the elderly population (BtAGSBCUE, 2019). A meta-analysis of observational studies published between 2002 and 2019 found that the pooled prevalence of PIMs among adults aged 65 years or older in primary care was 33.3% (Liew et al., 2020). In Chinese communities, the prevalence of PIMs ranged from 35.0% to 38.1% (Huang et al., 2020; Li et al., 2021; Su et al., 2022; Tian et al., 2022).

Studies conducted in the Netherlands, Canada, and the United States reported that the prevalence of PIM exposure in older adults with diabetes was 24.9%, 56.1%, and 39.9%, respectively (Gagnon et al., 2020; Nightingale et al., 2021; Oktora et al., 2021). The types and distribution of PIM exposure in older adults with diabetes differed from those without diabetes, as did the amount of medication taken by patients (Gagnon et al., 2020). In our previous study conducted in Shenzhen, China, we found that the prevalence of PIMs in older adults with diabetes ranged from 42% to 45% in outpatient settings (Lu et al., 2022).

Polypharmacy and PIMs have been found to be associated with the incidence of adverse health outcomes (AHO) in older patients, which might be related to drug–drug interactions, side effects of drugs, and reduced physiological functions in older adults, including syncope, dizziness, pain, and emergency department visits (Lohman et al., 2017; Wallace et al., 2017; Davies et al., 2020; Liew et al., 2020; Delgado et al., 2021; Su et al., 2022). However, few studies have examined the patterns of multimorbidity in patients, which are crucial for understanding the iatrogenic exposure to chronic polypharmacy and PIMs, as well as the incidence of AHO (Davies et al., 2020). Our previous research highlighted that the probabilities of exposure and ranking of PIMs in older adults with diabetes, combined with different comorbidities in outpatient visits, were not consistent with chronic polypharmacy (Lu et al., 2022). Considering the significant impact of associated AHO on the health of older adults with diabetes, addressing the issue of chronic polypharmacy and PIMs in older adults with diabetes is of utmost importance in health and drug management (Lohman et al., 2017; Wallace et al., 2017; Davies et al., 2020; Delgado et al., 2021; Su et al., 2022).

It is crucial to study the association between AHO and chronic polypharmacy and PIMs in older adults with diabetes simultaneously. Most studies evaluating the associated AHO of polypharmacy and PIMs were conducted outside China, with implications for different healthcare systems. In this study, we aim to answer two major questions. First, what is the prevalence of chronic polypharmacy and PIMs in older adults with diabetes in the Chinese community? Second, are chronic polypharmacy and PIMs associated with AHO, and is there a dose–response relationship in older adults with diabetes?

2 Methods

2.1 Data source and study population

This 2-year retrospective cohort study which was accomplished under the guidance of the STROBE checklist used the data on follow-up records of 92,166 diabetic patients registered by community health service centers from the Shenzhen Health Development Research and Data Management Center Database (SHDRDMCD) (Supplementary Table S1). SHDRDMCD also includes medical records of 83 hospitals and 702 primary care centers from 2014 to 2017 in Shenzhen, China. These medical records could entirely reflect each registered patient's medical institution visits from 2014 to 2017 in Shenzhen, China. Both the diagnostic code and diagnosis name were used for the accurate definition of chronic diseases. The drug name and its unique drug code, frequency, days, and route of administration were combined to embody the prescribed medication. With follow-up records of 92,166 diabetic patients from community health centers and medical records of 83 hospitals and 702 primary care centers, this study could reconstruct the diagnosis and treatment track of older adults with diabetes in Shenzhen, China. An anonymous and standardized medical database was created by assigning a unique identification number to each patient. All the data were checked and imported into the Oracle database by professional platform administrators and medical staff under the supervision of the Shenzhen Municipal Health Commission. According to article No. 32 of the Declaration of Helsinki, the database was approved for research by the Review Committee of the Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences (No. SIAT-IRB-151115- H0084).

The inclusion criteria were confirmed and documented type I and type II diabetic patients who were followed up in 702 community health centers in Shenzhen, China. The included people were aged 65 years or older before 1 January 2015. Older adults with diabetes had two or more medical institution visits and were prescribed at least one medication per visit between the beginning of the cohort (first medical institution visit in 2015) and the end of the cohort (outcomes were observed or 2 years

after the start of follow-up). The exclusion criteria were patients who were only prescribed traditional Chinese medicine or Chinese patent medicine at each medical institution visit.

2.2 Polypharmacy definition

None, moderate, and severe polypharmacy were defined as the use of 0–4, 5–9, and ≥10 chronically used drugs, respectively (Masnoon et al., 2017; Organization). Only medication that was used for a long term (defined by the use of drugs for more than 90 days or at least once a month) was investigated. The third level of the Anatomical Therapeutic Chemical (ATC) code was used to calculate the number of different chronic drugs used. Therefore, the use of chronically used drugs with different substances in the same pharmacological subgroup could be considered as the use of one chronically used drug, such as angiotensin receptor blockers (ATC code = C09C). Drugs prescribed for topical treatment, surgical dressing, contrast media, radiopharmaceuticals, and general nutrients, as well as drugs without ATC codes, such as Chinese patent medications, were excluded from the evaluation of polypharmacy. Drug combinations with different third-level ATC codes were defined as two drugs. The definition of chronic polypharmacy exposure was estimated during the inclusion period.

2.3 Potentially inappropriate medication definition

The American Geriatrics Society 2019 Beers Criteria were used to identify PIM exposure (BtAGSBCUE, 2019). Some PIM items could not be evaluated in older adults with diabetes in China for the following reasons. First, some laboratory data that were critical for PIM evaluation were lacking. Second, SHDRDMCD has an inconsistent presentation of drug doses, such as one capsule or one tablet. Third, the concomitant use of drugs in patients cannot be located. Therefore, PIM categories IV and V and parts of categories I, II, and III (Supplementary Table S2) of the Beers Criteria could not be assessed in this study. Some PIM items were not available in the Chinese healthcare system. We formulated a list of 42 PIM items in accordance with the characteristics of the Chinese healthcare system and SHDRDMCD to identify the exposure of PIMs in Chinese communities (Supplementary Table S2). The list also includes the corresponding notes for inclusion and reasons for exclusion of PIM items. We specified the patients' disease or syndrome by means of the 10th edition of the International Classification of Disease (ICD-10) codes, which required the category II PIM item assessment. PIMs in older adults with diabetes in Chinese communities were stratified into four levels: 0, 1, 2, and 3 or more PIM exposures. The definition of PIM exposure was estimated during the inclusion period.

2.4 Comorbidity definition

Patterns of multimorbidity must be associated with the emergence of chronic polypharmacy and PIMs, as well as their associated AHO in older adults with diabetes. The ATC drug code categories and patterns of multimorbidity in Chinese elderly individuals were consulted for the definition and selection of the investigated chronic disease (Wang et al., 2020; Han et al., 2022). Finally, 10 chronic diseases were selected for adjustment. The corresponding ICD-10 codes are attached to Supplementary Table S3. The earliest diagnoses and ICD-10 codes in SHDRDMCD before the start of the follow-up were accepted for the definition of chronic comorbidities, except for tumors, which were required within 5 years earlier. Comorbidities were presented with or without the chosen disease in addition to diabetes.

2.5 Covariates

Age, systolic blood pressure, diastolic blood pressure, body mass index, fasting blood glucose, 2-h postprandial glucose, and glycosylated hemoglobin were collected as continuous variables prior to the beginning of the cohort. Age was stratified into four groups of 65–69, 70–74, 75–79, and ≥80 years, and BMI was stratified into four groups of <18.5, 18.5–24.0, 24.0–28.0, and ≥28.0 kg/m^2. The complications of diabetes were presented with or without the terms of the diagnoses and corresponding ICD-10 codes in SHDRDMCD.

2.6 Associated adverse health outcomes

The AHO included all-cause hospital admission; hospital admission for coronary heart disease, stroke, dementia, and heart failure; emergency department visits; bone fractures; constipation; and diarrhea in this study. The follow-up ended with the first occurrence of AHO or lasted 2 years after the beginning of the cohort. Finally, AHO was collected as a dichotomous variable for analysis.

2.7 Statistical analysis

The prevalence of chronic polypharmacy and PIMs among older adults with diabetes is presented as percentages with 95% CIs. Chi-squared tests were used to compare the categorical variables of the baseline characteristics. The analysis of variance and the Kruskal–Wallis test were used for continuous variables with and without normal distribution, respectively.

Patients who had a diagnosis or the etiology of hospital admission same as AHO within 6 months prior to the start of the cohort were excluded from the statistical analysis. Univariable and multivariable logistic regression analyses were performed to assess the risk of AHO in older adults with diabetes who were exposed to chronic polypharmacy and PIMs (no exposure to chronic polypharmacy or PIMs as a reference). Multivariable logistic regression analyses were performed for adjusting by including all variables listed in the baseline characteristics. The classification and regression tree methods were used to perform multiple interpolations for missing values of variables. The sensitivity analysis which was used to compare the results of logistic regression before and after multiple interpolations is provided in Supplementary Tables S4, S5. A two-sided $\alpha = 0.05$ was considered

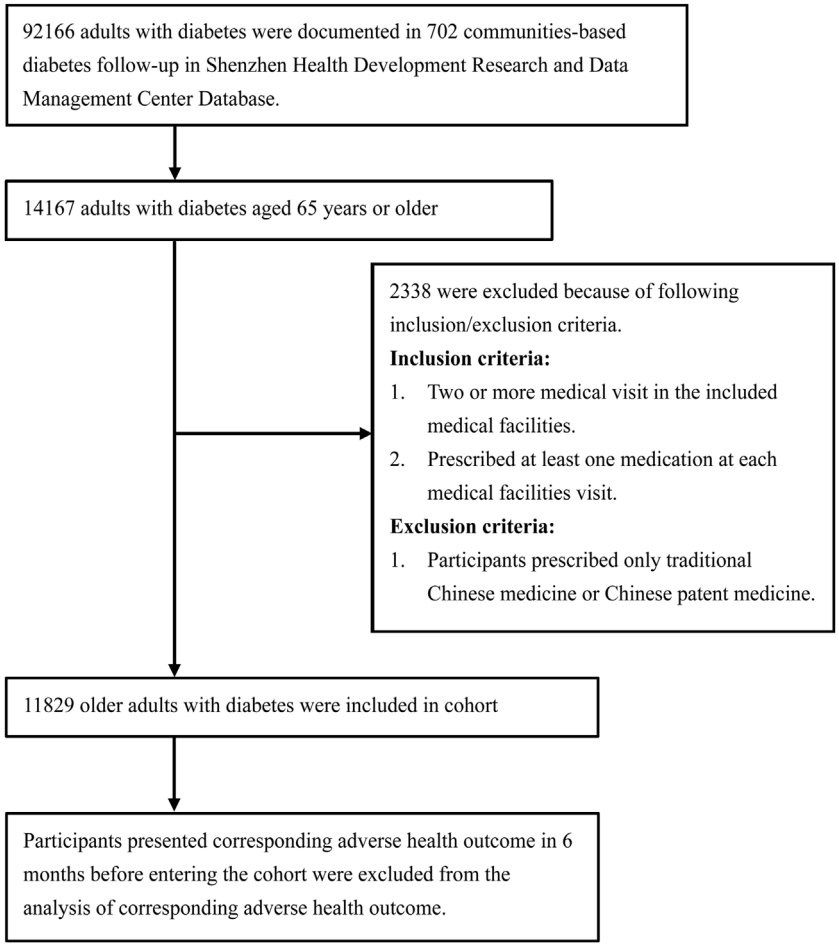

FIGURE 1
Flowchart of participant selection.

statistically significant. The generalized variance-inflation factors (GVIFs) were applied for a multicollinearity assessment of all variables included for adjusted logistic regression. A GVIF value >10 was considered a strong multicollinearity. All analyses were performed in R 4.1.2 (R Development Core Team).

3 Results

3.1 Baseline characteristics

A total of 11,829 community-followed older adults with diabetes were enrolled in this study, with 53.54% being women (Figure 1). The baseline characteristics of the included population are shown in Table 1. The number of patients who experienced all-cause hospital admission was 4,142 (35.02%), with 784 (6.63%) for hospital admission for coronary heart disease, 677 (5.72%) for hospital admission for stroke, 134 (1.13%) for hospital admission for dementia, 67 (0.57%) for hospital admission for heart failure, 3,110 (26.29%) for emergency department visits, 580 (4.90%) for bone fracture, 932 (7.88%) for constipation, and 167 (1.41%) for diarrhea.

3.2 Prevalence of polypharmacy and associated AHO

The prevalence of chronic polypharmacy in this cohort was 46.37% (95% CI: 45.55–47.19), with 36.45% (35.72–37.18) moderate polypharmacy and 9.93% (9.55–10.31) severe polypharmacy.

The univariable analysis revealed that chronic polypharmacy was associated with the incidence of any AHO. A multicollinearity test of the baseline characteristics of older adults with diabetes showed that none of the GVIF values were greater than 10, suggesting no significant multicollinearity among the variables (Supplementary Tables S6–S14). The results of the sensitivity test indicated that the effect size was stable before and after multiple interpolations (Supplementary Table S4). Multivariable logistic regression analysis revealed that chronic polypharmacy had a positive correlative dose–response relationship with the incidence of AHO (all-cause hospital admission: moderate: a OR = 1.95, 95% CI 1.76–2.17; severe: 2.86, 2.38–3.43; hospital admission for coronary heart disease: moderate: 2.00, 1.59–2.53; severe: 5.76, 4.28–7.78; stroke: moderate: 2.05, 1.62–2.60; severe: 2.48, 1.78–3.47; dementia: moderate: 1.80, 1.08–3.05; severe: 3.61, 1.84–7.15; and emergency department visit: moderate: 1.38,

TABLE 1 Baseline characteristics of included 11,829 community-followed older adults with diabetes.

	Potentially inappropriate medications					Polypharmacy			
	0	1	2	≥3	*p*	None	Moderate	Severe	*p*
Age, y (n = 11,829)					<0.001				<0.001
65–69	2,106 (17.80)	1,223 (10.34)	577 (4.88)	453 (3.83)		2,541 (21.48)	1,530 (12.93)	288 (2.43)	
70–74	1,371 (11.59)	887 (7.50)	405 (3.42)	367 (3.10)		1,627 (13.75)	1,132 (9.57)	271 (2.29)	
75–79	1,002 (8.47)	664 (5.61)	369 (3.12)	327 (2.76)		1,170 (9.89)	908 (7.68)	284 (2.40)	
≥80	833 (7.04)	543 (4.59)	310 (2.62)	392 (3.31)		1,006 (8.50)	741 (6.26)	331 (2.80)	
Gender (n = 11,829)					0.039				<0.001
Male	2,502 (21.15)	1,548 (13.09)	774 (6.54)	672 (5.68)		2,772 (23.43)	2,083 (17.61)	641 (5.42)	
Female	2,810 (23.76)	1,769 (14.95)	887 (7.50)	867 (7.33)		3,572 (30.20)	2,228 (18.84)	533 (4.51)	
SBP (n = 11,584)	129.93 (11.17)	129.57 (10.44)	129.75 (10.46)	129.51 (10.06)	0.165	129.59 (11.26)	130.03 (10.04)	129.57 (10.20)	0.264
DBP (n = 11,582)	78.23 (7.01)	77.94 (6.84)	77.74 (6.68)	77.77 (6.91)	<0.001	78.02 (7.06)	78.04 (6.68)	77.69 (6.93)	0.053
BMI (n = 11,616)					0.299				0.003
<18.5	105 (0.90)	55 (0.47)	25 (0.22)	29 (0.25)		135 (1.14)	57 (0.48)	22 (0.49)	
18.5–24	3,300 (28.41)	2,118 (18.23)	1,013 (8.72)	923 (7.95)		4,007 (33.87)	2,642 (22.33)	705 (5.96)	
24–28	1,529 (13.16)	908 (7.82)	518 (4.46)	464 (3.99)		1,774 (15.00)	1,287 (10.88)	358 (3.03)	
≥28	300 (2.58)	167 (1.44)	71 (0.61)	91 (0.78)		328 (2.77)	246 (2.08)	55 (0.46)	
FPG (n = 11,739)	7.2 (1.82)	7.11 (1.75)	7.1 (1.78)	7.07 (1.73)	0.004	7.21 (1.84)	7.06 (1.69)	7.08 (1.79)	<0.001
2 h-PBG (n = 10,014)	9.44 (2.30)	9.41 (2.15)	9.26 (2.13)	9.26 (2.13)	0.001	9.47 (2.25)	9.30 (2.14)	9.24 (2.32)	<0.001
HbA1c (n = 9,601)	6.49 (1.45)	6.48 (1.42)	6.52 (1.48)	6.40 (1.45)	0.04	6.50 (1.49)	6.46 (1.42)	6.42 (1.34)	0.037
Complication, n (%)									
DPN					<0.001				<0.001
With (n = 689)	183 (1.55)	212 (1.79)	131 (1.11)	163 (1.38)		168 (1.42)	364 (3.08)	157 (1.33)	
Without (n = 11,140)	5,129 (43.36)	3,105 (26.25)	1,530 (12.93)	1,376 (11.63)		6,176 (52.21)	3,947 (33.37)	1,017 (8.60)	
DKD					<0.001				<0.001
With (n = 441)	87 (0.74)	125 (1.06)	92 (0.78)	137 (1.16)		87 (0.74)	203 (1.72)	151 (1.28)	
Without (n = 11,388)	5,225 (44.17)	3,192 (26.98)	1,569 (13.26)	1,402 (11.85)		6,257 (52.90)	4,108 (34.73)	1,023 (8.65)	
DR					<0.001				<0.001
With (n = 354)	120 (1.01)	93 (0.79)	61 (0.52)	80 (0.68)		104 (0.88)	164 (1.39)	86 (0.73)	
Without (n = 11,475)	5,192 (43.89)	3,224 (27.25)	1,600 (13.53)	1,459 (12.33)		6,240 (52.75)	4,147 (35.06)	1,088 (9.20)	
Comorbidity, n (%)									
CRD					<0.001				<0.001
With (n = 1,095)	303 (2.56)	260 (2.20)	223 (1.89)	309 (2.61)		348 (2.94)	475 (4.02)	272 (2.30)	
Without (n = 10,734)	5,009 (42.35)	3,057 (25.84)	1,438 (12.16)	1,230 (10.40)		5,996 (50.69)	3,836 (32.43)	902 (7.63)	
OARA					<0.001				<0.001
With (n = 2,522)	666 (5.63)	747 (6.31)	498 (4.21)	611 (5.17)		892 (7.54)	1,168 (9.87)	462 (3.91)	
Without (n = 9,307)	4,646 (39.28)	2,570 (21.73)	1,163 (9.83)	928 (7.85)		5,452 (46.09)	3,143 (26.57)	712 (6.02)	
CLD					<0.001				<0.001
With (n = 369)	115 (0.97)	85 (0.72)	83 (0.70)	86 (0.73)		114 (0.96)	165 (1.39)	90 (0.76)	

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics of included 11,829 community-followed older adults with diabetes.

	Potentially inappropriate medications					Polypharmacy			
	0	1	2	≥3	*p*	None	Moderate	Severe	*p*
Without (n = 11,460)	5,197 (43.93)	3,232 (27.32)	1,578 (13.34)	1,453 (12.28)		6,230 (52.67)	4,146 (35.05)	1,084 (9.16)	
Hypertension					<0.001				<0.001
With (n = 8,363)	3,246 (27.44)	2,437 (20.60)	1,335 (11.29)	1,345 (11.37)		3,379 (28.57)	3,843 (32.49)	1,141 (9.65)	
Without (n = 3,466)	2,066 (17.47)	880 (7.44)	326 (2.76)	194 (1.64)		2,965 (25.07)	468 (3.96)	33 (0.28)	
Hyperlipidemia					<0.001				<0.001
With (n = 3,729)	1,286 (10.87)	1,138 (9.62)	629 (5.32)	676 (5.71)		956 (8.08)	2,035 (17.20)	738 (6.24)	
Without (n = 8,100)	4,026 (34.03)	2,179 (18.42)	1,032 (8.72)	863 (7.30)		5,388 (45.55)	2,276 (19.24)	436 (3.69)	
CBD					<0.001				<0.001
With (n = 1,626)	484 (4.09)	450 (3.80)	308 (2.60)	384 (3.25)		395 (3.34)	827 (6.99)	404 (3.42)	
Without (n = 10,203)	4,828 (40.81)	2,867 (24.24)	1,353 (11.44)	1,155 (9.76)		5,949 (50.29)	3,484 (29.45)	770 (6.51)	
CKD					<0.001				<0.001
With (n = 667)	144 (1.22)	168 (1.42)	129 (1.09)	226 (1.91)		135 (1.14)	292 (2.47)	240 (2.03)	
Without (n = 11,162)	5,168 (43.69)	3,149 (26.62)	1,532 (12.95)	1,313 (11.10)		6,209 (52.49)	4,019 (33.98)	934 (7.90)	
CGD					<0.001				<0.001
With (n = 117)	20 (0.17)	23 (0.19)	29 (0.25)	45 (0.38)		24 (0.20)	43 (0.36)	50 (0.42)	
Without (n = 11,712)	5,292 (44.74)	3,294 (27.85)	1,632 (13.80)	1,494 (12.63)		6,320 (53.43)	4,268 (36.08)	1,124 (9.50)	
CVD					<0.001				<0.001
With (n = 4,510)	1,460 (12.34)	1,324 (11.19)	795 (6.72)	931 (7.87)		1,261 (10.66)	2,299 (19.44)	950 (8.03)	
Without (n = 7,319)	3,852 (32.56)	1,993 (16.85)	866 (7.32)	608 (5.14)		5,083 (42.97)	2,012 (17.01)	224 (1.89)	
Tumor					<0.001				<0.001
With (n = 393)	113 (0.96)	113 (0.96)	80 (0.68)	87 (0.74)		140 (1.18)	183 (1.55)	70 (0.59)	
Without (n = 11,436)	5,199 (43.95)	3,204 (27.09)	1,581 (13.37)	1,452 (12.27)		6,204 (52.45)	4,128 (34.90)	1,104 (9.33)	

Notes: none, moderate, and severe polypharmacy were defined as 0–4, 5–9, and ≥10 chronic used drugs, respectively. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting plasma glucose; 2 h-PBG, 2-h postprandial blood glucose; HbA1c = glycated hemoglobin; DPN, diabetic peripheral disease; DKD, diabetic kidney disease; DR, diabetic retinal; CRD, chronic respiratory disease; OARA, osteoarthritis and rheumatoid arthritis; CLD, chronic liver disease; CBD, cerebrovascular disease; CKD, chronic kidney disease; CGD, chronic gastrointestinal disease; CVD, cardiovascular disease. SBP, DBP, FPG, 2 h-PBG, and HbA1c were presented as mean (SD), and the rest of indicators were presented as n (%).

1.23–1.55; severe: 1.75, 1.45–2.10; Table 1). However, there was no relevance between chronic polypharmacy and the occurrence of hospital admission for heart failure, bone fracture, constipation, and diarrhea in older adults with diabetes (Table 2).

3.3 Prevalence of PIMs and associated AHO

The prevalence of at least one PIM exposure in this cohort was 55.09% (95% CI: 54.19–55.99). Among them, 28.04% (27.40–28.68), 14.04% (13.59–14.49), and 12.01% (11.59–12.43) of patients had one, two, and three or more PIM exposures, respectively. When we classified PIMs into drug classes, the top five most commonly used PIMs were diuretics (15.04%), benzodiazepines (13.63%), first-generation antihistamines (11.65%), sulfonylureas (5.86%), and insulin (sliding scale) (5.09%). The specific PIMs identified in this cohort are listed in Supplementary Table S15.

A univariable logistic regression showed that PIMs were associated with any AHO. The sensitivity test presented stable effect sizes (Supplementary Table S5). Multivariable logistic regression revealed that PIMs were positively associated with the incidence of AHO, with a dose–response relationship (bone fracture: 1 PIM: aOR = 1.82, 95% CI 1.44–2.31; 2 PIMs: 2.13, 1.61–2.81; 3 or more PIMs: 2.73, 2.03–3.67; constipation: 1 PIM: 1.18, 0.97–1.43; 2 PIMs: 1.43, 1.14–1.78; 3 or more PIMs: 2.00, 1.59–2.52; diarrhea: 1 PIM: 1.12, 0.69–1.80; 2 PIMs: 2.70, 1.68–4.34; 3 or more PIMs: 2.78, 1.64–4.73; emergency department visiting: 1 PIM: 1.66, 1.49–1.86; 2 PIMs: 1.99, 1.73–2.28; 3 or more PIMs: 2.92, 2.50–3.40; and all-cause hospital admission: 1 PIM: 1.22, 1.10–1.35; 2 PIMs: 1.38, 1.21–1.57; 3 or more PIMs: 1.62, 1.39–1.87; Table 3). However, PIMs had no impact on the incidence of hospital admission for coronary heart disease and dementia. An increased number of PIM exposures was related to the occurrence of hospital admission for stroke (3 or more PIMs:

TABLE 2 Associated adverse health outcomes of polypharmacy in community-followed older adults with diabetes.

	Univariate analyses			Adjusted logistic regression		
	OR	95% CI	*p*	aOR	95% CI	*p*
All-cause hospital admission (n = 4,142)						
Moderate	2.91	(2.67, 3.17)	<0.001	1.95	(1.76, 2.17)	<0.001
Severe	7.11	(6.21, 8.14)	<0.001	2.86	(2.38, 3.43)	<0.001
Hospital admission for coronary heart disease (n = 784)						
Moderate	3.47	(2.85, 4.24)	<0.001	2.00	(1.59, 2.53)	<0.001
Severe	14.77	(12.01, 18.24)	<0.001	5.76	(4.28, 7.78)	<0.001
Hospital admission for stroke (n = 677)						
Moderate	3.27	(2.70, 3.96)	<0.001	2.05	(1.62, 2.60)	<0.001
Severe	6.69	(5.35, 8.37)	<0.001	2.48	(1.78, 3.47)	<0.001
Hospital admission for dementia (n = 134)						
Moderate	2.56	(1.68, 3.98)	<0.001	1.80	(1.08, 3.05)	0.025
Severe	7.45	(4.74, 11.83)	<0.001	3.61	(1.84, 7.15)	<0.001
Hospital admission for heart failure (n = 67)						
Moderate	1.77	(0.89, 3.56)	0.103	0.69	(0.30, 1.58)	0.369
Severe	12.59	(6.97, 23.86)	<0.001	1.59	(0.62, 4.25)	0.343
Emergency department admission (n = 3,110)						
Moderate	2.55	(2.33, 2.80)	<0.001	1.38	(1.23, 1.55)	<0.001
Severe	6.58	(5.76, 7.52)	<0.001	1.75	(1.45, 2.10)	<0.001
Bone fracture (n = 580)						
Moderate	1.48	(1.22, 1.78)	<0.001	0.93	(0.74, 1.17)	0.539
Severe	3.11	(2.47, 3.90)	<0.001	1.13	(0.80, 1.59)	0.484
Constipation (n = 932)						
Moderate	2.11	(1.81, 2.45)	<0.001	1.19	(0.97, 1.45)	0.119
Severe	4.02	(3.23, 4.86)	<0.001	1.22	(0.92, 1.61)	0.166
Diarrhea (n = 167)						
Moderate	1.61	(1.12, 2.30)	0.009	0.80	(0.52, 1.24)	0.32
Severe	4.15	(2.78, 6.15)	<0.001	0.91	(0.49, 1.67)	0.765

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; 95% CI, 95% confidence interval. Multivariate adjusted logistic regression was achieved by including every variable presented in baseline characteristics table.

OR = 1.35, 95% CI 1.03–1.77) and heart failure (2 PIMs: 3.17, 1.13–9.37; 3 or more PIMs: 6.97, 2.60–20.48) (Table 3).

4 Discussion

This study provides estimates for chronic polypharmacy and PIM prevalence and their associated AHO in a large, representative sample of community-dwelling older adults with diabetes in China. The prevalence of chronic polypharmacy and PIMs in older adults with diabetes in the Chinese community was 46.37% and 55.09%, respectively. Remarkably, after adjusting for patients' baseline characteristics and three complications of diabetes, as well as ten comorbidities, PIM exposure was associated with the incidence of bone fracture, constipation, diarrhea, emergency department visits, all-cause hospital admissions, and hospital admissions for stroke and heart failure in older adults with diabetes. In contrast to PIM use, chronic polypharmacy was associated with the incidence of all-cause hospital admissions, emergency department visits, and hospital admissions for coronary heart disease, stroke, and dementia.

The prevalence of chronic polypharmacy among older adults with diabetes in Chinese communities was 46.37%, indicating that it

TABLE 3 Associated adverse health outcomes of potentially inappropriate medications in community-followed older adults with diabetes.

	Univariate analyses			Adjusted logistic regression		
	OR	95% CI	*p*	aOR	95% CI	*p*
All-cause hospital admission (n = 4,142)						
1	1.65	(1.50, 1.81)	<0.001	1.22	(1.10, 1.35)	<0.001
2	2.45	(2.18, 2.75)	<0.001	1.38	(1.21, 1.57)	<0.001
≥3	4.19	(3.72, 4.72)	<0.001	1.62	(1.39, 1.87)	<0.001
Hospital admission for coronary heart disease (n = 784)						
1	2.03	(1.66, 2.48)	<0.001	1.28	(0.96, 1.66)	0.123
2	2.66	(2.13, 3.33)	<0.001	1.11	(0.86, 1.43)	0.411
≥3	4.90	(4.00, 6.01)	<0.001	1.04	(0.80, 1.36)	0.758
Hospital admission for stroke (n = 677)						
1	1.54	(1.25, 1.90)	<0.001	1.06	(0.85, 1.33)	0.605
2	2.19	(1.73, 2.76)	<0.001	1.16	(0.89, 1.51)	0.266
≥3	3.49	(2.82, 4.31)	<0.001	1.35	(1.03, 1.77)	0.033
Hospital admission for dementia (n = 134)						
1	2.28	(1.42, 3.71)	<0.001	1.69	(0.93, 2.91)	0.141
2	3.12	(1.85, 5.27)	<0.001	1.66	(0.87, 3.01)	0.182
≥3	4.36	(2.67, 7.19)	<0.001	1.40	(0.76, 2.62)	0.283
Hospital admission for heart failure (n = 67)						
1	2.52	(0.99, 6.86)	0.056	2.09	(0.80, 5.84)	0.139
2	5.05	(1.98, 13.74)	<0.001	3.17	(1.13, 9.37)	0.03
≥3	19.19	(9.11, 47.03)	<0.001	6.97	(2.60, 20.48)	<0.001
Emergency department admission (n = 3,110)						
1	2.09	(1.88, 2.33)	<0.001	1.66	(1.49, 1.86)	<0.001
2	3.10	(2.73, 3.51)	<0.001	1.99	(1.73, 2.28)	<0.001
≥3	6.16	(5.43, 6.98)	<0.001	2.92	(2.50, 3.40)	<0.001
Bone fracture (n = 580)						
1	2.04	(1.62, 2.56)	<0.001	1.82	(1.44, 2.31)	<0.001
2	2.61	(2.02, 3.38)	<0.001	2.13	(1.61, 2.81)	<0.001
≥3	4.32	(3.42, 5.47)	<0.001	2.73	(2.03, 3.67)	<0.001
Constipation (n = 932)						
1	1.55	(1.29, 1.85)	<0.001	1.18	(0.97, 1.43)	0.125
2	2.13	(1.74, 2.60)	<0.001	1.43	(1.14, 1.78)	0.002
≥3	3.71	(3.09, 4.46)	<0.001	2.00	(1.59, 2.52)	<0.001
Diarrhea (n = 167)						
1	1.28	(0.80, 2.04)	0.293	1.12	(0.69, 1.80)	0.656
2	3.50	(2.27, 5.42)	<0.001	2.70	(1.68, 4.34)	<0.001
≥3	4.61	(3.05, 7.03)	<0.001	2.78	(1.64, 4.73)	<0.001

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; 95% CI, 95% confidence interval. Multivariate adjusted logistic regression was achieved by including every variable presented in baseline characteristics table.

was an un-neglected issue in the management of polypharmacy. Only chronically used medication and the third level of the ATC codes that were applied may partly explain the lower prevalence of polypharmacy than in previous studies of polypharmacy prevalence among older adults with diabetes around the world (Remelli et al., 2022). A 5-year repeated cross-sectional study showed that the change in polypharmacy prevalence was smaller in older adults with diabetes than in middle-aged patients, which might be related to the steady type and number of chronic diseases in older adults with diabetes (Oktora et al., 2021). Assessing the prevalence of chronic polypharmacy will be more suitable for older adults with diabetes. We accurately assessed the prevalence of iatrogenic chronic polypharmacy of older adults with diabetes in the Chinese community as 46.37% with the medical records of 83 hospitals and 702 primary care centers documented in SHDMDRCD.

The 55.09% prevalence of PIMs is also an urgent concern in the health and medication management of older adults with diabetes in China. With SHDRDMCD and 39 out of 42 PIM items in the 2019 Beers Criteria, this study provides a complete representation of the iatrogenic PIM exposure rate in community-dwelling older adults with diabetes in Shenzhen, China. The prevalence of PIMs in this study is significantly higher than those of existing cross-sectional studies in the Netherlands (24.9%) and the United States (39.9%) but is similar to the retrospective cohort study conducted in Canada (56.1%) (Gagnon et al., 2020; Nightingale et al., 2021; Oktora et al., 2021). It must be related to the fact that only 24 PIM items of the 2015 Beers Criteria were evaluated in 60 community pharmacies in the Netherlands, and 40 PIM items of the 2019 Beers Criteria were evaluated in an emergency department in the United States. Similar to this study, all accessible healthcare facilities were evaluated in a retrospective cohort study in Quebec, Canada. This indicates that iatrogenic PIM exposure in older adults with diabetes could exceed 50%.

In older adults with diabetes, inappropriate medication was associated with an increased risk of cardiovascular disease, stroke, dementia, gastrointestinal autonomic dysfunction, and osteoporosis (Ling et al., 2000; Cukierman-Yaffe et al., 2009; Cavender et al., 2015; Pan et al., 2019; Gerontology NCo et al., 2021). The health status of older adults with diabetes will be seriously affected once they are hospitalized for coronary heart disease, heart failure, dementia, stroke, bone fracture, constipation, and diarrhea (Cukierman-Yaffe et al., 2009; Cavender et al., 2015; Gilbert and Pratley, 2015; Pan et al., 2019; Gerontology NCo et al., 2021). In response to such a high prevalence of chronic polypharmacy and PIMs in older adults with diabetes, it was critical to investigate whether it would cause a negative impact on the patient's health.

Importantly, this study simultaneously investigates the relationship between exposure to chronic polypharmacy and PIMs with AHO. A systematic review summarized that evidence of adverse drug events, falls, bone fractures, gastrointestinal symptoms, and circulatory disease in older individuals exposed to polypharmacy was inconsistent or contradictory (Davies et al., 2020). The same phenomenon could be observed in studies concentrating on PIMs (Liew et al., 2020; Weir et al., 2020; Bories et al., 2021). Considering that different probabilities and inconsistent rankings of exposure to chronic polypharmacy and PIMs in older adults with diabetes combined with different chronic comorbidities and increasing exposure to polypharmacy increased the probability of PIM exposure, we presumed that separately exploring the AHO of polypharmacy and PIM exposure would uncover the real evidence (Miller et al., 2017; Lu et al., 2022). To avoid confounding factors, people who suffered from the investigated AHO within 6 months before the start of the follow-up were excluded from the corresponding analysis. Ultimately, with SHDRDMCD, we found different associated AHO between exposure to chronic polypharmacy and PIMs in older adults with diabetes. Compared with chronic polypharmacy, PIMs were associated with more AHO-like bone fractures, constipation, and diarrhea, in older adults with diabetes. This study suggests that more attention should be paid to the substitution or withdrawal of PIMs in older adults with diabetes in clinical practice and drug management to reduce AHO.

Optimization of the drug list concerning chronic polypharmacy and PIMs in clinical practice should pay more attention to the comorbidity of patients and possible AHO. The risk of all-cause hospital admission and emergency department visits, which are commonly explored in existing studies, could not provide specific adverse health impacts of exposure to chronic polypharmacy and PIMs, regardless of the angle of the clinical practitioner or patient. The results of this study could serve as a basis for a drug-list review to avoid excessive blood glucose fluctuations due to drug–drug interactions and a high risk of bleeding, which might lead to hospital admission for dementia, stroke, and coronary heart disease. For example, repaglinide may enhance and/or prolong the hypoglycemic effect of repaglinide and, thereby, increase the risk of hypoglycemia when combined with clopidogrel, ketoconazole, and angiotensin-converting enzyme inhibitors (Plosker and Figgitt, 2004; Takayama et al., 2021). The combination of acarbose and warfarin will increase the risk of bleeding by increasing the international normalized ratio of prothrombin (Dash et al., 2018). Replacement or withdrawal of drugs by reviewing the possible risk of AHO in older adults with diabetes who were exposed to PIMs was practical. For example, short-acting insulin and sulfonylureas predispose patients to hypoglycemia, which can increase the risk of falling and, thus, fracture (BtAGSBCUE, 2019). Precise indications for possible AHO of chronic polypharmacy and PIMs are important in optimizing treatment.

5 Practical implications

This observational study highlights that chronic polypharmacy and PIMs were prevalent in community-dwelling older adults with diabetes. The study's findings contribute to improving the awareness among primary healthcare workers regarding the AHO of polypharmacy and PIMs use in older adults with diabetes. The quantity of medications and the utilization of PIMs may serve as significant mediators for AHO, making them valuable indicators for primary healthcare workers to periodically review the medication needs of older patients with diabetes.

Patient-centered medication review was required in disease management for older adults with diabetes regarding chronic polypharmacy and PIM use in primary care facilities in China. Many specialty clinics may add new drugs to address specific issues without fully considering the comprehensive health status of older

diabetes patients and their existing medication regimens for other chronic conditions. Since the widespread adoption of disease management for older adults with diabetes in primary care facilities in China, medication reviews for older patients with diabetes are limited to the antihyperglycemics they are currently taking (Li et al., 2017). Interventional studies aiming to optimize prescriptions for chronic polypharmacy and PIM use in older adults with diabetes in primary care facilities in China are also warranted.

6 Strengths and limitations

The strengths of our study are listed herein. A large-sample community-followed cohort of older adults with diabetes and SHDRDMCD covering medical records of 83 hospitals and 702 primary care centers in Shenzhen, China, were available. Three out of 5 categories of the 2019 Beers Criteria (including 39 out of 42 PIM items) were investigated. Only chronically used drugs were calculated for chronic polypharmacy assessment. The associated AHO of exposure to chronic polypharmacy and PIMs was explored simultaneously. The dose–response relationship between AHO and chronic polypharmacy and PIMs was studied. To reduce the potential bias of the results of this study, the following limitations were unsettled. Categories IV and V of the 2019 Beers Criteria were not evaluated due to a lack of some laboratory data and information on the concurrent use of drugs. Older adults with diabetes who did not use any drugs or only used Chinese patent medicine were excluded from this study, which might lead to an overestimation of the prevalence of PIMs. Patients' adherence could not be evaluated with an electronic medical record, which might overestimate or underestimate the risk of AHO in older adults with diabetes who are exposed to chronic polypharmacy and/or PIMs. The prevalence of chronic polypharmacy in this study was not comparable among studies with the definition of only the number of drugs or the fourth and fifth ATC levels. Finally, the incidence of hospital admission for heart failure and dementia was low during the 2-year follow-up, which might affect the power of the test.

In conclusion, chronic polypharmacy and PIMs were prevalent in older adults with diabetes in Chinese communities. Iatrogenic exposure to chronic polypharmacy and PIMs is associated with a higher incidence of different AHO. This observational evidence highlights the necessity of patient-centered medication reviews for chronic polypharmacy and PIM use in older patients with diabetes in primary care facilities in China and attracts attention for the caution of polypharmacy, especially PIM using in older adults with diabetes in clinical practice.

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 Review Committee of Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences. 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

LL: conceptualization, formal analysis, methodology, investigation, software, validation, and writing–original draft. SW: formal analysis, investigation, methodology, writing–original draft, data curation, resources, and supervision. JC: formal analysis, investigation, methodology, writing–original draft, conceptualization, software, and validation. YY: methodology, software, data curation, resources, supervision, and writing–review and editing. KW: methodology, software, conceptualization, formal analysis, investigation, validation, and writing–original draft. JZ: software, data curation, project administration, resources, supervision, and writing–review and editing. PG: software, conceptualization, formal analysis, investigation, methodology, validation, and writing–original draft. YC: methodology, software, data curation, funding acquisition, project administration, resources, supervision, and writing–review and editing. QZ: funding acquisition, methodology, project administration, resources, supervision, writing–review and editing, conceptualization, and 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.

Publisher's note

Supplementary material

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Dose-response association of metformin use and risk of age-related macular degeneration among patients with type 2 diabetes mellitus: a population-based study

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Background: Recent studies have demonstrated that patients with type 2 diabetes mellitus (T2DM) who receive metformin have a decreased risk of developing age-related macular degeneration (AMD). However, other studies have also suggested that metformin may increase the risk of AMD development. Therefore, this study investigated the association between treatment with metformin and the risk of AMD in patients with T2DM by using Taiwan' National Health Insurance Research Database.

Methods: Patients who received a diagnosis of new-onset T2DM between 2002 and 2013 were enrolled in this study. The patients were divided into patients treated and not treated with metformin to evaluate the risk of AMD after 5 years of follow-up. The logistic regression was used to estimate the risk of AMD associated with the intensity of treatment with metformin.

Result: A total of 7 517 patients (103.16 patients per 10,000 people) developed AMD in 5 years after DM diagnosis. After adjusting for the relevant variables, patients with T2DM treated with <5 defined daily dose (DDD)/month of metformin had a lower risk of AMD (odds ratios [OR]: 0.93; 95% confidence interval [CI]: 0.88 0.99). Patients treated with >25 DDD/month of metformin had a higher risk of AMD (OR: 1.39; 95% CI: 1.08-1.78).

Conclusion: Metformin use may be associated with a risk of AMD among patients with T2DM in a dose-dependent association manner, with the greater benefit at lower DDD/month. However, higher DDD/month exhibited an increased risk of AMD.

KEYWORDS

age-related macular degeneration, metformin, type 2 diabetes mellitus, Pharmacoepidemiology, real world evidence (RWE)

Introduction

Age-related macular degeneration (AMD) is the major cause of central irreversible blindness or visual loss among patients aged >50 years in developed countries (Chakravarthy et al., 2010). AMD is typically classified into early and late forms. Patients with early AMD are usually asymptomatic, whereas patients in the late stage of AMD may develop severe progressive vision loss. AMD can be categorized into the 2 following clinical types: nonexudative (dry) and exudative (wet) AMD (Fernandes et al., 2022). Incidence rates of AMD lesions increase substantially with age (Mitchell et al., 2002).

The pathogenesis of AMD is complicated and can be associated with several risk factors, including aging, ocular disorders, systemic diseases, cigarette smoking, diet, body mass index, genetic susceptibility, and environmental conditions (Lim et al., 2012; Ersoy et al., 2014). Studies have investigated whether type 2 diabetes mellitus (T2DM) play a role in AMD development and progression. Several studies have found a positive correlation between T2DM and AMD (Nitsch et al., 2008; Topouzis et al., 2009; Chen et al., 2014; He et al., 2018), whereas some other studies expressed no such effect (Fraser-Bell et al., 2008; Xu et al., 2009). In addition, an inverse association was observed in the Age-Related Eye Disease Study (Clemons et al., 2006).

Several retrospective clinical studies demonstrated that metformin may have a potential role in AMD development (Chen et al., 2019; Lee et al., 2019; Blitzer et al., 2021), while active treatment with metformin is associated an increased risk of dry AMD (Eton et al., 2022). In addition, a meta-analysis study show that metformin is not protective against AMD development (Romdhoniyyah et al., 2021). A study reported that treatment with metformin of low-to-moderate doses is associated with a lower risk of AMD, while higher doses of metformin use did not have reduced risk of AMD development (Blitzer et al., 2021). Conflicting data on the association between metformin exposure dosage and the risk of AMD development. Therefore, we conducted a large-scale nationwide study to determine the association between treatment with metformin and the risk of AMD in patients with T2DM by using data from the National Health Insurance Research Database (NHIRD).

Material and method

Data source

This study used the Longitudinal Health Insurance Database (LHID) from 2001 to 2018 as the study database provided by the Health and Welfare Data Science Center (HWDC) of the Ministry of Health and Welfare in Taiwan. The LHID encompasses data pertaining to every individual who is registered within Taiwan's National Health Insurance (NHI) program. The NHI contains health insurance claims data for 99% of Taiwan's 23 million residents. Disease diagnoses were coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) and *ICD, 10th Revision, Clinical Modification* (*ICD-10-CM*). The NHIRD can be used to obtain real-world evidence to support clinical decisions and healthcare policy-making (Chang et al., 2017; Hsieh et al., 2019; Lai et al., 2020). Therefore, we used data from the LHID to analyze the dose-response association of metformin use and risk of AMD among T2DM patients in Taiwan.

Ethics approval

This study was exempted from informed consent because the personal identification data were encrypted and transformed in the LHID. This study protocol was approved by the Central Regional Research Ethics Committee of China Medical University, Taiwan (No. CRREC-109-011).

Study participants

This study enrolled patients with new-onset diabetes mellitus (DM) aged ≥50 years from 2002 to 2013. DM (*ICD-9-CM*: 250) was indicated by the presence of 3 outpatient diagnoses. Metformin of the present study was defined according to the Anatomical Therapeutic Chemical (ATC) code A10BA02. The study participant exclusion criteria contained (Chakravarthy et al., 2010) type 1 DM patients, (Fernandes et al., 2022), patients having a diagnosis of AMD before DM, (Mitchell et al., 2002), patients having a diagnosis of AMD in the first year after DM, and (Lim et al., 2012) patients hospitalized within 1 year after DM diagnosis. After selection (Figure 1). There were a total of 728 703 patients with new-onset DM were included in the study. Patients treated with and without metformin were 377 878 patients and 350 825 patients, respectively.

Study design

This study was a cross-sectional study and used the defined daily dose (DDD) for assessing metformin intake. The DDD is characterized by the World Health Organization as the anticipated average daily maintenance dose for adults. However, the DDD does not necessarily reflect the recommended or prescribed daily dose (Grimmsmann and Himmel, 2011). The DDD of metformin is 2 g (Wellington, 2005), and the observation period prior to treatment with metformin in the present study was 1 year after DM. Based on the study design from previous studies (Chang et al., 2018; Huang et al., 2022a; Huang et al., 2022b), we categorized patients according to the average monthly DDD (expressed as DDD/month) into 5 ranges: 0, <5, 5 15, 15–25, and >25, respectively.

All patients were observed for a 5-year period to investigate the risk of incident AMD. The definition of incident AMD (*ICD-9-CM*: 362.50-362.52, 362.57; *ICD-10-CM*: H35.31-H35.32, H35.36) was indicated by 3 or more outpatient visits within 1 year. Control variables were sex, age, income level, urbanization, diabetes complications severity (DCSI), and AMD-related comorbidities. The DCSI was used to assess the severity of diabetes (Young et al., 2008; Chang et al., 2012). The comorbidities were hyperlipidemia (*ICD-9-CM*: 272.0-272.4), hyperuricemia (*ICD-9-CM*: 790.6), cerebrovascular disease

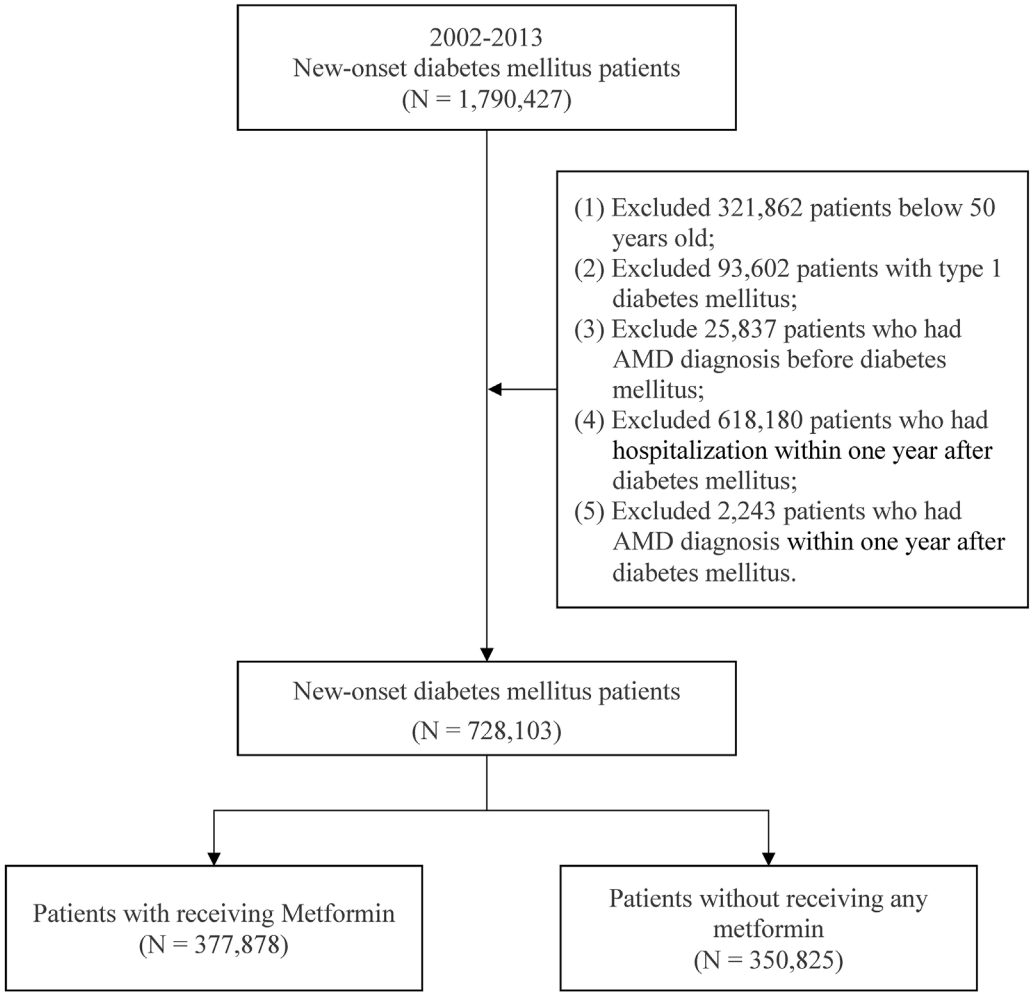

FIGURE 1
Patient selection process.

(CVD; ICD-9-CM: 430-438), obesity (*ICD-9-CM*: 278.00), alcoholism (*ICD-9-CM*: 303), nonalcoholic fatty liver disease (NAFLD; *ICD-9-CM*: 571.8), rheumatoid arthritis (RA; *ICD-9-CM*: 714), hypothyroidism (*ICD-9-CM*: 244.9), hepatitis B virus (HBV; *ICD-9-CM*: 070.33), hepatitis C virus (HCV; *ICD-9-CM*: 070.54), sleep disturbance (*ICD-9-CM*: 780), systematic lupus erythematosus (SLE; *ICD-9-CM*: 710.0), chronic kidney disease (CKD; *ICD-9-CM*: 585), migraine (*ICD-9-CM*: 346.90), and hyperthyroidism (*ICD-9-CM*: 242.9).

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States). The chi-square test was used to evaluate differences between patients treated with and without metformin. Multiple logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for AMD risk after adjustment for sex, age, income level, urbanization, diabetes severity, and comorbidities. All statistical results with $p < .05$ were regarded as statistically significant.

Results

Table 1 presents the baseline characteristics of all patients. The average age of all patients was 62.06 ± 8.83 years, and 51.42% of all patients were women. Regarding age groups, 23.72% were 50–54 years old, 22.82% were 55–59 years old, 18.00% were 60–64 years old, 13.96% were 65–69 years old, 10.51% were 70–74 years old, and 10.99% were above 75 years old. In patients treated with metformin, the average age was 61.21 ± 8.43 years.

Table 2 presents the incidence rate per 10,000 people of AMD and the risk of AMD after 5 years of follow-up. Patients not treated with metformin were 350 825 and the incidence rate of AMD was 111.88 patients per 10,000 people; patients treated with metformin <5 DDD/month were 168 198 and the incidence rate of AMD was 94.12 patients per 10,000 people; patients treated with metformin 5–15 DDD/month were 158 992 and the incidence rate of AMD was 95.85 patients per 10,000 people; patients treated with metformin 15–25 DDD/month were 45 478 and the incidence rate of AMD was 93.01 patients per 10,000 people; patients treated with metformin >25 DDD/month were 5210 and the incidence rate of AMD was 119.00 patients per 10,000 people.

TABLE 1 The characteristics of patients with diabetes mellitus.

Variables	Total		Metformin				
			Non-users		Users		*p*-value
	N	%	N	%	N	%	
Total	728,703	100.00	350,825	100.00	377,878	100.00	
Sex							<0.001
Female	374,706	51.42	185,681	52.93	189,025	50.02	
Male	353,997	48.58	165,144	47.07	188,853	49.98	
Age (year)							<0.001
50–54	172,863	23.72	74,579	21.26	98,284	26.01	
55–59	166,290	22.82	74,969	21.37	91,321	24.17	
60–64	131,178	18.00	62,907	17.93	68,271	18.07	
65–69	101,691	13.96	50,466	14.38	51,225	13.56	
70–74	76,584	10.51	40,604	11.57	35,980	9.52	
≥75	80,097	10.99	47,300	13.48	32,797	8.68	
Mean ± SD	62.06 ± 8.83		62.98 ± 9.16		61.21 ± 8.43		
Income level (NTD.)							<0.001
≤21,000	377,872	51.86	186,084	53.04	191,788	50.75	
21,001–33,000	172,793	23.71	77,497	22.09	95,296	25.22	
≥33,001	178,038	24.43	87,244	24.87	90,794	24.03	
Urbanization							<0.001
Level 1	200,346	27.49	102,111	29.11	98,235	26.00	
Level 2	235,727	32.35	112,688	32.12	123,039	32.56	
Level 3	113,396	15.56	52,002	14.82	61,394	16.25	
Level 4	102,480	14.06	48,430	13.80	54,050	14.30	
Level 5	17,112	2.35	8,350	2.38	8,762	2.32	
Level 6	31,238	4.29	14,389	4.10	16,849	4.46	
Level 7	28,404	3.90	12,855	3.66	15,549	4.11	
DCSI score [a]							<0.001
0	442,189	60.68	209,108	59.60	233,081	61.68	
1	155,131	21.29	74,328	21.19	80,803	21.38	
2+	131,383	18.03	67,389	19.21	63,994	16.94	
Hyperlipidemia							<0.001
No	574,597	78.85	264,377	75.36	310,220	82.10	
Yes	154,106	21.15	86,448	24.64	67,658	17.90	
Hyperuricemia							<0.001
No	722,413	99.14	347,304	99.00	375,109	99.27	
Yes	6,290	0.86	3,521	1.00	2,769	0.73	
Cerebrovascular disease							<0.001
No	690,054	94.70	329,884	94.03	360,170	95.31	
Yes	38,649	5.30	20,941	5.97	17,708	4.69	
Obesity							0.003
No	725,531	99.56	349,382	99.59	376,149	99.54	
Yes	3,172	0.44	1,443	0.41	1,729	0.46	
Alcoholism							0.985
No	728,261	99.94	350,612	99.94	377,649	99.94	
Yes	442	0.06	213	0.06	229	0.06	
NAFLD [a]							<0.001
No	722,530	99.15	347,661	99.10	374,869	99.20	
Yes	6,173	0.85	3,164	0.90	3,009	0.80	
RA [a]							<0.001
No	722,471	99.14	347,479	99.05	374,992	99.24	
Yes	6,232	0.86	3,346	0.95	2,886	0.76	

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TABLE 1 (*Continued*) The characteristics of patients with diabetes mellitus.

Variables	Total		Metformin				
			Non-users		Users		*p*-value
	N	%	N	%	N	%	
Hypothyroidism							<0.001
No	725,490	99.56	348,848	99.44	376,642	99.67	
Yes	3,213	0.44	1,977	0.56	1,236	0.33	
HBV [a]							0.299
No	728,574	99.98	350,757	99.98	377,817	99.98	
Yes	129	0.02	68	0.02	61	0.02	
HCV [c]							<0.001
No	725,443	99.55	349,073	99.50	376,370	99.60	
Yes	3,260	0.45	1,752	0.50	1,508	0.40	
Sleep disturbance							<0.001
No	569,717	78.18	270,541	77.12	299,176	79.17	
Yes	158,986	21.82	80,284	22.88	78,702	20.83	
SLE [a]							0.024
No	728,319	99.95	350,618	99.94	377,701	99.95	
Yes	384	0.05	207	0.06	177	0.05	
CKD [a]							<0.001
No	722,880	99.20	346,514	98.77	376,366	99.60	
Yes	5,823	0.80	4,311	1.23	1,512	0.40	
Migraine							0.989
No	725,088	99.50	349,085	99.50	376,003	99.50	
Yes	3,615	0.50	1,740	0.50	1,875	0.50	
Hyperthyroidism							<0.001
No	724,367	99.40	348,106	99.22	376,261	99.57	
Yes	4,336	0.60	2,719	0.78	1,617	0.43	

[a]Abbreviations: DCSI, diabetes complications severity index; NAFLD, non-alcoholic fatty liver disease; RA, rheumatoid arthritis; HBV, hepatitis B virus; HCV, hepatitis C virus; SLE, systemic lupus erythematosus; CKD.

After adjusting for the relevant variables containing sex, age, income level, urbanization, DCSI, and AMD-related comorbidities, we determined that patients with DM treated with metformin at <5, 5–15, 15–25, and >25 DDD/month for AMD had ORs of 0.93 (95% CI: 0.88–0.99), 1.00 (95% CI: 0.95-1.07), 1.01 (95% CI: 0.91-1.12), and 1.39 (95% CI: 1.08-1.78), respectively. Patients aged ≥75 years had an OR of 6.40 (95% CI: 5.82-7.05) compared to patients aged 50–54 years. Patients with a DCSI score of 2 had a higher risk of AMD (OR: 1.20, 95% CI: 1.13-1.27). Moreover, Patients with comorbid hypothyroidism (OR: 1.47, 95% CI: 1.12-1.93), sleep disturbance (OR: 1.08, 95% CI: 1.02-1.13) had a higher risk of AMD at 5-year follow-up. However, patients with comorbid hyperlipidemia, hyperuricemia, CVD, obesity, alcoholism, NAFLD, RA, HBV, HCV, SLE, CKD, migraine, or hyperthyroidism did not exhibit a notable risk of AMD.

Discussion

This study found that treatment with metformin may be associated with the risk of AMD among patients with T2DM in a dose-response relationship manner. The results suggest that the intensity of treatment with metformin <5 DDD/month is associated with a lower risk of AMD at 5 years after initial DM diagnosis. However, patients with T2DM treated with >25 DDD/month of metformin experienced higher risks of AMD at 5 years. In addition, we found that among patients T2DM treated with metformin, older patients and patients with a higher DCSI score had a higher risk of AMD. Furthermore, patients with T2DM with comorbid sleep disturbance and hypothyroidism had a higher risk of AMD.

DM may play a significant role in the progression and development of AMD. Previous studies have demonstrated a positive correlation between DM and AMD (Nitsch et al., 2008; Topouzis et al., 2009; Choi et al., 2011; Chen et al., 2014; Khotcharrat et al., 2015; Vassilev et al., 2015; He et al., 2018). Several pathophysiological mechanisms may be associated with DM and AMD. Oxidative stress and chronic inflammation may explain the correlation between DM and the risk of AMD. Oxidative stress causes outer blood–retinal barrier degeneration that contributes to AMD progression (Jung et al., 2022), and oxidative stress is a risk factor for the development of insulin resistance through insulin signal disruption (Houstis et al., 2006; Newsholme et al., 2019).

Metformin achieves its antioxidative and anti-inflammatory effects through the activation of AMP-activated protein kinase (AMPK) (Lee et al., 2013; Zhao et al., 2020) and reduction in reactive oxygen species (Hou et al., 2010). Recent studies have

TABLE 2 Five-year follow-up of incident age-related macular degeneration.

Variables	Five-year follow-up of incident age-related macular degeneration						
	Total N	Events N	Incidence rate per 10,000 people	*p*-value	Adjusted model		
					OR	95% CI	*p*-value
Total	728,703	7,517	103.16				
Intensity of metformin use				<0.001			
Non-users	350,825	3925	111.88		1		
<5	168,198	1583	94.12		0.93	(0.88–0.99)	0.014
5~15	158,992	1524	95.85		1.00	(0.95–1.07)	0.894
15~25	45,478	423	93.01		1.01	(0.91–1.12)	0.846
>25	5,210	62	119.00		1.39	(1.08–1.78)	0.011
Sex				0.722			
Female	374,706	3,850	102.75		1		
Male	353,997	3667	103.59		1.08	(1.03–1.13)	0.002
Age (year)				<0.001			
50–54	172,863	580	33.55		1		
55–59	166,290	1010	60.74		1.80	(1.63–2.00)	<0.001
60–64	131,178	1241	94.60		2.79	(2.53–3.08)	<0.001
65–69	101,691	1440	141.61		4.14	(3.75–4.56)	<0.001
70–74	76,584	1455	189.99		5.53	(5.02–6.10)	<0.001
≥75	80,097	1,791	223.60		6.40	(5.82–7.05)	<0.001
Income level (NTD)				<0.001			
≤21,000	377,872	4,498	119.04		1		
21,001–33,000	172,793	1394	80.67		0.83	(0.78–0.88)	<0.001
≥33,001	178,038	1625	91.27		0.93	(0.88–0.99)	0.014
Urbanization				<0.001			
Level 1	200,346	2300	114.80		1		
Level 2	235,727	2335	99.06		0.86	(0.81–0.91)	<0.001
Level 3	113,396	1025	90.39		0.75	(0.69–0.80)	<0.001
Level 4	102,480	1067	104.12		0.78	(0.72–0.84)	<0.001
Level 5	17,112	231	134.99		0.88	(0.77–1.01)	0.063
Level 6	31,238	312	99.88		0.69	(0.61–0.77)	<0.001
Level 7	28,404	247	86.96		0.62	(0.55–0.71)	<0.001
DCSI score [a]				<0.001			
0	442,189	3929	88.85		1		
1	155,131	1729	111.45		1.10	(1.04–1.17)	<0.001
≥2	131,383	1859	141.49		1.20	(1.13–1.27)	<0.001
Hyperlipidemia				<0.001			
No	574,597	5,802	100.98		1		
Yes	154,106	1715	111.29		1.03	(0.97–1.08)	0.383
Hyperuricemia				0.696			
No	722,413	7,449	103.11		1		
Yes	6,290	68	108.11		0.93	(0.74–1.19)	0.577
Cerebrovascular disease				<0.001			
No	690,054	6,926	100.37		1		
Yes	38,649	591	152.91		0.97	(0.89–1.06)	0.524
Obesity				0.039			
No	725,531	7,496	103.32		1		
Yes	3,172	21	66.20		0.75	(0.49–1.15)	0.189
Alcoholism				0.463			
No	728,262	7,514	103.18		1		
Yes	441	3	60.23		0.87	(0.28–2.71)	0.816

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TABLE 2 (*Continued*) Five-year follow-up of incident age-related macular degeneration.

Variables	Five-year follow-up of incident age-related macular degeneration						
	Total N	Events N	Incidence rate per 10,000 people	*p*-value	Adjusted model		
					OR	95% CI	*p*-value
NAFLD [a]				0.293			
No	722,530	7,445	103.04		1		
Yes	6,173	72	116.64		1.17	(0.93–1.47)	0.192
RA [a]				0.109			
No	722,471	7,440	102.98		1		
Yes	6,232	77	123.56		1.07	(0.85–1.34)	0.560
Hypothyroidism				<0.001			
No	725,490	7,465	102.90		1		
Yes	3,213	52	161.84		1.47	(1.12–1.93)	0.006
HBV [a]				0.773			
No	728,574	7,514	103.16		1		
Yes	129	3	77.52		0.88	(0.12–6.27)	0.901
HCV [a]				0.013			
No	725,443	7,469	102.96		1		
Yes	3,260	48	147.24		1.33	(0.99–1.77)	0.051
Sleep disturbance				<0.001			
No	569,717	5,534	97.14		1		
Yes	158,986	1983	124.73		1.08	(1.02–1.13)	0.007
SLE [a]				0.125			
No	728,319	7,510	103.11		1		
Yes	384	7	182.29		1.77	(0.84–3.72)	0.130
CKD [a]				<0.001			
No	722,880	7,427	102.74		1		
Yes	5,823	90	154.56		0.96	(0.77–1.18)	0.689
Migraine				0.203			
No	725,088	7,472	103.05		1		
Yes	3,615	45	124.48		1.28	(0.96–1.72)	0.098
Hyperthyroidism				0.681			
No	724,367	7,475	103.19		1		
Yes	4,336	42	96.86		1.00	(0.74–1.35)	0.982

[a]Abbreviations: DCSI, diabetes complications severity index; NAFLD, non-alcoholic fatty liver disease; RA, rheumatoid arthritis; HBV, hepatitis B virus; HCV, hepatitis C virus; SLE, systemic lupus erythematosus; CKD, chronic kidney disease.

demonstrated that AMPK plays a major role in the regulation of systemic glucose homeostasis and metabolic stress. AMPK is a conserved energy sensor and master regulator of glucose metabolism, which restores cellular energy balance during metabolic stress (Garcia and Shaw, 2017) and might be involved in AMD pathogenesis (Brown et al., 2019a). Metformin inhibited oxidative stress on human retinal pigment epithelium (RPE) cells by stimulating the AMPK signaling pathway in a mouse model of AMD (Xu et al., 2018). Antioxidant and anti-inflammatory effects of metformin can protect the RPE cells against the lesions of early AMD (Jiang et al., 2022).

Our findings demonstrated that patients with T2DM treated with <5 DDD/month of metformin had a lower risk of AMD at 5 years after initial DM diagnosis. Animal studies and physiology studies have suggested that metformin may play a beneficial role in the prophylaxis of AMD (Amin et al., 2022). Several studies suggested that metformin may have a role in AMD development and progression (Romdhoniyyah et al., 2021; Chen et al., 2019; Blitzer et al., 2021). A large-scale study reported the protective outcomes of metformin use in the development of AMD, with a 42% reduction (Brown et al., 2019b). A systematic review and meta-analysis study found that treatment with metformin is not associated with a significant lower risk of AMD (Romdhoniyyah et al., 2021). Another large case-control study reported that treatment with metformin is associated with a lower risk of AMD, with the lowest ORs associated with low-to-moderate doses (Blitzer et al., 2021). This study suggests that metformin use more than 2 years in patients aged 55 years and older is correlated with 5%–10% decreased odds ratio of AMD development.

Our findings revealed that patients treated with >25 DDD/month of metformin exhibited a higher risk of AMD after 5 years of follow-up. A case–control study observed no significant associations between AMD risk and cumulative duration or exposure of treatment with

metformin (Lee et al., 2019). Another study with a small sample size found a conflicting relationship between metformin exposure and dry AMD, with the findings based on assessment of metformin cumulative dosage and the intensity of the treatment with metformin (Eton et al., 2022). A study based on medical claims from a large US insurer also indicated that conflicting associations between metformin exposure and development of dry AMD. Cumulative metformin dosage model showed a significant association between the risk of dry AMD with cumulative dosage, with the lowest dosage quartile associated with a decreased risk of dry AMD and the highest dosage associated with an increased risk (Eton et al., 2022). Active treatment with metformin is associated with an increased risk of dry AMD, whereas prior treatment with metformin is associated with decreased risk (Eton et al., 2022). Our findings are similar to a large nationwide case-control study revealed that the use of metformin may protect against AMD development in a dose-dependent manner (Blitzer et al., 2021). This research found that metformin may be useful as a preventive treatment for AMD with strongest at low to moderate doses, while higher dose did not have reduced risk of AMD development. This study reported that doses of greater than 1080 g of metformin use more than 2 years did not have decreased risk of AMD development, while was particularly for low to moderate doses of metformin revealed the greatest potential benefit (Blitzer et al., 2021). The greatest reduction in AMD risk was observed at metformin doses of 271–600 g over 2 years with an OR of 0.91, and doses of 1–270 g and 600–1080 g over 2 years were also correlated with decreased OR, 0.93 and 0.95, respectively (Blitzer et al., 2021).

Vitamin B12 deficiency may play a role in AMD development in patients with T2DM receiving long-term treatment with metformin. Treatment with metformin can induce vitamin B12 malabsorption by increasing bacterial overgrowth, altering gut bacterial flora in the enteric canal, and binding to the vitamin B12 intrinsic factor (Zhang et al., 2016). Malabsorption contributes to a decreased serum vitamin B12 plasma level. Current evidence suggests that metformin impairs vitamin B12 status in a dose-dependent and duration-dependent association manner (Infante et al., 2021). A meta-analysis suggest a negative association between metformin use and vitamin B12 plasma levels in T2DM patients (Chapman et al., 2016), and higher cumulative exposure and longer duration of metformin treatment were associated with an increased risk of vitamin B12 deficiency (Khattar et al., 2016; Huang et al., 2022a; Huang et al., 2022b; Huang et al., 2023). Patients received metformin with therapy duration ≥ 5 years and a metformin dose of ≥ 1500 mg/day for a duration of at least 6 month was associated vitamin B12 deficiency, especially the highest risk has been found in patients with a daily metformin dose of ≥ 2000 mg (Infante et al., 2021). T2DM patients received metformin dosage of >2,000 mg/day increased the risk of vitamin B12 deficiency 22 times (Ko et al., 2014). However, the underlying mechanism accounting for metformin-induced vitamin B12 deficiency in patients with long-term and high-dose of metformin use remains unclear. Nevertheless, the proposed underlying mechanisms due to the alteration in small intestine motility, resulting in small intestinal bacterial overgrowth and subsequent B12 deficiency or by directly decreasing vitamin B12 absorption (Ting et al., 2006; Damiao et al., 2016); malabsorption leads to a decreased serum vitamin B12 level. Vitamin B12 and homocysteine may play a role in reducing the risk of AMD. Vitamin B12 deficiencies, folate, or elevated serum homocysteine levels were used as predictors of a high risk of AMD (Gopinath et al., 2013). Vitamin B12 is essential for the conversion of homocysteine to methionine in the methionine cycle (Allen, 2012). Vitamin B12 deficiency can impair the remethylation of homocysteine; moreover, metformin-induced vitamin B12 deficiency is potentially associated with hyperhomocysteinemia (Russo et al., 2011). An animal study found that excess homocysteine levels on the structure and function of retinal pigment epithelial that contribute to the development of AMD-like features (Ibrahim et al., 2016). Human study have reported that plasma homocysteine level was elevated in patients with AMD and highlighted a strong correlation between hyperhomocysteinemia and the development of AMD (Huang et al., 2015). A cross-sectional study found that increased total serum homocysteine and low vitamin B12 concentrations were independently associated with a higher risk of AMD (Rochtchina et al., 2007). The beneficial effects of vitamin B12 and folate on the risk of AMD are partly mediated by lowering the concentration of serum homocysteine (Rochtchina et al., 2007). Although treatment with metformin can decrease the risk of AMD (Brown et al., 2019a; Xu et al., 2018; Jiang et al., 2022), when long-term and high-dose or high cumulative dosage of metformin use were associated with biochemical B12 deficiency and hyperhomocysteinemia (Russo et al., 2011), may offset the protection effect of metformin and could lead to enhance the risk of AMD (Rochtchina et al., 2007). Routine assessment of vitamin B12 levels in individuals treated with metformin should be considered (Aroda et al., 2016; Al-Hamdi et al., 2020). Due to the clinical benefits of metformin use, its associated side effects such as metformin-induced vitamin B12 deficiency is often overlooked in T2DM patients. However, the diagnosis of metformin-induced vitamin B12 deficiency may be difficult (Al-Hamdi et al., 2020). The underlying mechanisms of metformin cumulative dosage and the risk of AMD remain unclear. Thus, further prospective clinical trials are warranted to investigate the protective effect of metformin on AMD, especially regarding duration and dosage of therapy.

Our findings showed that T2DM patients treated with metformin, older patients, and having a higher DCSI score linked to an increased risk of AMD. Previous studies have identified several risk factors for AMD, including aging, ocular disorders, systemic diseases, smoking, diet, genetic susceptibility, and environmental risk factors (Lim et al., 2012), with aging being the strongest risk factor (Aldebert et al., 2018). In the general population, vitamin B12 plasma levels decline with age, and thus, the prevalence of vitamin B12 deficiency increases with age. Age is a strong risk factor for the development of AMD, and individuals aged <50 years have a lower risk of AMD (Jiang et al., 2022) compared with older adults, who also have a higher risk of vitamin B12 deficiency (Gonzalez-Gross et al., 2007). The DCSI is a useful tool for adjusting for baseline severity of disease and predicting mortality and the risk of hospitalization among patients with DM (Young et al., 2008). Our study showed that patients with T2DM treated with metformin with higher DCSI scores had an increased risk of AMD. Thus, DCSI may be used as an indicator for assessing the risk of AMD development.

Our study results demonstrated that patients with T2DM treated with metformin and with comorbid sleep disturbance and hypothyroidism had a higher risk of AMD. A Taiwan population-based study indicated that insomnia is an independent indicator of an increased risk of AMD (Tsai et al., 2020). Thyroid disease is associated with an increased risk of AMD (Xu et al., 2021).

This study adopted a population-based design and used data from the NHIRD. Because we included the entire Taiwanese

population in this study, the sample size is large and sufficient for reducing selection bias and providing high-quality data. Second, the characteristics of the database provide sufficient statistical power for investigating the association between treatment with metformin and the risk of AMD among patients with T2DM. Finally, the intensity of treatment with metformin (DDD/month) was <5, 5–15, 15–25, >25 for determining the relationship between patients with T2DM and the risk of AMD.

This population-based cohort study has several limitations. First, information regarding family histories of AMD among patients with T2DM was unavailable. Second, patients' personal data and their lifestyle habits, such as body mass index, cigarette smoking habits, alcohol consumption, dietary habits, and physical activity (factors that are associated with AMD risk), were unavailable. Due to the limitations of the Taiwan National Health Insurance inpatient medical claims system, the information on the medication dosage during hospitalization was lacking from the NHIRD. Therefore, the use of metformin during hospitalization was not included in the present study, which may result in an underestimation of metformin's DDD in our study. Third, the diagnoses of AMD and other comorbidities were coded in accordance with the *ICD-9-CM* and *ICD-10-CM*. Nonetheless, the NHI Bureau of Taiwan randomly reviews the charts and interviews patients to assess the accuracy of the diagnoses, which improves the accuracy and validity of the NHIRD. Fourth, Information regarding biochemical parameters (e.g., fasting glucose, HbA1C, urine protein) is unavailable in the database but may affect developing AMD factors. The severity of DM and the disease duration of DM may also affect developing AMD. Therefore, the present study enrolled the new-onset DM patients as the study subjects and used the DCSI to adjust the severity of DM to reduce the bias. This study was a nationwide population-based study. Thus, the study results have accuracy and representativeness. Finally, this study is a type of epidemiology observational study that analyzes data from a nationwide database. The study result can only provide evidence to demonstrate that metformin is related to incident AMD. It is essential to obtain more information from other databases or questionnaires to conduct a prospective study or randomized controlled trial to analyze the cause-effect relation in future research.

Conclusion

In conclusion, this study provides evidence that treatment with metformin may be associated with the risk of AMD among patients with T2DM in a dose-dependent association manner. Patients treated with <5 DDD/month of metformin had a decreased risk of AMD at 5 years. However, >25 DDD/month exhibited an increased risk of AMD.

Data availability statement

The database used to support the findings of this study was provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW) under license and so cannot be made freely available. Requests for access to these data should be made to HWDC (https://dep.mohw.gov.tw/dos/cp-5119-59201-113.html).

Ethics statement

The studies involving humans were approved by Central Regional Research Ethics Committee of China Medical University, Taiwan. 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 database is anonymous to protect their privacy. The requirement for informed consent was waived.

Author contributions

K-HH: Conceptualization, Formal Analysis, Funding acquisition, Writing–original draft, Writing–review and editing. Y-LC: Conceptualization, Writing–original draft, Writing–review and editing. CL: Conceptualization, Writing–original draft, Writing–review and editing. S-YG: Conceptualization, Writing–original draft, Writing–review and editing. T-HT: Conceptualization, Formal Analysis, Writing–original draft, Writing–review and editing. N-JC: Conceptualization, Writing–original draft, Writing–review and editing. C-YL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Writing–original draft, 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

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Comparative effectiveness of tenofovir versus entecavir in patients with hepatitis B virus-related cirrhosis in Taiwan: a retrospective cohort study

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Background: Tenofovir and entecavir demonstrated substantial effectiveness in the reversion of fibrosis and reversed cirrhosis in patients with hepatitis B virus (HBV)-related cirrhosis. However, there has not been a definitive conclusion regarding the association between entecavir and tenofovir on the risk of cirrhosis-related complications. Therefore, this study aimed to investigate the comparative effectiveness between tenofovir and entecavir in HBV-related cirrhosis patients.

Methods: This was a retrospective study using Taiwan's Health Insurance Research Database. We enrolled newly diagnosed HBV-related cirrhosis patients who initiated entecavir and tenofovir between 2011 and 2019. Treatment groups were determined by the initial HBV antiviral medication prescribed. The primary composite outcome was the development of hepatocellular carcinoma (HCC), death from any causes, and liver transplantation. The secondary outcomes included all the individual components of the primary outcome. The incidence rate was calculated for each outcome for both treatment groups using the Fine–Gray subdistribution hazard models. Propensity score adjustment was used to balance treatment groups.

Results: A total of 7,316 propensity score-matched treatment-naïve patients and 3,524 propensity score-matched treatment-experienced patients were included. Within treatment-naïve patients, those receiving tenofovir showed significantly lower hazards of developing the composite outcome (HR, 0.79; $p < 0.0001$), hepatocellular carcinoma (HR, 0.86; $p = 0.027$), mortality (HR, 0.75; $p < 0.0001$), and liver transplantation (HR, 0.70; $p = 0.0189$) than those receiving entecavir. As for treatment-experienced patients, tenofovir was associated with a significantly lower risk of the composite outcome (HR, 0.82; $p = 0.0033$) and hepatocellular carcinoma (HR, 0.60; $p < 0.0001$), but it did not show a significantly different risk of all-cause mortality (HR, 0.93; $p = 0.3374$) or liver transplantation (HR, 1.17; $p = 0.5112$) compared to entecavir.

Conclusion: Tenofovir presented a significantly lower incidence of cirrhosis-related complications than entecavir in patients with hepatitis B virus-related cirrhosis. However, no statistically significant difference in death and liver transplantation was seen in treatment-experienced patients.

KEYWORDS

tenofovir, entecavir, effectiveness, hepatitis B virus, cirrhosis

Introduction

Cirrhosis is the leading cause of hepatocellular carcinoma (HCC) and results in approximately 1.16–1.32 million annual deaths globally (GBD, 2017 Cirrhosis Collaborators, 2020). Cirrhosis due to hepatitis B virus infection, namely, hepatitis B virus (HBV)-related cirrhosis, is responsible for over 50% of cirrhosis-related deaths in Asian nations (Sarin et al., 2020). In patients with HBV-related cirrhosis, clinicians would administer HBV antiviral drugs to suppress viral replication, reduce viral load, and thereby prevent cirrhosis progression and even reverse cirrhosis (Marcellin and Asselah, 2013; Calvaruso and Craxì, 2014; Rockey, 2016; Udompap and Kim, 2020).

Among the available nucleos(t)ide analogs (NAs), entecavir (ETV) and tenofovir (TDF/TAF) are recommended as first-line treatments for HBV-related cirrhosis considering their high antiviral efficacy and low rates of resistance (Sarin et al., 2016; European Association for the Study of the Liver, 2017; Terrault et al., 2018). As shown by previous randomized controlled trials, TDF/TAF and ETV demonstrated substantial effectiveness in the reversion of fibrosis and reversed cirrhosis in patients with HBV-related cirrhosis (Schiff et al., 2008; Yokosuka et al., 2010; Schiff et al., 2011; Marcellin et al., 2013).

Previous studies have indicated that TDF/TAF or ETV use may result in different effects on cirrhosis-related outcomes. The reason was that TDF/TAF belongs to the class of acyclic nucleoside phosphonates (ANPs) (De Clercq and Holý, 2005), and its structure differs from that of nucleoside analogs such as ETV. ANPs are characterized by prolonged action (De Clercq and Holý, 2005) and may exhibit better anti-HCC (Sato et al., 2006; Abushahba et al., 2010; Murata and Mizokami, 2023; Yang et al., 2023) and anti-HBV (Murata et al., 2020) effects. However, real-world evidence and experimental research regarding the comparative effectiveness between TDF/TAF and ETV in cirrhosis patients showed conflicting results (Choi et al., 2019; Papatheodoridis et al., 2020; Lee et al., 2021). Therefore, there has not been a definitive conclusion regarding the association between ETV and TDF/TAF on the risk of cirrhosis-related complications. Furthermore, there was a lack of evidence regarding the comparative effectiveness between TDF/TAF and ETV in treatment-experienced cirrhosis patients.

Therefore, this study aimed to investigate the hazards of cirrhosis-related complications, including HCC and liver transplantation, and mortality in patients with HBV-related cirrhosis receiving ETV and TDF/TAF.

Materials and methods

Study design and data sources

This retrospective cohort study was conducted using data from the National Health Insurance Research Database (NHIRD), which covered the healthcare data of approximately 100% of Taiwan's population (National Health Insurance Administration, 2023a). The healthcare information in the database included that of diagnoses, treatments, operations, and prescription details. The study period was from 1 January 2010 to 31 December 2020. This study was approved by the Institutional Review Board (IRB) of Kaohsiung Medical University Hospital (IRB number: KMUHIRB-E(I)-20230042).

Study population and exposure

Our study population included newly diagnosed HBV-related cirrhosis patients (adults), who had initiated ETV and TDF/TAF between 2011 and 2019. HBV-related cirrhosis was defined as chronic hepatitis B (CHB) diagnosed with cirrhosis after the initial CHB diagnosis. At least one inpatient visit or three outpatient visits were required to determine the number of CHB patients and for cirrhosis diagnosis. Diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) were used to enroll HBV-related cirrhosis patients. The population entry date was defined as the date of the first diagnosis of cirrhosis. The baseline period was the time period within 1 year before the population entry date.

Patients who were below 20 years of age at the population entry date; had incomplete demographic information (including age, gender, or premium insurance); had a history of cirrhosis, liver transplantation, or HCC during the baseline period; or initiated ETV and TDF/TAF together were excluded from the study. Cirrhosis and liver transplantation were identified by the presence of ICD codes, while patients with HCC were defined by the presence of the ICD codes for HCC and inclusion in the Taiwan Cancer Registry long-form database (Kao et al., 2021).

Eligible patients were those with HBV-related cirrhosis who filled their first prescription for either ETV or TDF/TAF after the population entry date. Patients were divided into ETV or TDF/TAF groups based on the initial HBV antiviral medication prescribed after the population entry date. The index date was defined as the first day of receiving ETV or TDF/TAF following the population entry date. Follow-up began on the index date. Patients were stratified into the previously untreated (PUT) cohort and previously treated (PT) cohort (Supplementary eMethods 1) for the analysis.

Study outcomes and follow-up

One primary outcome was evaluated: the composite outcome of HCC, liver transplantation, and all-cause death. Secondary

outcomes were individual components of the primary outcome. The detailed definition of each outcome event is shown in Supplementary eMethods 2. Patients who had experienced the outcome event before the index date were excluded from the corresponding outcome analyses. Patients were followed up from the index date to the occurrence of the corresponding outcome, switching antiviral treatment, or the end date of the database (31 December 2020), whichever came first. Patients with discontinuation were censored until they switched treatment or re-initialized treatment. Discontinuation was defined as a gap of more than 30 days between the end of a prescription and the next. In each outcome analysis, patients were not censored if other outcomes (except for the corresponding outcome) had occurred earlier.

Covariates and confounders

Patients' baseline characteristics and medical information were retrieved from the database. The demographic information including age and gender was obtained from the most recent insurance record prior to the population entry date. Comorbidities were defined as diseases diagnosed at least once in an inpatient or twice in an outpatient setting within 1 year before the population entry date. Detailed information on comorbidities is summarized in Supplementary eTable S1. The Charlson Comorbidity Index (CCI) was used to quantify the comorbidity status of the included patients (Charlson et al., 1987). Co-medications being regarded as confounders were collected (Hayward and Weersink, 2020), and medications prescribed for a minimum of 28 days within the year before the population entry date were co-medications. The disease progression period and treatment gap period were retrieved. The disease progression period was defined as the period between the first CHB diagnosis and the population entry date. The treatment gap period was defined as the period from the population entry date to the index date.

Propensity score methods

Two propensity score methods, namely, propensity score matching (PSM) and stabilized inverse probability of treatment weighting (IPTW), were used to generate comparable treatment groups before data analyses.

The PSM was performed using the 1:1 nearest-neighbor matching approach, with a caliper width set at 0.2 of the standard deviation of the logit of the propensity score (PS) (Austin, 2011a; Austin, 2011b). Confounders adjusted were age, gender, disease progression time, treatment gap duration, diabetes, hypertension, CCI, HCV/HDV/HEV co-infection, alcoholic cirrhosis, biliary cirrhosis, history of cirrhosis-related complications, and chronic kidney disease (CKD).

Statistical analyses

HBV-related cirrhosis patients were stratified into PUT patients and PT patients to obtain results. In the baseline analysis, descriptive statistics were stratified by groups. Continuous variables were presented as mean and standard deviation (SD). Categorical variables were represented using the number (N) and percentage (%). To assess the balance in each covariate, standardized mean difference (SMD) was employed, with a value below 0.1 indicating negligible differences between the groups (Austin, 2009a; Austin, 2009b).

Fine–Gray subdistribution hazard models, accounting for the competing risk events of death and liver transplantation, were used to investigate subdistribution HRs with a 95% confidence interval (CI) for each outcome analysis (except for the composite outcome and all-cause death analysis because no competing risk events existed). The proportional hazard assumptions were evaluated before analyses. We conducted sensitivity analyses to evaluate the robustness of our findings. We used the negative control outcome, myocardial infarction, to indirectly evaluate whether potential confounders existed (Lipsitch et al., 2010).

A statistically significant difference was defined as a two-tailed probability value less than 0.05. Data management and statistical analyses were processed with SAS software version 9.4.

Results

Patient characteristics

The original study population contained 18,351 patients after applying inclusion and exclusion criteria. When PSM was used, 3,658 patients each were included in the ETV and TDF/TAF users in the PUT sub-cohort and 1,762 each were included in the ETV and TDF/TAF users in the PT sub-cohort. After applying stabilized IPTW, a weighted pseudopopulation consisted of 8,204 ETV users and 3,663 TDF/TAF users in the PUT sub-cohort and 4,717 ETV users and 1,764 TDF/TAF users in the PT sub-cohort. The enrollment process for the study population is illustrated in Figure 1. All patients in our study were included in the analysis of death outcome, and the baseline characteristics are presented in Table 1; Supplementary eTable S3. Overall, the mean age ranged from 54 to 57 years, and the majority were men (73%–77%). The mean disease progression period was 2.30–3.69 years. The baseline characteristics of patients for the analysis of the composite outcome, HCC, and liver transplantation are presented in Supplementary eTables S4–S9, respectively.

Hazards of developing cirrhosis-related outcomes in the PUT cohort

In the analyses with PSM, the incidence rate of the composite outcome, HCC, and mortality was significantly lower in the TDF/TAF users. TDF/TAF showed significantly lower hazards of developing the composite outcome [HR, 0.78 (95% CI, 0.72 to 0.85); $p < 0.0001$], HCC [HR, 0.87 (95% CI, 0.76 to 0.99); $p = 0.0396$], mortality [HR, 0.76 (95% CI, 0.68 to 0.83); $p < 0.0001$], and liver transplantation [HR, 0.72 (95% CI, 0.53 to 0.97); $p = 0.0327$] in unadjusted analysis accounting for competing risk. After adjusting for baseline confounders, similarly lower hazards of developing the composite outcome, HCC, mortality, and liver transplantation were seen in TDF/TAF users (Table 2 Panel A). The differences in

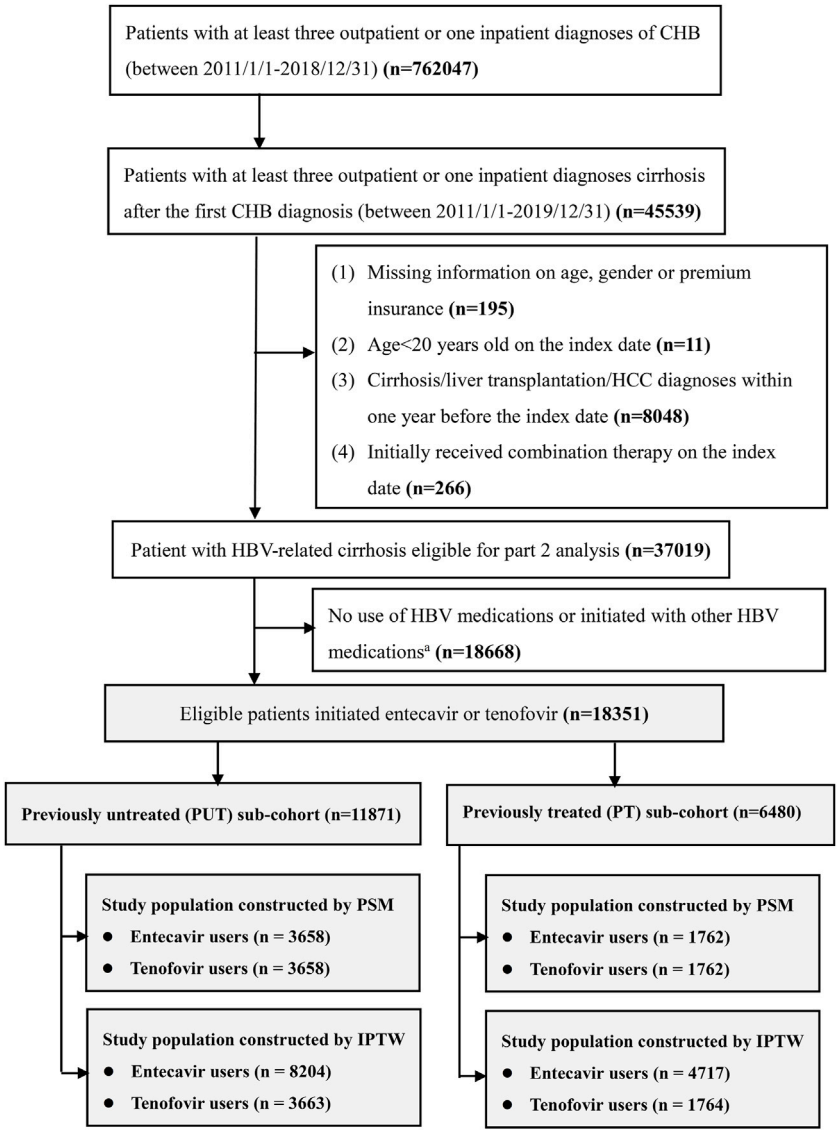

FIGURE 1
Flowchart of patients' enrollment. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma [a]; other HBV medications include lamivudine, telbivudine, adefovir, and interferon.

cumulative incidence curves between treatment groups within the PUT cohort for four outcomes are shown in Figure 2. In the analyses with stabilized IPTW, similar hazards of the lower composite outcome, mortality, and liver transplantation were found in TDF/TAF users than in ETV users (Table 2 Panel B; Supplementary eFigure S1).

Hazards of developing cirrhosis-related outcomes in the PT cohort

In the analyses with PSM, the incidence rate of HCC was significantly lower in the TDF/TAF users. In unadjusted analysis accounting for competing risk, TDF/TAF showed significantly lower hazards of developing composite outcomes [HR, 0.81 (95% CI, 0.71 to 0.93); p = 0.0021] and HCC [HR, 0.61 (95% CI, 0.49 to 0.76); $p < 0.0001$]. TDF/TAF was associated with a lower incidence rate of death, but the result did not achieve statistical significance. After adjusting for baseline confounders, similarly lower hazards of developing composite outcomes and HCC were seen in TDF/TAF users. The risks of death and developing transplantation were not statistically different between the two groups (Supplementary eTable S10 Panel A). The cumulative incidence curves between treatment groups within the PT cohort for four outcomes are shown in Figure 3.

In the analyses with stabilized IPTW, similarly lower incidence rates of the composite outcome and HCC were seen in patients treated with TDF/TAF. TDF/TAF was associated with a lower incidence rate of mortality, but the result did not achieve statistical significance. The univariate and multivariate analyses accounting for competing risk events showed a similar trend of lower composite outcome and HCC hazards in TDF/TAF users than

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TABLE 1 Baseline characteristics of HBV-related cirrhosis patients within the PUT cohort after applying propensity score methods.

Characteristics	Population after PSM			Population after IPTW		
	ETV (*n* = 3,658)	TDF/TAF (*n* = 3,658)	ASMD[a]	ETV (*n* = 8,204)	TDF/TAF (*n* = 3,663)	ASMD[a]
Mean age (SD), y	55.14 (11.71)	55.05 (11.70)	0.008	56.74 (11.83)	56.70 (11.77)	0.003
Gender, *n* (%)						
Male	2,702 (73.87)	2,705 (73.95)	0.002	6,019 (73.37)	2,689 (73.42)	0.001
Female	956 (26.13)	953 (26.05)	0.002	2,185 (26.63)	973 (26.58)	0.001
Comorbidities, *n* (%)						
HCV co-infection	133 (3.64)	144 (3.94)	0.016	339 (4.13)	149 (4.08)	0.002
HDV co-infection	<3	<3	0.016	<3	<3	0.291
HEV co-infection	<3	<3	0.016	<3	<3	0.017
HIV co-infection	15 (0.41)	20 (0.55)	0.090	8 (0.1)	21 (0.58)	0.084
Alcoholic cirrhosis	91 (2.49)	88 (2.41)	0.005	205 (2.49)	91 (2.49)	0.000
Biliary cirrhosis	<3	<3	0.005	<3	<3	0.000
Hypertension	1,140 (31.16)	1,120 (30.62)	0.012	2,830 (34.50)	1,262 (34.45)	0.001
Hyperlipidemia	646 (17.66)	629 (17.2)	0.012	1,493 (18.20)	663 (18.1)	0.003
Diabetes	833 (22.77)	829 (22.66)	0.003	2092 (25.51)	938 (25.62)	0.003
Chronic kidney disease	85 (2.32)	95 (2.6)	0.018	377 (4.60)	165 (4.50)	0.005
History of complications, *n* (%)						
Ascites	107 (2.93)	106 (2.9)	0.002	295 (3.59)	128 (3.51)	0.005
Hepatic encephalopathy	405 (11.07)	396 (10.83)	0.008	965 (11.76)	435 (11.87)	0.003
EVB	50 (1.37)	51 (1.39)	0.002	116 (1.42)	53 (1.45)	0.003
Hepatorenal syndrome	<3	<3	0.014	11 (0.13)	4 (0.11)	0.006
Charlson Comorbidity Index						
Mean (SD)	1.43 (1.58)	1.38 (1.58)	0.025	1.59 (1.73)	1.59 (1.77)	0.038
Disease progression period (y)	2.51 (2.35)	2.46 (2.33)	0.019	2.30 (2.27)	2.30 (2.27)	0.002
Treatment gap period (y)	1.04 (1.73)	1.05 (1.72)	0.008	1.02 (1.71)	1.03 (1.70)	0.004
Co-medications, *n* (%)						
ACEIs/ARBs	709 (19.38)	661 (18.07)	0.034	1746 (21.28)	752 (20.54)	0.018
β-blockers	473 (12.93)	471 (12.88)	0.002	1,111 (13.54)	532 (14.51)	0.028
Non-selective	212 (5.80)	218 (5.96)	0.007	501 (6.11)	246 (6.71)	0.024
Selective	276 (7.55)	271 (7.41)	0.005	669 (8.15)	312 (8.51)	0.013
CCBs	610 (16.68)	585 (15.99)	0.018	1,481 (18.05)	672 (18.36)	0.008
Diuretics	498 (13.61)	434 (11.86)	0.052	1,253 (15.28)	511 (13.96)	0.037
Furosemide	138 (3.77)	100 (2.73)	0.059	393 (4.79)	131 (3.58)	0.061
Spironolactone	91 (2.49)	69 (1.89)	0.041	235 (2.86)	83 (2.28)	0.037
Insulin	112 (3.06)	110 (3.01)	0.003	324 (3.95)	130 (3.55)	0.021
Biguanide	532 (14.54)	525 (14.35)	0.005	1,269 (15.47)	578 (15.79)	0.009
Meglitinide	41 (1.12)	42 (1.15)	0.003	144 (1.76)	51 (1.39)	0.029
Sulfonylurea	424 (11.59)	376 (10.28)	0.042	1,008 (12.28)	420 (11.47)	0.025

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics of HBV-related cirrhosis patients within the PUT cohort after applying propensity score methods.

Characteristics	Population after PSM			Population after IPTW		
	ETV (*n* = 3,658)	TDF/TAF (*n* = 3,658)	ASMD[a]	ETV (*n* = 8,204)	TDF/TAF (*n* = 3,663)	ASMD[a]
α-glucosidase inhibitors	110 (3.01)	101 (2.76)	0.015	237 (2.89)	115 (3.13)	0.014
Thiazolidinediones	88 (2.41)	75 (2.05)	0.024	222 (2.69)	86 (2.36)	0.021
DPP-4 inhibitors	271 (7.41)	237 (6.48)	0.037	631 (7.70)	266 (7.26)	0.016
SGLT2 inhibitors	20 (0.55)	34 (0.93)	0.045	42 (0.51)	35 (0.95)	0.052
GLP1 agonists	8 (0.22)	5 (0.14)	0.019	10 (0.12)	4.82 (0.13)	0.004
Statin	369 (10.09)	358 (9.79)	0.010	868 (10.58)	398 (10.87)	0.009
Fibrates	86 (2.35)	79 (2.16)	0.013	180 (2.20)	79.49 (2.17)	0.002
Silymarin	871 (23.81)	884 (24.17)	0.008	1933 (23.56)	911 (24.86)	0.030

IPTW, inverse probability of treatment weighting; ASMD, absolute standardized mean difference; ETV, entecavir; TDF/TAF, tenofovir disoproxil fumarate/tenofovir alafenamide fumarate; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, hepatitis I virus; EVB, esophageal varices with bleeding; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium-channel blockers; SGLT2, sodium-glucose cotransporter-2; GLP1, glucagon-like peptide-1; y: year.
[a]The absolute standardized mean difference less than 0.1 indicates well-balanced between groups.

in ETV users. The risks of death and developing transplantation were not statistically different between the two groups (Supplementary eTable S10 Panel B; Supplementary eFigure S2).

Results of sensitivity analysis

Regarding the analysis for the negative control outcome, the outcome did not show a significant association with TDF/TAF treatment (Supplementary eTable S11).

Discussion

Our study demonstrated a significantly reduced risk of developing cirrhosis-related complications among TDF/TAF users, consistent with previous studies suggesting a lower risk of HCC in individuals with HBV-related cirrhosis who received TDF/TAF than those receiving ETV (Choi et al., 2019). The negative control outcome, namely, MI, supported the conclusion that the lower hazards of cirrhosis-related outcomes and death in TDF/TAF compared to ETV were robust.

Our study could not determine the exact mechanism underlying the better outcomes with TDF/TAF treatment. However, several reasons might explain our findings. First, TDF/TAF might show superior virologic response profiles compared to ETV, as presented in previous studies (Koike et al., 2018; Chen et al., 2019; Choi et al., 2019; Choi et al., 2021). These better virologic outcomes might lead to different levels of effectiveness in preventing cirrhosis-associated complications between TDF/TAF and ETV therapy. Second, the antitumor effects of TDF/TAF have been reported. The reason was that higher interferon-λ3 levels were induced by ANPs (such as TDF/TAF), but not by nucleoside analogs (such as ETV) (Sato et al., 2006; Abushahba et al., 2010; Murata and Mizokami, 2023; Yang et al., 2023). Interferon-λ3 demonstrated potent antitumor effects in murine cancer models, including HCC (Sato et al., 2006; Abushahba et al., 2010; Murata and Mizokami, 2023; Yang et al., 2023). The antitumor activity might explain the differences in risks in developing outcomes between TDF/TAF and ETV. Third, TDF/TAF was anticipated to generate favorable immune responses toward anti-HBV effects. As presented by Murata et al. (2020), TDF/TAF could inhibit interleukin (IL)-10 production and thereby promote the release of IL-12 and tumor necrosis factor (TNF)-α, which was not observed in ETV. Suppressed IL-10 and increased IL-12 would stimulate T cells and NK cells to induce IFN-γ (Henry et al., 2008; Smith et al., 2018). Both IFN-γ and TNF-α promoted anti-HBV effects by inhibiting HBV replication and decreasing HBV covalently closed circular DNA (cccDNA) levels (Cavanaugh et al., 1997; Rehermann and Bertoletti, 2015; Xia et al., 2016).

In the PUT cohort after propensity score matching methods, TDF/TAF showed a significantly lower rate in each outcome. However, TDF/TAF was significantly associated with a lower hazard in the composite outcome and HCC, but not in death or liver transplantation. The inconsistent results among outcomes might be explained as follows: the lack of difference in incidence of death can be attributed to a higher proportion of patients in the ETV groups experiencing deaths unrelated to HCC, compared to the TDF/TAF groups (data not shown). No difference in incidence of liver transplantation represented that most patients received liver transplants because of complications of decompensation rather than HCC (data not shown) (European Association for the Study of the Liver, 2018).

To date, only a few real-world studies have compared cirrhosis-related outcomes between TDF/TAF and ETV in HBV-related cirrhosis patients (Choi et al., 2019; Papatheodoridis et al., 2020). However, real-world evidence investigating the comparative effectiveness between TDF/TAF and ETV in Taiwanese patients with HBV-related cirrhosis was limited. Furthermore, the evidence comparing cirrhosis-related outcomes within treatment-experienced cirrhosis patients was scarce. Our study successfully addresses the current knowledge gap.

Strengths and limitations

The main strengths of our study were as follows: this was a large-scale cohort study using the NHIRD to describe patients'

TABLE 2 Clinical outcomes within PUT patients after applying propensity score methods.

Panel A. Population after PSM								
Outcome[a]	Patients, *n*	Events, *n*	PY	Rate[b] (95% CI)	csHR[c] (95% CI)	*p*-value	asHR[d] (95% CI)	*p*-value
Composite outcome								
Tenofovir	3,417	850	11,004	7.72 (7.21–8.26)	0.78 (0.72–0.85)	<0.0001	0.79 (0.72–0.86)	<0.0001
Entecavir	3,417	1,124	11,838	9.49 (8.95–10.07)	1.00 (reference)		1.00 (reference)	
Hepatocellular carcinoma								
Tenofovir	3,423	579	13,368	4.33 (3.99–4.70)	0.87 (0.76–0.99)	0.0396	0.86 (0.75–0.98)	0.027
Entecavir	3,423	748	14,438	5.18 (4.82–5.57)	1.00 (reference)		1.00 (reference)	
Death								
Tenofovir	3,658	686	12,877	5.33 (4.94–5.74)	0.76 (0.68–0.83)	< 0.0001	0.75 (0.67–0.82)	< 0.0001
Entecavir	3,658	941	13,668	6.88 (6.45–7.34)	1.00 (reference)		1.00 (reference)	
Liver transplantation								
Tenofovir	3,651	80	14,623	0.55 (0.43–0.68)	0.72 (0.53–0.97)	0.0327	0.70 (0.51–0.94)	0.0189
Entecavir	3,651	105	16,245	0.65 (0.53–0.78)	1.00 (reference)		1.00 (reference)	
Panel B. Population after IPTW								
Outcome[a]	Patients, *n*	Events, *n*	PY	Rate[b] (95% CI)	cHR[c] (95% CI)	*p*-value	aHR[d] (95% CI)	*p*-value
Composite outcome								
Tenofovir	3,420	919	10,867	8.46 (7.92–9.02)	0.78 (0.72–0.84)	<0.0001	0.79 (0.73–0.85)	<.0001
Entecavir	7,464	2,653	25,361	10.46 (10.07–10.87)	1.00 (reference)		1.00 (reference)	
Hepatocellular carcinoma								
Tenofovir	3,427	621	13,471	4.61 (4.25–4.99)	0.93 (0.83–1.04)	0.182	0.92 (0.82–1.03)	0.1429
Entecavir	7,496	1,675	32,281	5.19 (4.94–5.44)	1.00 (reference)		1.00 (reference)	
Death								
Tenofovir	3,663	754	12,830	5.88 (5.47–6.31)	0.77 (0.71–0.84)	< 0.0001	0.77 (0.71–0.84)	< 0.0001
Entecavir	8,204	2,277	30,855	7.38 (7.08–7.69)	1.00 (reference)		1.00 (reference)	
Liver transplantation								
Tenofovir	3,655	79	14,804	0.53 (0.42–0.67)	0.67 (0.51–0.88)	0.0038	0.66 (0.50–0.87)	0.0028
Entecavir	8,160	247	37,226	0.66 (0.58–0.75)	1.00 (reference)		1.00 (reference)	

Abbreviations: PSM, propensity score matching; PY, person-year; cHR, crude hazard ratio; aHR, adjusted hazard ratio.
[a]Patients who had already encountered the relevant outcome before the index date were excluded in every outcome analysis.
[b]Rate was determined by dividing the number of events by the total person-years and presented as per 100 person-years.
[c]Crude HR was calculated by the subdistribution COX proportional hazards model.
[d]Adjusted HR was calculated by the subdistribution COX proportional hazards model adjusted for all variables.

characteristics and the novel findings that comprehensively evaluated comparative effectiveness between TDF/TAF and ETV in Taiwanese HBV-related cirrhosis patients. Additionally, our findings were consistent with those of a previous cohort (Choi et al., 2019). Moreover, our study addressed the knowledge gap and provided information with comparative effectiveness evidence in patients with prior exposure to NA. Furthermore, our conclusion remained consistent across different propensity score methods and sensitivity analyses.

We acknowledge that some limitations remain in this study. First, HBV-related (e.g., HBV viral load and HBeAg status), liver function-related (e.g., AST and ALT), HCC-related (e.g., α-fetoprotein, family history of HCC, smoking status, alcohol status, and BMI), and cirrhosis-related (platelet count, bilirubin, albumin, prothrombin time, serum creatinine, and fibrosis markers) lab data and Chinese medicine exposure data could not be obtained in our database (Hsu et al., 2014; Chen et al., 2017; Zhang et al., 2021; Kanwal et al., 2023). For HBV-related and liver function-related lab

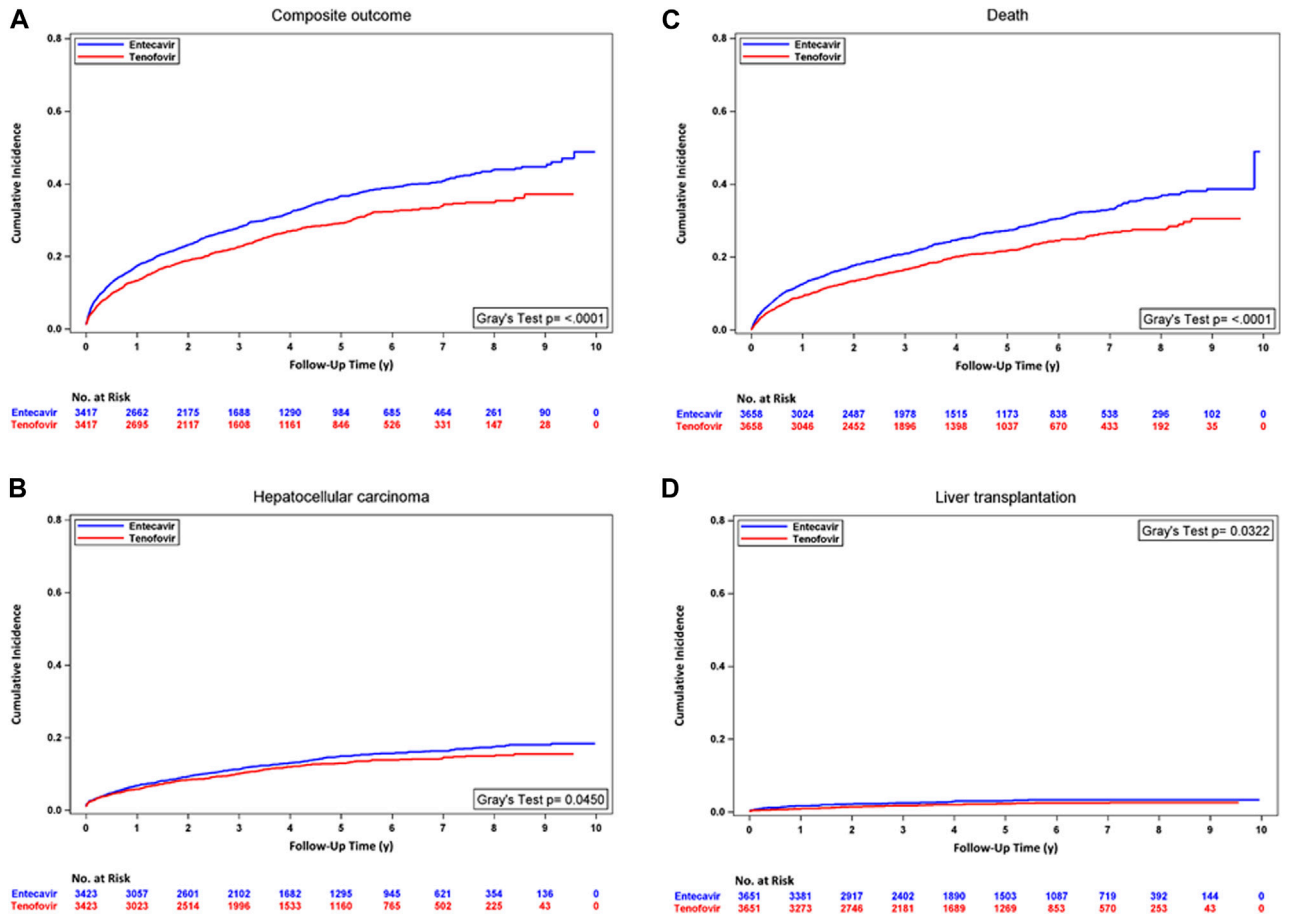

FIGURE 2
Cumulative incidence curves for TDF/TAF users versus ETV users within PUT cohorts after PSM. **(A)** Composite outcome, **(B)** hepatocellular carcinoma, **(C)** death, and **(D)** liver transplantation.

data, the ETV and TDF/TAF could continue to be reimbursed regardless of HBV viral load, HBeAg status, or results of liver function tests in HBV-related cirrhosis patients under the NHI payment guidelines (National Health Insurance Administration, 2023b). Therefore, the absence of information would not substantially affect our findings because the missing information was unlikely to induce treatment selection bias. However, the lack of cirrhosis-related information could impact our ability to assess the severity of liver cirrhosis and hepatic failure. This could misidentify individuals without cirrhosis as having cirrhosis, and *vice versa*. In addition, the lack of HCC-related data was an unmeasured confounder in our study, which might influence our estimated results. Second, we used ICD codes to identify cirrhosis patients, which hindered our ability to accurately determine cirrhosis status. The generation of misclassification bias resulted from the absence of information concerning diagnostic procedures for cirrhosis in clinical practice (for example, liver biopsy, ultrasound, CT, MRI, and liver stiffness evaluation) (RadiologyInfo, 2022). Third, despite the use of propensity score methods to address confounding variables, unknown or unmeasured confounders might still exist. Fourth, there were potential reasons that would induce selection bias between treatment groups. Given that ETV had been approved 3 years before TDF/TAF, ETV users tended to be older and have more advanced diseases than TDF/TAF users. This "patient warehousing" phenomenon was similarly observed in previous studies (Lok et al., 2016; Hsu et al., 2020; Yip et al., 2020). Moreover, there were a few additional potential explanations for the relatively younger age and milder liver disease of TDF/TAF patients. One reason could be the preference for TDF/TAF among young women of childbearing age due to its safety during pregnancy. Additionally, concerns regarding renal toxicity and osteoporosis might lead to the avoidance of TDF in the elderly population (Sarin et al., 2016; European Association for the Study of the Liver, 2017; Terrault et al., 2018). Nonetheless, because our study was an active comparison design with similar indications, the misclassification population, difference in baseline characteristics, and other unmeasured confounders could be reduced (Yoshida et al., 2015). Fifth, our study used data from the NHIRD; therefore, it is necessary to conduct further studies to validate whether our findings could be extrapolated to other countries or regions.

Our study provided updated information regarding the comparative effectiveness between ETV and TDF/TAF. Further studies could evaluate the comparative cost-effectiveness between two treatments to guide the optimal distribution of healthcare system resources.

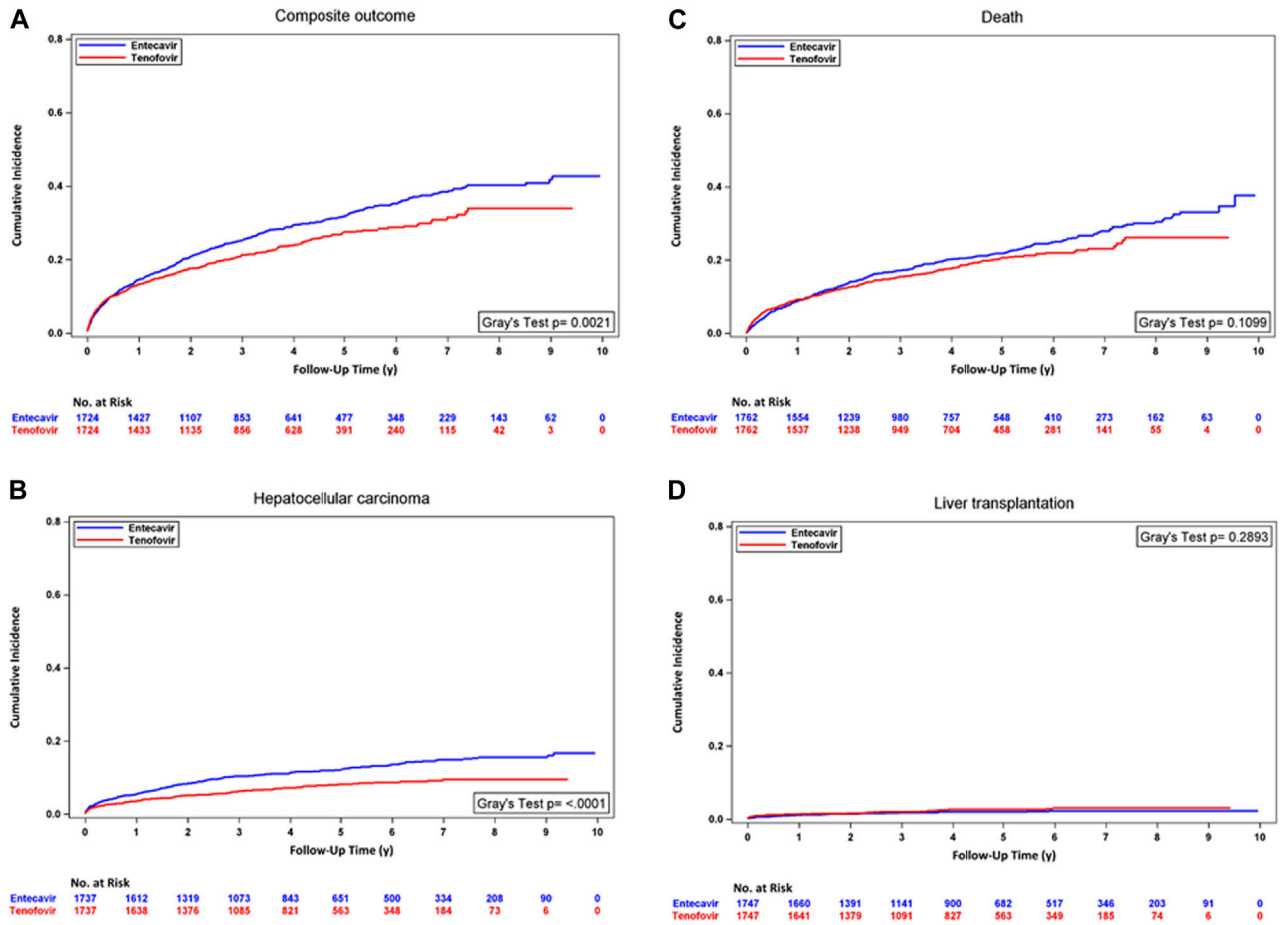

FIGURE 3
Cumulative incidence curves for TDF/TAF users versus ETV users within PT cohorts after PSM. **(A)** Composite outcome, **(B)** hepatocellular carcinoma, **(C)** death, and **(D)** liver transplantation.

Conclusion

TDF/TAF treatment was associated with a significantly lower risk of cirrhosis-related complications, and mortality, in patients with HBV-related cirrhosis compared with ETV treatment. However, no statistically significant difference in death and liver transplantation was seen in treatment-experienced patients. Further studies are necessary to ensure the replicability of our findings.

Data availability statement

The data analyzed in this study are subject to the following licenses/restrictions: C-YC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data are available from the National Health Insurance Research Database (NHIRD), published by the Bureau of National Health Insurance (BNHI) of the Ministry of Health and Welfare. Owing to the legal restrictions imposed by the Government of Taiwan related to the Personal Information Protection Act, the database cannot be made publicly available. The conclusions presented in this study are those of the authors and do not necessarily reflect the views of the BNHI, the Ministry of Health and Welfare. Requests to access these datasets should be directed to C-YC jk2975525@hotmail.com.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) of Kaohsiung Medical University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

Y-HH: data curation, formal analysis, investigation, methodology, validation, visualization, and writing–original draft. C-WS: conceptualization, investigation, software, and writing–review and editing. C-YC: conceptualization, formal analysis, investigation, methodology, project administration, resources, software, supervision,

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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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Drug-induced QT prolongation and torsade de pointes: a real-world pharmacovigilance study using the FDA Adverse Event Reporting System database

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Introduction: Drug-induced QT prolongation and (or) Torsade de Pointes (TdP) is a well-known serious adverse reaction (ADR) for some drugs, but the widely recognized comprehensive landscape of culprit-drug of QT prolongation and TdP is currently lacking.

Aim: To identify the top drugs reported in association with QT prolongation and TdP and provide information for clinical practice.

Method: We reviewed the reports related to QT prolongation and TdP in the FDA Adverse Event Reporting System (FAERS) database from January 1, 2004 to December 31, 2022, and summarized a potential causative drug list accordingly. Based on this drug list, the most frequently reported causative drugs and drug classes of QT prolongation and TdP were counted, and the disproportionality analysis for all the drugs was conducted to in detect ADR signal. Furthermore, according to the positive–negative distribution of ADR signal, we integrated the risk characteristic of QT prolongation and TdP in different drugs and drug class.

Results: A total of 42,713 reports in FAERS database were considered to be associated with QT prolongation and TdP from 2004 to 2022, in which 1,088 drugs were reported as potential culprit-drugs, and the largest number of drugs belonged to antineoplastics. On the whole, furosemide was the most frequently reported drugs followed by acetylsalicylic acid, quetiapine, citalopram, metoprolol. In terms of drug classes, psycholeptics was the most frequently reported drug classes followed by psychoanaleptics, analgesics, beta blocking agents, drugs for acid related disorders. In disproportionality analysis, 612 drugs showed at least one positive ADR signals, while citalopram, ondansetron, escitalopram, loperamide, and promethazine were the drug with the maximum number of positive ADR signals. However, the positive-negative distribution of ADR signals between different drug classes showed great differences, representing the overall risk difference of different drug classes.

Conclusion: Our study provided a real-world overview of QT prolongation and TdP to drugs, and the presentation of the potential culprit-drug list, the proportion

of reports, the detection results of ADR signals, and the distribution characteristics of ADR signals may help understand the safety profile of drugs and optimize clinical practice.

KEYWORDS

QT prolongation, torsade de pointes, FDA adverse event reporting system, disproportionality analysis, pharmacovigilance, adverse reaction

1 Introduction

Drug-induced QT prolongation leading to torsade de pointes (TdP) is a type of cardiotoxic adverse reaction (ADR) mainly caused by the interference of drugs in the cardiac potassium current, which can be characterized by a "twisting of the points" around the isoelectric line and exaggerated prolongation of the QT interval on the electrocardiogram (Lazzara, 1997; Roden, 2016). In the general population, it is reported that the annual incidence of drug-triggered QT prolongation and TdP is estimated to be 2.5 per million for men and 4.0 per million for women (Sarganas et al., 2014). Although the incidence of such cardiotoxic ADR is very low, it can be life-threatening, and its mortality can reach an astonishing 10%–20% (Shah, 2013).

The "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) issued the E14 clinical guidance in May 2005 to standardize the risk assessment and identification of QT prolongation of drugs before marketing, and it has currently become a standard component in new drug development programs (Darpo, 2010). However, although the safety of drugs has been strictly evaluated in clinical trials, these pre-marketing studies are usually limited to size and duration and exclude high-risk populations, so it is difficult to fully represent real-world populations and roundly detect rare but potentially life-threatening ADRs (Singh and Loke, 2012; Trifirò and Crisafulli, 2022). To facilitate a better understanding of the QT prolongation and TdP risk of drugs, the Arizona Center for Education and Research on Therapeutics (AZCERT) has summarized a drug list known as QTdrugs, which includes over 220 drugs and divides them into four risk categories based on its association with QT prolongation and TdP (Woosley et al., 2018). Undoubtedly, such a list highlights the drugs that need to be focused on and helps guide clinical management in patients who are at risk, exposed to QT-prolonging medication, or have QT prolongation (Page et al., 2016; Woosley et al., 2018; Khatib et al., 2021). However, the QTdrugs list only issued the risk information of fewer than 300 drugs, and some drugs with the potential risk of QT prolongation and TdP may not be identified and emphasized. Therefore, it is necessary to further comprehensively investigate and summarize the possible high-risk drugs related to QT interval prolongation and TdP.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems, and currently, using real-world data in pharmacovigilance databases to explore and summarize drug risk characteristics has become an important measure to evaluate drug safety (Beninger, 2018; Lucas et al., 2022). To some extent, it can break the inherent limitations of size, duration, and population selection in preclinical research and provide a real-time overview of main toxicities in a cost-effective manner, thereby providing information for clinical practice (Li et al., 2023a). In this respect, the FDA Adverse Event Reporting System (FAERS) database, a freely accessible pharmacovigilance database with massive real-world data and wide geographic coverage, provides an unprecedented opportunity to comprehensively investigate and summarize the risk of QT prolongation and TdP triggered by drugs.

In this study, we reviewed all the reports in the FAERS database that are associated with the occurrence of QT prolongation and TdP and conducted ADR signal detection for all the drugs that were reported as culprit-drugs of QT prolongation and TdP using disproportionality analysis, aiming at providing a comprehensive overview of drugs that potentially induced QT prolongation and TdP from the pharmacovigilance perspective and informing clinical practice.

2 Methods

2.1 Data source

This pharmacovigilance study was carried out based on the FAERS database, which contained post-marketing adverse event (AE) reports on drugs and therapeutic biologic products submitted by healthcare professionals, consumers, and manufacturers. At present, the FAERS database has published more than 16 million AE reports received by the FDA since 2004 on the openFDA website (https://open.fda.gov/apis/drug/), and the data are updated quarterly. The data recorded in the AE report mainly consist of seven parts: patient demographic information, drug information, adverse event information, patient outcome information, report source information, drug therapy date information, and drug indication (Cirmi et al., 2020). Those data are highly structured, so they can be retrieved and downloaded by constructing a reasonable retrieval formula through the application program interface (API) (Kass-Hout et al., 2016).

2.2 Determination of reports of interest

In FAERS, AE-related information is standardized to preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) (Brown, 2003). Standardized MedDRA Queries (SMQs) are a group containing multiple PTs, which represent signs, symptoms, diagnoses, syndromes, physical findings, and laboratory and other physiological test data likely to be relevant to the medical condition of interest (Mozzicato, 2007). There are two

TABLE 1 Preferred terms (PTs) contained in the narrow-scope search of "torsade de pointes/QT prolongation (SMQs)."

Preferred term	MedDRA code
Electrocardiogram QT prolonged	10014387
Ventricular tachycardia	10047302
Torsade de pointes	10044066
Long QT syndrome	10024803
Electrocardiogram QT interval abnormal	10063748
Long QT syndrome congenital	10057926
Torsade de pointes/QT prolongation (SMQs)[a]	20000001

[a]This is an SMQ term which includes six preferred terms in the narrow-scope search. MedDRA, Medical Dictionary for Drug Regulatory Activities; SMQs, Standardized MedDRA Queries.

TABLE 2 Two-by-two contingency table for disproportionality analysis.

	Drug of interest	Other drugs	Total
AE of interest	a	b	a + *b*
Other AEs	c	d	c + d
Total	a + c	b + d	a + *b* + c + d

AE, adverse event.

types of applications for most SMQs, namely, narrow-scope search and broad-scope search. The narrow-scope search consists of PTs that have no reasonable doubt about the medical condition of interest, while the broad-scope search contains PTs of the narrow search and the PTs that could be related to the medical condition of interest but have some uncertainty (Cirmi et al., 2020). In order to ensure the accuracy of target event recognition, in this study, only PTs contained in the narrow-scope search of "torsade de pointes/QT prolongation (SMQs)" in MedDRA 23.0 were used to identify target AE cases (Table 1).

2.3 Adverse reaction signal detection method

The reporting odds ratio (ROR) is a classic disproportionality analysis method widely used in detecting ADR signals (Sakaeda et al., 2013). The principle of the ROR method is to compare the drug exposure of cases of an AE of interest with that of cases with other reported AEs, thus reflecting the degree of correlation between the target drug and target AE (Faillie, 2019). According to the two-by-two contingency table (Table 2), the ROR value and its corresponding 95% confidence intervals (CIs) can be calculated using the following equations:

$$\mathbf{ROR} = \frac{a/c}{b/d} = \frac{ad}{bc}, \tag{1}$$

$$\mathbf{95\%\ CI} = e^{ln(ROR) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}. \tag{2}$$

Referring to the number of cases and the value of the lower limit of 95% CI, the ADR signal detection results can be further classified into negative and positive signals. A signal is considered positive when there are at least three cases (a ≥3 in Table 2) and the lower limit of 95% CI > 1, while a signal is considered negative when the number of cases or the lower limit of 95% CI cannot meet the aforementioned criteria (Li et al., 2023a).

2.4 Data processing and analysis

Referring to the API retrieval construction instructions of openFDA (https://open.fda.gov/apis/drug/event/how-to-use-the-endpoint/), the retrieval and downloading of AE reports can be realized by using the API. The returned data are in the form of a structured dataset stored in JSON format, which is convenient for further data processing and analysis. The detailed data processing and analysis steps of this study are as follows:

First, the PTs in Table 1 were used to call the API and download all the AE reports associated with QT prolongation and TdP from 1 January 2004 to 31 December 2022 from the FAERS database. If one of the PTs in Table 1 is recorded in the "patient.reaction.reactionmeddrapt" field of the AE report, we consider it a target AE report that is related to QT prolongation and TdP.

Second, the R packages "jsonlite" and "dplyr" were used to read and sort out information recorded in the downloaded dataset, including safety report ID number, patient demographic information, report years, report sources, drug use, and AE outcomes.

Third, pharmacists reviewed the generic names of the primary suspect drugs ("patient.drug.drugcharacterization" field = 1) recorded in the "patient.drug.openfda.generic_name" field in AE reports and coded the primary suspect drug based on the Anatomical Therapeutic Chemical (ATC) classification system, obtaining a final drug list with ambiguous drug names removed and synonymous drug names integrated.

Fourth, categorical statistics were conducted to summarize the top 10 drugs and ATC drug classes (second ATC level) with the highest reporting proportions in the PT and SMQ levels.

Fifth, based on the above drug list, ADR signal detection was performed on each drug at the PT and SMQ levels, yielding seven signal detection results (one for the SMQ level and six for the PT level).

Finally, based on the signal detection results at the PT and SMQs levels, the number of positive signals of each drug and the positive–negative distribution characteristics of ADR signals were summarized and integrated.

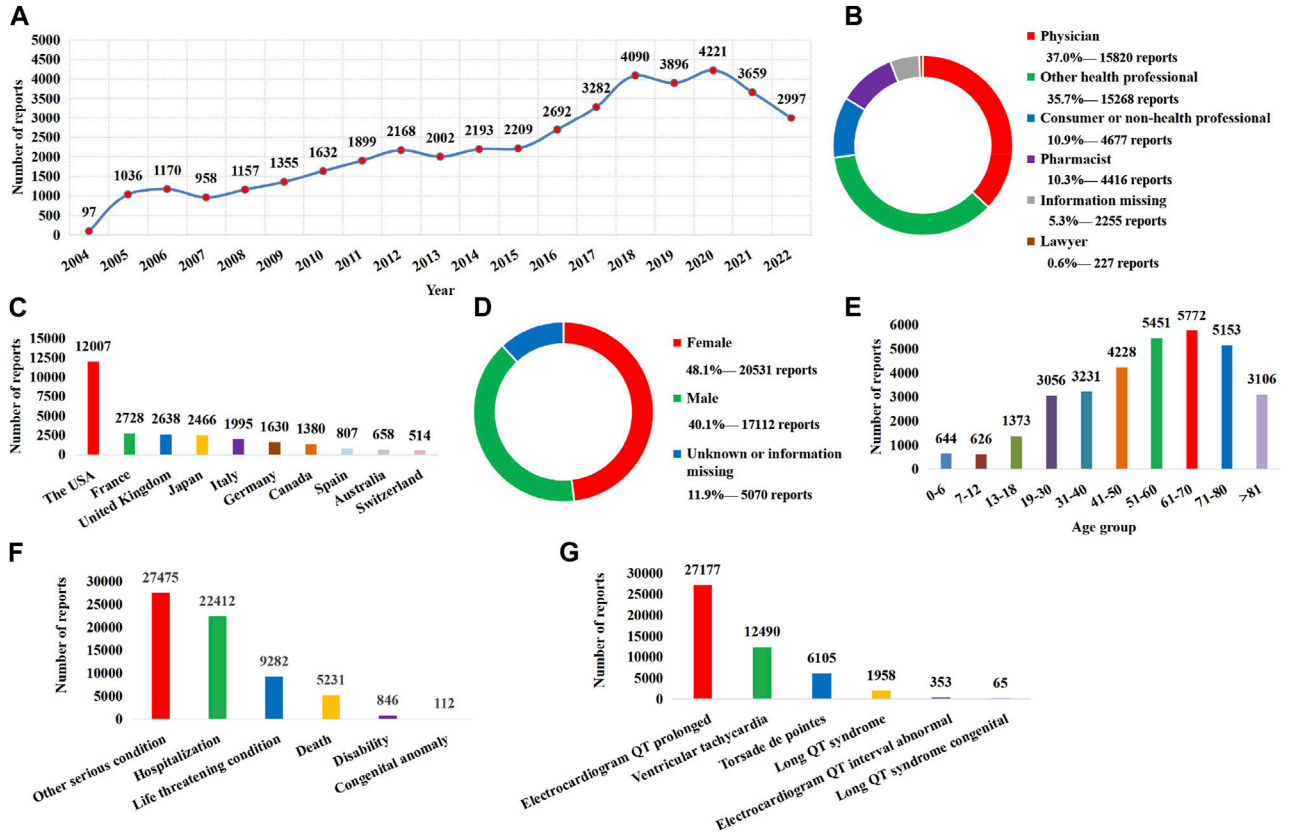

FIGURE 1
Basic information and clinical characteristics of the report associated with QT prolongation and torsade de pointes. **(A)** Distribution of the reporting years. **(B)** Distribution of report submitters. **(C)** Top 10 countries with the largest number of reports. **(D)** Sex distribution of patients. **(E)** Age distribution of patients. **(F)** Distribution of patient outcome. **(G)** Distribution of adverse event of preferred terms (PTs).

In this study, all the data processing and analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Basic information of AE reports

From 1 January 2004 to 31 December 2022, a total of 16,010,899 AE reports were included in the FAERS database, among which 42,713 were identified as target AE reports using the narrow-scope search of "torsade de pointes/QT prolongation (SMQs)." The annual distribution of AE reports related to QT prolongation and TdP is shown in Figure 1A, in which 2020 had the highest number of reports received. In terms of source and type of the report, health professionals (37.0% for physicians, 35.7% for other health professionals, and 10.3% for pharmacists) were the main submitters (Figure 1B), and the AE reports were mainly from the United States (Figure 1C). In terms of patients, the rate of women was higher than that of men (Figure 1D), and 61–70 years was the age group with the largest number of cases (Figure 1E). With regard to patient outcomes, hospitalizations accounted for 52.5% of cases, while death accounted for 12.2% of cases (Figure 1F). In the narrow-scope search of "torsade de pointes/QT prolongation (SMQs)," electrocardiogram QT prolonged is the PT involving the largest number of AE reports (Figure 1G).

3.2 Determining the drug list associated with QT prolongation and TdP

Due to an AE report usually listing multiple drugs that may be responsible for an AE of interest, there were a total of 255,992 drugs exposed to patients in 42,713 target AE reports during target AE occurrence. To obtain a final drug list to summarize the distribution of the culprit-drug and conduct ADR signal detection, non-primary suspect drugs (n = 137,527), drugs missing generic names (n = 37,288), and duplicate drugs (n = 79,746) were excluded. After that, the drug list was checked by a professional pharmacist to exclude drugs with ambiguous names (n = 95) and integrate drugs with the same active ingredient (e.g., acetaminophen and paracetamol). Finally, we obtained a drug list containing 1,088 drugs (Figure 2), each of which was considered to be responsible for the target AE occurrence in at least one report. Further associating 1,088 drugs with specific PT, the electrocardiogram QT prolonged (PT) group contained the largest number of drugs, while the long QT syndrome congenital (PT) group included the least number of drugs (Table 3).

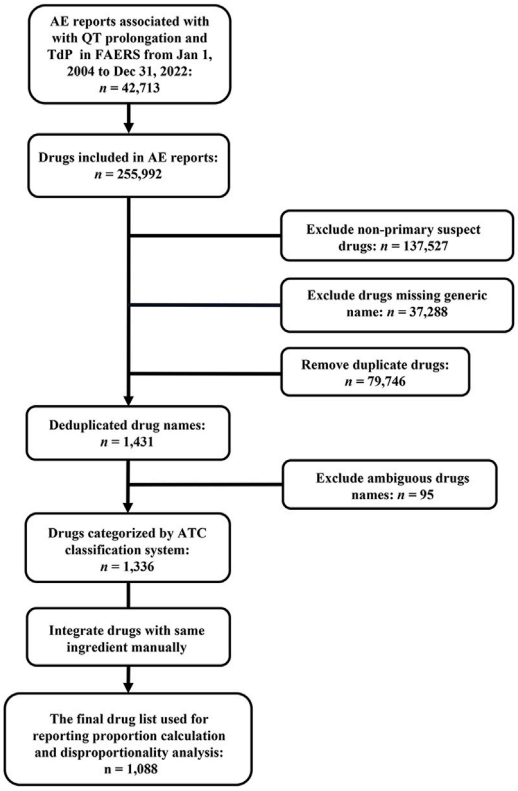

FIGURE 2
Flowchart of target report identification and potential culprit-drug summarization. AE, adverse event; ATC, Anatomical Therapeutic Chemical; FAERS, FDA Adverse Event Reporting System; TdP, torsade de pointes.

3.3 Proportional distribution of drugs in AE reports

Based on the counts of AE reports, the reporting distribution of 1,088 drugs was summarized. The top 10 most frequently reported drugs at the SMQ and PT levels are shown in Figure 3A. On the whole (at the SMQ level), furosemide (8.43%) was the most frequently reported drug, followed by acetylsalicylic acid (6.33%), quetiapine (5.60%), citalopram (4.39%), metoprolol (4.22%), olanzapine (4.14%), omeprazole (4.00%), levothyroxine sodium (3.77%), bisoprolol (3.57%), and amlodipine (3.57%). Using the ATC classification system, the 1,088 drugs were classified as the second ATC level. Similarly, according to the counts of AE reports, the top 10 most frequently reported drug classes at the SMQ and PT levels are shown in Figure 3B. On the whole (at the SMQ level), psycholeptics (24.66%) were the most frequently reported drug class, followed by psychoanaleptics (22.49%), analgesics (14.31%), beta-blocking agents (13.65%), drugs for acid-related disorders (13.17%), antineoplastic agents (12.01%), diuretics (11.85%), antibacterials (11.50%), agents acting on the renin–angiotensin system (11.02%), and cardiac therapy (10.62%).

3.4 ADR signal detection results

To evaluate the potential risk of QT prolongation and TdP for 1,088 drugs, each drug in the list was combined with PT and SMQs in Table 1, respectively, to conduct disproportionality analysis, namely, yielding seven ADR signals for each drug (one for the SMQ level and six for the PT level). Details of the ADR signal detection results of 1,088 drugs are shown in Supplementary Table S1.

For the SMQ-level group and each PT-level group, the positive–negative distribution of ADR signals of drugs and the corresponding drug category distribution are summarized in Figure 4. On the whole, there were more negative-signal drugs than positive-signal drugs in most groups. In terms of the drug class (ATC second level), antineoplastic agents (L01), antivirals for systemic use (J05), antibacterials for systemic use (J01), psycholeptics (N05), immunosuppressants (L04), antidepressants (N06), cardiac therapy (C01), agents acting on the renin–angiotensin system (C09), drugs used in diabetes (A10), and analgesics (N02) were the top ten suspicious causative drug classes involved in most groups. However, it is noteworthy that there was a big difference in ADR signal distribution between different drug classes.

To further summarize the risk characteristics of 1,088 drugs, we integrated the total number of positive signals of each drug. For each drug that underwent disproportionality analysis, the sum of the number of positive signals may be between 0 and 7, and the positive-signal number distribution of 1,088 drugs is shown in Table 4.

TABLE 3 Number of drugs associated with the SMQ group and PT subgroup.

Group	No. (%) of drugs
Electrocardiogram QT prolonged	983 (90.3)
Ventricular tachycardia	966 (88.8)
Torsade de pointes	675 (62.0)
Long QT syndrome	524 (48.2)
Electrocardiogram QT interval abnormal	276 (25.4)
Long QT syndrome congenital	52 (4.8)
Torsade de pointes/QT prolongation (SMQs)[a]	1,088 (100.0)

[a]This is an SMQ term, which includes six preferred terms in the narrow-scope search. SMQs, Standardized MedDRA Queries.

A

PT group	Reporting proportions of the top 10 drugs									
	1	2	3	4	5	6	7	8	9	10
EQTP (n =27,177)	Quetiapine (7.41%)	Furosemide (6.72%)	Olanzapine (5.51%)	Citalopram (5.36%)	Acetylsalicylic acid (4.38%)	Omeprazole (4.07%)	Clozapine (4.04%)	Levothyroxine sodium (3.96%)	Amlodipine (3.81%)	Fluoxetine (3.76%)
VT (n =12,490)	Furosemide (12.07%)	Acetylsalicylic acid (11.16%)	Metoprolol (7.46%)	Digoxin (6.17%)	Spironolactone (5.19%)	Clopidogrel (4.82%)	Carvedilol (4.56%)	Bisoprolol (4.43%)	Warfarin (4.08%)	Pantoprazole (3.98%)
TdP (n =6,105)	Furosemide (12.56%)	Citalopram (6.04%)	Ondansetron (5.96%)	Methadone (5.67%)	Acetylsalicylic acid (5.05%)	Fluoxetine (5.03%)	Metoprolol (4.90%)	Digoxin (4.68%)	Amiodarone (4.44%)	Bisoprolol (4.32%)
LQTS (n =1,958)	Furosemide (8.07%)	Ondansetron (6.33%)	Omeprazole (6.33%)	Citalopram (5.98%)	Quetiapine (5.92%)	Acetylsalicylic acid (5.67%)	Escitalopram (5.01%)	Fluoxetine (4.49%)	Olanzapine (4.34%)	Clarithromycin (3.63%)
EQTIA (n =353)	Quetiapine (10.76%)	Olanzapine (5.67%)	Citalopram (5.38%)	Ribociclib (5.38%)	Risperidone (5.10%)	Clozapine (5.10%)	Acetylsalicylic acid (4.82%)	Nilotinib (3.97%)	Escitalopram (3.68%)	Metoprolol+3 (3.40%) [a]
LQTSC (n =65)	Ondansetron (27.69%)	Fluoxetine (13.85%)	Propofol (13.85%)	Ampicillin (13.85%)	Levofloxacin (12.31%)	Omeprazole (10.77%)	Furosemide (9.23%)	Lidocaine (9.23%)	Midazolam (9.23%)	Amlodipine+6 (7.69%) [b]
SMQs (n =42,713)	Furosemide (8.43%)	Acetylsalicylic acid (6.33%)	Quetiapine (5.60%)	Citalopram (4.39%)	Metoprolol (4.22%)	Olanzapine (4.14%)	Omeprazole (4.00%)	Levothyroxine sodium (3.77%)	Bisoprolol (3.57%)	Amlodipine (3.57%)

B

PT group	Reporting proportions of the top 10 chemical drug subclasses									
	1	2	3	4	5	6	7	8	9	10
EQTP (n =27,177)	Psycholeptics N05 (30.18%)	Psychoanaleptics N06 (27.11%)	Antineoplastic agents L01 (13.47%)	DARD A02 (13.10%)	Analgesics N02 (12.51%)	Antibacterials J01 (11.96%)	Beta blocking agents C07 (10.85%)	Diuretics C03 (9.57%)	AARAS C09 (8.66%)	Antiepileptics N03 (8.40%)
VT (n =12,490)	Beta blocking agents C07 (19.62%)	Analgesics N02 (19.15%)	Cardiac therapy C01 (17.82%)	Diuretics C03 (17.01%)	AARAS C09 (16.98%)	Antithrombotic agents B01 (14.79%)	DARD A02 (13.75%)	Psycholeptics N05 (13.39%)	Psychoanaleptics N06 (13.10%)	Antineoplastic agents L01 (10.42%)
TdP (n =6,105)	Psychoanaleptics N06 (22.92%)	Psycholeptics N05 (19.34%)	Antibacterials J01 (16.94%)	Diuretics C03 (16.86%)	Beta blocking agents C07 (16.48%)	Cardiac therapy C01 (15.74%)	DARD A02 (12.76%)	Analgesics N02 (11.43%)	AARAS C09 (10.11%)	Antithrombotic agents B01 (8.70%)
LQTS (n =1,958)	Psychoanaleptics N06 (25.33%)	Psycholeptics N05 (23.65%)	Antibacterials J01 (16.75%)	DARD A02 (14.50%)	Analgesics N02 (11.75%)	Beta blocking agents C07 (10.98%)	Diuretics C03 (10.52%)	AARAS C09 (7.35%)	Antiepileptics N03 (7.15%)	Cardiac therapy C01 (6.59%)
EQTIA (n =353)	Psycholeptics N05 (31.73%)	Psychoanaleptics N06 (20.40%)	Antineoplastic agents L01 (18.41%)	Analgesics N02 (11.05%)	AARAS C09 (8.78%)	DARD A02 (7.65%)	Beta blocking agents C07 (7.65%)	Immunosuppressants L04 (6.80%)	Lipid modifying agents C10 (5.95%)	Cardiac therapy+1 C01 (5.10%) [c]
LQTSC (n =65)	Psychoanaleptics N06 (33.85%)	AA A04 (27.69%)	Anesthetics N01 (18.46%)	Antibacterials J01 (15.38%)	Psycholeptics N05 (13.85%)	DARD A02 (10.77%)	Antihistamines R06 (10.77%)	Antithrombotic agents B01 (9.23%)	Diuretics C03 (9.23%)	Analgesics+2 N02 (7.69%) [d]
SMQs (n =42,713)	Psycholeptics N05 (24.66%)	Psychoanaleptics N06 (22.49%)	Analgesics N02 (14.31%)	Beta blocking agents C07 (13.65%)	DARD A02 (13.17%)	Antineoplastic agents L01 (12.01%)	Diuretics C03 (11.85%)	Antibacterials J01 (11.50%)	AARAS C09 (11.02%)	Cardiac therapy C01 (10.62%)

FIGURE 3
Proportional distribution of drugs associated with QT prolongation and torsade de pointes in adverse event reports. **(A)** Top 10 highest reporting proportion agents at the Standardized MedDRA Queries (SMQs) and preferred term (PT) levels. **(B)** Top 10 highest reporting proportion drug classes at the SMQ and PT levels. AA, antiemetics and antinauseants; AARAS, agents acting on the renin–angiotensin system; DARD, drugs for acid-related disorders; EQTIA, electrocardiogram QT interval abnormal; EQTP, electrocardiogram QT prolonged; LQTS, long QT syndrome; LQTSC, long QT syndrome congenital; TdP, torsade de pointes; VT, ventricular tachycardia. [a] There are three other drugs (lorazepam, lithium, and fingolimod) with the same reporting proportion as that of metoprolol. [b] There are six other drugs (bupropion, promethazine, warfarin, fentanyl, alprazolam, and methylphenidate) with the same reporting proportion as that of amlodipine. [c] There is one other drug class, antiepileptics (N03) with the same reporting proportion as that of cardiac therapy. [d] There are two other drug classes, muscle relaxants (M03) and calcium channel blockers (C09) with the same reporting proportion as that of analgesics (N02).

Among 1,088 drugs, 476 (43.8%) drugs did not show any positive ADR signal. Among the drugs that had at least one positive ADR signal, five drugs (citalopram, ondansetron, escitalopram, loperamide, and promethazine) contained the maximum number of positive ADR signals, i.e., each drug contained seven positive ADR signals. The sum of the number of positive signals of each drug is listed in Supplementary Table S1.

4 Discussion

Drug-induced QT prolongation and TdP is an interdisciplinary drug safety issue that has received much attention, which can result in sudden cardiac death. This study comprehensively evaluated the AE reports of drug-induced QT prolongation and TdP in the real world based on the FAERS database. We described the basic characteristics of the AE report of QT prolongation and TdP and summarized a list containing 1,088 drugs that were reported as the potential culprit-drugs of QT prolongation and TdP. Meanwhile, based on this drug list, we made statistics on the reporting proportion of different drugs and drug classes and conducted ADR signal detection and signal distribution integration for each drug.

In this study, a drug list containing all the primary suspected culprit-drugs of QT prolongation and TdP in FAERS was provided. To the best of our knowledge, this list, which contained 1,088 potential causative drugs of QT prolongation and TdP, is the most comprehensive list summarized using a pharmacovigilance database so far. Although previous studies have tried to use a pharmacovigilance database to explore and summarize high-risk drugs associated with QT prolongation and TdP (Poluzzi et al., 2010; Teng et al., 2019; Cirmi et al., 2020; Ali et al., 2021; He et al., 2021; Wu et al., 2022; Yu and Liao, 2022; Chen et al., 2023), the list provided by these studies is not comprehensive enough. The most related studies only pay attention to a certain drug class and, on this basis, evaluate and compare the risks of limited drugs, such as H1-antihistamines (Ali et al., 2021), antifungal triazoles (Yu and Liao, 2022), antibacterial drugs (Teng et al., 2019), antipsychotics (He et al., 2021), tyrosine kinase inhibitors (Cirmi et al., 2020), and antidepressants (Chen et al., 2023). Although those studies highlighted the drugs worthy of attention in the same category, it is difficult to rationally integrate them into a list because of the difference in data time included, inclusion and exclusion criteria of AE reports, and ADR signal detection methods. In order to overcome those limitations, Wu et al. (2022) investigated and evaluated all risky drugs associated with TdP according to the FAERS database with a unified standard. However, it only selected one of the PTs (torsade de pointes, MedDRA code: 10044066) in "torsade de pointes/QT prolongation (SMQs)" to identify target AE reports and only showed the top 50 most frequently reported drugs and the top 50 risky drugs with the

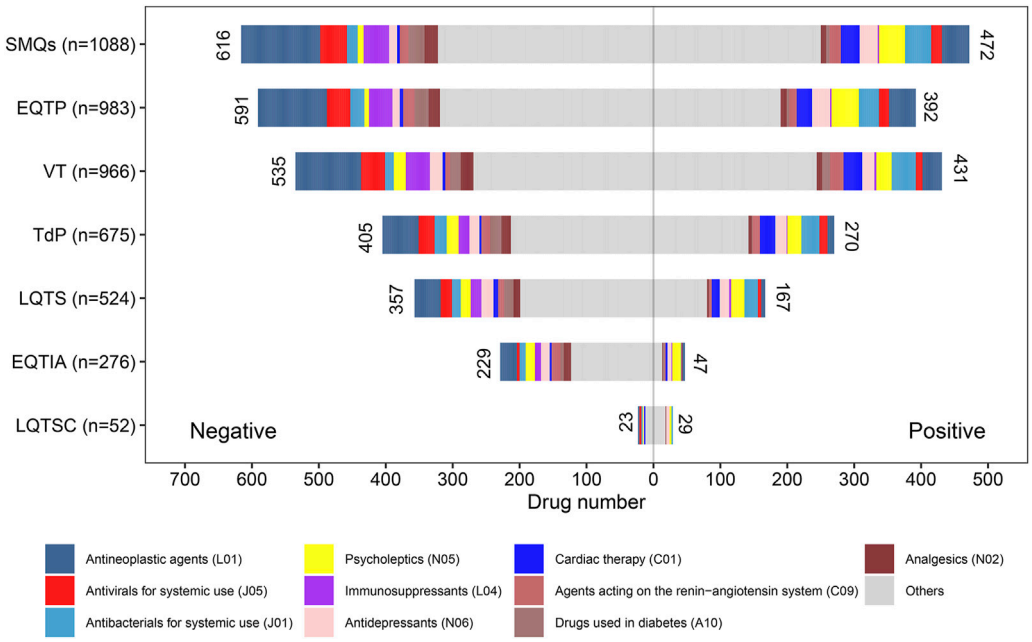

FIGURE 4
Drug class distribution of potential culprit-drugs and the positive–negative distribution of adverse reaction signals at the Standardized MedDRA Queries (SMQs) and preferred term (PT) levels. EQTIA, electrocardiogram QT interval abnormal; EQTP, electrocardiogram QT prolonged; LQTS, long QT syndrome; LQTSC, long QT syndrome congenital; TdP, torsade de pointes; VT, ventricular tachycardia.

TABLE 4 Distribution of the number of positive ADR signals.

Number of positive ADR signals	No. (%) of drugs
7	5 (0.5%)
6	38 (3.5%)
5	88 (8.1%)
4	98 (9.0%)
3	117 (10.8%)
2	137 (12.6%)
1	129 (11.9%)
0	476 (43.8%)
Total	1,088 (100.0%)

ADR, adverse reaction.

highest ADR signal strength. As shown in Table 1, QT prolongation and TdP are medical conditions consisting of a series of closely related PTs, which means that "torsade de pointes (PT)" can only be used to identify part of AE reports associated with QT prolongation and TdP and summarize part of potential causative drugs related to QT prolongation and TdP (Figure 1G; Table 3). Therefore, the limitation of target AE report identification and drug display cannot fully support it to provide a precise and comprehensive drug list for QT prolongation and TdP. In our study, the narrow search of "torsade de pointes/QT prolongation (SMQs)" was used to identify target AE reports, which greatly ensured the rationality and completeness of our drug list.

In addition to offering a complete drug list, this study also provided a multi-dimensional evaluation perspective. First, we showed the top 10 most frequently reported drugs and drug classes at the SMQ and PT levels, respectively, to locate the drugs and drug classes worthy of attention. For example, furosemide was the most frequently reported drug at the SMQ level in our study. Previous studies have shown that exposure to furosemide is a risk factor for QT prolongation and TdP, and the potential mechanism underlying it may be related to the electrolyte disorder caused by furosemide (Drew et al., 2010). Similarly, psycholeptics (N05) were the most frequently reported drugs at the SMQ level in our study, and previous studies have also proven that psycholeptics are closely related to QT prolongation and TdP (Beach et al., 2013). Therefore, according to this report's proportion result, we can use it to quickly understand the drugs and drug classes that commonly result in QT prolongation and TdP in the real world. However, it is worth noting that a high reporting ratio does not always represent a high risk because, for different drugs, the frequency of drug use will vary greatly, which will directly affect the proportion of ADR reports.

Based on the reasons mentioned above, we introduced the disproportionality analysis method as a uniform standard to evaluate the risk of QT prolongation and TdP of drugs. Although previous studies have used similar ADR signal mining methods to explore the QT prolongation and TdP risk of drugs, the scope of those research studies mainly focused on specific drug classes and specific PTs (Poluzzi et al., 2010; Teng et al., 2019; Cirmi et al., 2020; Ali et al., 2021; He et al., 2021; Wu et al., 2022; Yu and Liao, 2022; Chen et al., 2023). Therefore, it is

difficult to use the results of those studies to reasonably compare the QT prolongation and TdP risks of drugs in different drug categories. In our study, based on a comprehensive drug list containing 1,088 drugs, the ADR signals at the SMQ and PT levels were thoroughly detected (Supplementary Table S1), which eliminated the obstacles of cross-drug class and cross-PT risk comparison. In addition, in order to present the risk characteristics of a drug as a whole (Li et al., 2023a; Li et al., 2023b), the sum of the number of positive signals for each drug was calculated. Among the 1,088 drugs, 612 drugs have at least one positive ADR signal, which suggests that we need to pay attention to the QT prolongation and TdP risk of these drugs, especially those with multiple positive ADR signals. For example, the drugs with seven positive ADR signals, citalopram (Beach et al., 2013; Fung et al., 2021), ondansetron (Hafermann et al., 2011; Lee et al., 2017), escitalopram (Fung et al., 2021), loperamide (Swank et al., 2017), and promethazine (Ali et al., 2021), have been reported as potential high-risk drugs for QT prolongation and TdP. In this connection, if we use this index reasonably, it can be used as a quick tool to understand the risk characteristics of a certain drug and provide its safety information.

Furthermore, based on the results of drug ADR signal detection, we also paid special attention to the positive–negative distribution of ADR signals across different drug categories at the SMQ and PT levels (Figure 4). On the whole (at SMQs level), antineoplastic agents (L01) are the drug class involving the largest number of drugs reported as potential culprit-drugs, and it is also the drug class that contains the largest number of drugs with positive ADR signals. Although previous studies have recognized the potential association between antineoplastic agents and cardiac rhythm disorders (Alexandre et al., 2018; Roden, 2019; Salem et al., 2021) and put forward corresponding risk evaluation and management measures (Sarapa and Britto, 2008; Coppola et al., 2018), the status of antineoplastic agents was not prominent among various risk drug classes. Our results suggest that antineoplastic agents have become the top drug class that trigger QT prolongation and TdP, so we should pay more attention to the heart safety of antineoplastic drugs, especially under the current background concerning the development and clinical application of antineoplastic drugs. Following antineoplastic agents (L01), antivirals for systemic use (J05), antibacterials for systemic use (J01), psycholeptics (N05), and immunosuppressants (L04) were the drug classes with the largest number of drugs that were reported to trigger QT prolongation and TdP. However, it is noteworthy that there was a big difference in ADR signal positive–negative distribution among the above-mentioned drug classes, in which most drugs in antibacterials for systemic use (J01) and psycholeptics (N05) showed a positive ADR signal, while most drugs in antivirals for systemic use (J05) and immunosuppressants (L04) showed a negative ADR signal. To some extent, such a difference in ADR signal positive–negative distribution can be explained by the risk difference of QT prolongation and TdP in different drug classes. In the previous literature, the risk of QT prolongation and TdP is well-recognized and prominent in antibacterials and psycholeptics (Straus et al., 2004; Sicouri and Antzelevitch, 2008; Ray et al., 2009; Abo-Salem et al., 2014), but such a risk is undefined in antivirals and immunosuppressants, which means that the overall QT prolongation and TdP risk of antibacterials and psycholeptics may be higher than that of antivirals and immunosuppressants. In this regard, our study provided a landscape to understand and compare the overall risk of different drug categories.

We acknowledge that our study also has some inherent limitations. First, the true incidence of QT prolongation and TdP with the use of drugs cannot be evaluated because the exact denominator of patients exposed to each drug is unknown. Second, due to the voluntary nature of reporting to FAERS, AE reports with variable degrees of exhaustivity may have an uncertain influence on the result. Third, multiple factors, such as the extent of use of the product, publicity, the nature of the reactions, underreporting, Weber effect, and notoriety bias (Hoffman et al., 2014; Alatawi and Hansen, 2017; Bihan et al., 2020; Neha et al., 2021), may influence the final number of AE reports for a particular drug and drug class, thereby causing a deviation on report proportion statistics and ADR signal detection. Forth, many factors, including sex, age, drug–drug interactions induced by concomitant drugs (Kim et al., 2020), dosage and duration of drugs used, and complications of the patients, may potentially affect the occurrence of QT prolongation and TdP. However, it is almost impossible to shield the potential interference of those confounding factors to the ADR detection results due to the inherent limitations of the pharmacovigilance database, so it is necessary to further investigate the potential influence of these factors on the occurrence of QT prolongation and TdP in a well-designed study. Finally, the results of ADR signal detection only reflect the statistical correlation between the target drug and the target AE, and all hypotheses generated require validation by translational mechanistic or prospective studies.

5 Conclusion

Based on the review of the publicly available FAERS data, our study summarized a comprehensive potential culprit-drug list of QT prolongation and TdP, obtained the statistics of the most frequently reported causative drugs and drug classes of QT prolongation and TdP, conducted ADR signal detection, and integrated the ADR signal detection results. To some extent, our study provided a preliminary whole picture of the potential culprit-drugs for QT prolongation and TdP in the real world, which can help regulators, health professionals, and others involved in drug management better understand the risk of QT prolongation and TdP for different drugs and optimize clinical practice. However, our study also has many limitations due to the nature of the pharmacovigilance database. It is particularly noteworthy that ADR signals only represent a statistical relationship between drugs and AE, and the real causal relationship between them needs further verification in a well-designed study. Therefore, in clinical practice, ADR signals can only be used as reference evidence and cannot replace the professional opinions of cardiologists and (or) clinical pharmacists.

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

DL: data curation, formal analysis, methodology, visualization, writing–original draft, and writing–review and editing. SC: data curation, formal analysis, methodology, writing–original draft, and writing–review and editing. HW: data curation, visualization, and writing–review and editing. JD: data curation and writing–review and editing. CQ: data curation and writing–review and editing. DD: data curation and writing–review and editing. YW: data curation and writing–review and editing. QD: conceptualization, writing–original draft, and writing–review and editing. SL: conceptualization, writing–original draft, and 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.2023.1259611/full#supplementary-material

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Contrastive analysis on the safety of brand and generic nebivolol: a real-world pharmacovigilance study based on the FDA adverse event reporting system

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Background: The equivalence of generic drugs to their brand-name counterparts is a controversial issue. Current literature indicates disparities between the generic nebivolol (GN) and the brand nebivolol (BN).

Aim: The study is designed to investigate the safety difference between GN and BN and provide reference information for clinical practice.

Methods: We reviewed adverse event (AE) reports that recorded nebivolol as the primary suspect drug in the FDA Adverse Event Reporting System (FAERS) database from 2004 to 2022, conducted a disproportional analysis to detect signals for the GN and BN respectively, and compared the AE heterogeneity between them using the Breslow-Day test.

Results: A total of 2613 AE reports of nebivolol were recorded in the FAERS database from 2004 to 2022, of which 2,200 were classified as BN, 346 as GN, and 67 unclassifiable AE reports were excluded. The signals of 37 AEs distributed in cardiac, gastrointestinal, psychiatric, and nervous systems were detected in disproportional analysis. 33 out of 37 AEs were positive signals, with 21 not previously listed on the drug label, indicating an unrecognized risk with nebivolol. In the heterogeneity analysis of AE signals between GN and BN, the GN generally showed a higher AE signal value than BN, especially 15 AEs distributed in the cardiac, neurological, and psychiatric systems that showed statistically significantly higher risk by taking GN.

Conclusion: Our study shows some previously overlooked adverse effects of nebivolol. It suggests that the risk of GN's adverse effects may be higher than those in BN, which deserves further attention and investigation by healthcare professionals, regulators, and others.

KEYWORDS

nebivolol, original drug, generic drug, FDA adverse event reporting system, disproportional analysis, adverse reaction

1 Introduction

Brand drugs are original drugs that undergo extensive testing and clinical trials before being approved for marketing, in which substantial financial resources and time are invested. Correspondingly, generic drugs refer to the equivalent substitute manufactured based on the original drug formula, which is the same as brands in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use (Rana and Roy, 2015). Since generic drugs usually have a lower cost of running and market prices than brands, they have accounted for a significant share of the global pharmaceutical market, accounting for 86% in the United States, 68.6% in Canada, and 17%–83% in Europe (Bayram et al., 2021). Generic drugs have indeed become the cornerstone for providing affordable medicines to patients. However, although generic drugs and brands have the same active ingredient, generic drugs may be different from brands in an inert binder, tablet color, and manufacturing process, which may result in variations in safety profiles (van der Meersch et al., 2011; Andrade, 2015). Meanwhile, studies have demonstrated that the generic drugs may not be clinically equivalent to brands. For example, one study showed that generic clopidogrel might have a higher safety risk in real-world than the original drug, and another study showed that the development of seizures or unexpected may occur when brand antiepileptics such as sodium valproate and lamotrigine are switched to the generic drugs (Bialer and Midha, 2010; Serebruany et al., 2019). Therefore, clinicians, scientific societies, and patients have expressed many concerns about generic drugs' long-term efficacy and safety and the consequences of potentially multiple switches being dictated by economic pressure rather than medical needs (Sarzi-Puttini et al., 2019). Generic drugs typically have shorter development cycles and they are approved for clinical use based on small bioequivalence studies. The inherent limitations of generic drugs' development make them invariably focus on observing effectiveness indicators and need long-term or large-sample safety studies (Glerum et al., 2020). Therefore, it is necessary to continue to pay attention to the difference in efficacy and safety between generics and brands and explore feasible evaluation strategies.

Nebivolol is a novel beta-blocker (β-blocker) approved by the US Food and Drug Administration (FDA) in 2007, which exhibits highly selective in β1 receptors and exerts unique pharmacological properties by activating the nitric oxide synthase (NOS) pathway by activating β3 receptor in the endothelium (Fongemie and Felix-Getzik, 2015). Compared with other β-blocker, nebivolol has certain advantages in the treatment of hypertension, including the significant improvements in endothelial dysfunction, central hemodynamics, the degree of erectile dysfunction in men, a beneficial metabolic profile, and a more favorable side effect profile (Olawi et al., 2019). In recent years, the generic nebivolol (GN) has been emerging. However, there is still a lack of comparative data between GN and brand nebivolol (BN) to guide clinicians in deciding whether generic substitution is appropriate. Moreover, a study that compared the difference between GN and BN in pharmacokinetic and pharmacodynamic properties attracts our attention. The study showed that although the comparison of the pharmacokinetic parameters of GN and BN met the criteria, a difference existed in the impact on the heart rate of the subjects between them (Bambysheva et al., 2016), which stimulated our interest in further exploring the difference in efficacy and safety between GN and BN.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem, and the establishment and application of a pharmacovigilance database is an essential integral part of it (Beninger, 2018). The pharmacovigilance databases are widely used to conduct post-marketing surveillance of drugs in the real world and to provide the public with information on possible adverse drug events (AEs). In this regard, the FDA Adverse Event Reporting System (FAERS) database, a database with a large population, comprehensive geographic coverage, and publicly available accessibility, has become one of the essential data sources that is commonly used for research in the field of pharmacovigilance (Li et al., 2023). Meanwhile, previous literature has also confirmed the feasibility of using FAERS to explore safety differences between generic drugs and brands (Rahman et al., 2017b; Cheng et al., 2018). In this study, we reviewed and analyzed the AE data in the FAERS database to investigate drug safety differences for BN and GN, expecting to provide health professionals and patients with information on drug safety for clinical use and selection.

2 Methods

2.1 Data source

The FAERS database is generated from the FDA's post-marketing safety surveillance program. It contains AE and medication error reports submitted by healthcare professionals, consumers, manufacturers, or others aware of AEs in patients. The AE data in the FAERS database is highly structured and available, and all the AEs are converted to standardized terminology called Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The FAERS database has publicly opened more than 10 million AE reports received by the FDA since 2004 and is updated quarterly. In this study, we used OpenVigil 2.1 (http://h2876314.stratoserver.net:8080/OV2/search/), an open tool for data mining and analysis of pharmacovigilance data using cleaned FAERS adverse event reports, to retrieve and extract the structured data of nebivolol in the FAERS database from the first quarter of 2004 to the fourth quarter of 2022 (Li et al., 2022).

2.2 AE reports extraction, processing, and differentiation

The present study investigated the BN and GN in the FAERS database. Firstly, we extracted all the raw data of AE reports containing nebivolol in the FAERS database from 2004 to 2022 through OpenVigil 2.1. Secondly, to accurately collect the AE reports mainly attributed to nebivolol, we screened out the reports with nebivolol as the primary suspect according to the recorded role of nebivolol in the AE report. Thirdly, we went through each AE case according to the safety report ID (ISR) number and reviewed the trade name, manufacturer, and new drug application (NDA) or abbreviated new drug application (ANDA) number to classify nebivolol into BN and GN. If the nebivolol is

TABLE 1 The two-by-two contingency table for disproportional analysis.

	Drug of interest	Other drugs	Total
AEs of interest	a	b	a+b
Other AEs	c	d	c + d
Total	a+c	b + d	a+b + c + d

AEs, adverse events.

recorded with the tradename "BYSTOLIC," the NDA number "021742," or the submitter is from Allergan or Frost, we consider it the BN. On the contrary, if the submitter is from Ani, Alkem, Watson, Glenmark, Hetero, Indchemie, Torrent, Micro Labs, Cadila, Aurobindo, Prinston, Reyoung, Ajanta, Unichem, Mankind, Beximco, or the ANDA number is the same as the generic drug on file (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021742), we consider it as the GN. When the AE report is indistinguishable, we exclude it. Finally, according to the ISR number, the report characteristics of BN and GN were counted, including patient age, sex, and AE outcomes.

2.3 Data statistics and analysis

To determine the target ADR for analysis, we searched the most common ADRs based on literature and the label from the FDA official website. The most common AEs were headache, dizziness, nausea, diarrhea, tiredness, and bradycardia, of which bradycardia, nausea, and headache may lead to discontinuation (Riva and Lip, 2011; Hanif et al., 2023). We mapped the above ADRs to their primary system organ class (SOC) according to MedDRA 26.0, mainly involving nervous system disorders, gastrointestinal disorders, and cardiac disorders. Moreover, highly lipid-soluble β-blockers are centrally enriched in the central nervous system and may lead to psychiatric disorders (Kumar et al., 2007), and this SOC is also the one that the label of nebivolol focuses attention on. Therefore, this study explored the AE signals in the above four SOCs to compare the safety difference between GN and BN.

In this study, the reporting odds ratio (ROR), a well-established algorithm of disproportional analysis method, was used to detect ADR signals. The two-by-two contingency table used for the calculation is shown in Table 1, and the ROR value and its corresponding 95% confidence interval (CI) can be calculated by following the formula (Sakaeda et al., 2013):

$$\mathbf{ROR} = \frac{a/c}{b/d} = \frac{ad}{bc} \tag{1}$$

$$\mathbf{95\%\ CI} = e^{ln(ROR) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}} \tag{2}$$

A positive ADR signal is defined as the number of AE reports greater than or equal to 3 (a ≥3 in Table 1) and the lower-bound 95% CI of ROR value greater than 1, while a negative signal is defined as the number of AE reports or the lower-bound 95% CI of ROR value cannot reach above criterion (Li et al., 2023). Besides, referring to previous literature (Rahman et al., 2017a), the Breslow-Day test was used to test the heterogeneity of ROR between GN and BN, and significantly statistical difference was existed when $p < 0.01$.

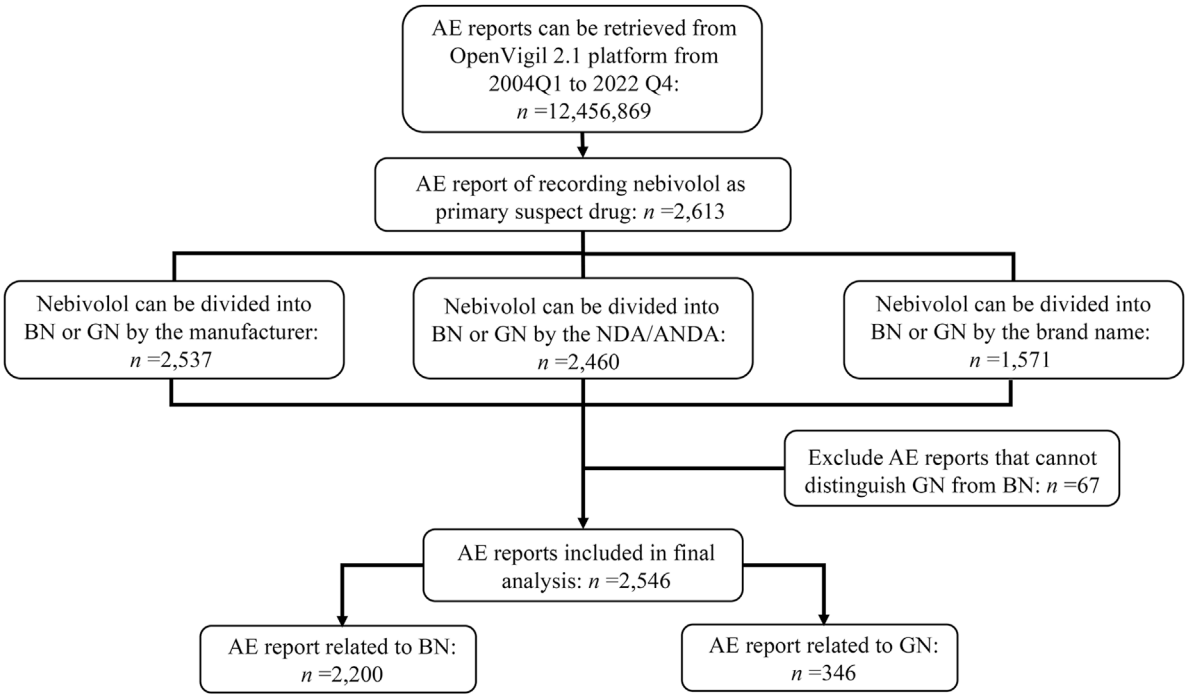

FIGURE 1
Flowchart of target reports identification and reporting subgroup summarization. Abbreviate: Q, quarter; NDA, new drug application; ANDA, abbreviated new drug application; BN, brand nebivolol; GN, generic nebivolol.

TABLE 2 Demographic characteristics of patients for nebivolol.

Parameters	BN		GN	
	Number of AE reports (N = 2200)	Ratio (%)	Number of AE reports (N = 346)	Ratio (%)
Gender				
Female	1186	53.91	135	39.02
Male	766	34.82	133	38.44
Information missing	248	11.27	78	22.54
Age group				
<18	51	2.32	37	10.69
18–44	127	5.77	22	6.36
45–64	443	20.14	68	19.65
>64	564	25.64	132	38.15
Information missing	1015	46.14	87	25.15
Patient outcomes				
Hospitalization or prolonged	334	15.18	161	46.53
Death	68	3.09	16	4.62
Life-Threatening	42	1.91	29	8.38
Disability	17	0.77	3	0.87
Congenital Anomaly	2	0.09	9	2.60
Other serious conditions	546	24.82	181	52.31

A report contains more than one outcome. BN, brand nebivolol; GN, generic nebivolol.

3 Results

3.1 Descriptive analysis

12,456,869 AE reports were retrieved using the OpenVigil 2.1 platform between the first quarter of 2004 and the fourth quarter of 2022, in which 2,613 reports recorded nebivolol as the primary suspect drug. Further, examining the corresponding trade names, NDA/ANDA number, and manufacturer of nebivolol, 67 reports that cannot be distinguished between GN and BN were excluded. Of the remaining 2,546 ADR reports, 2,200 were classified into BN, and 346 were classified into GN. The identification details of GN's and BN's reports are shown in Figure 1. The demographic features of those reports are tallied in Table 2. Among patients suffering AEs of nebivolol, BN and GN share the same trend in gender, with more females than males, and the patients are mainly aged (>64 years old). Regarding patient outcome, the outcomes of cases affected by BN and GN were mainly hospitalization-initial or prolonged, accounting for 334 (15.18%) and 161 (46.53%), respectively.

3.2 AE signal detection results

In our study, we detected 37 AE signals in four interested SOCs by the ROR method and compared the statistical differences of AE signals for BN and GN in different PTs using the Breslow-Day test. GN and BN totally detected 33 positive AE signals. Among the positive signals we detected, 12 PTs were recorded in the drug label, and 21 were not. The result of the AE signal detected in the cardiac system (SOC) was shown in Figure 2, which contained seven PTs related to cardiac AEs recorded in the insert and two PTs not recorded. Among the evaluated nine PTs, three PTs, namely, cardiac arrest, ventricular tachycardia, and unstable angina, showed opposition between negative and positive signals. However, only angina unstable instability showed statistical significance ($p < 0.001$) according to the Breslow-Day test, suggesting a higher risk for GN. Furthermore, although both the BN and GN showed a positive ADR signal in atrial fibrillation and arrhythmia, the risk of the GN was significantly higher ($p < 0.001$).

A similar analysis was performed on the gastrointestinal system (SOC), and seven PTs were evaluated (Figure 3). Results showed that the BN and GN only exhibited a significant difference in nausea ($p < 0.001$), an AE recorded in the package insert. In addition, although two positive signals, namely, abdominal pain, and vomiting, were only detected in BN, the risk difference between BN and GN cannot be compared due to the missing ADR signal in GN.

In the psychiatric system (SOC), the ADR signals of nine PTs were evaluated (Figure 4), in which only one PT (insomnia) was recorded in the package insert. On the whole, GN showed a higher ADR risk in the psychiatric system than BN, especially significant in anxiety ($p < 0.001$), suicide attempt ($p = 0.003$),

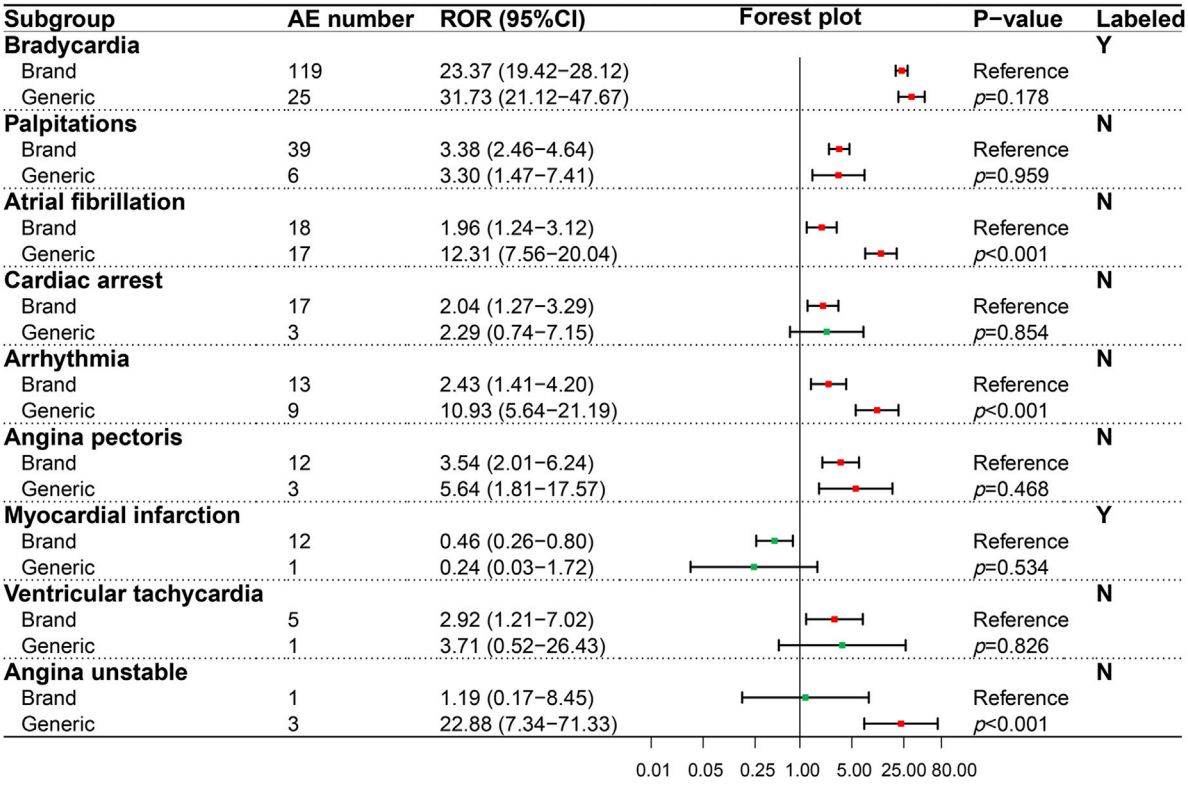

FIGURE 2
Comparison of detected AE signals for brand and generic nebivolol in the cardiac system. Abbreviate: AE, adverse event; ROR, reporting odd ratio; CI, confidence interval. Note: Red points indicate positive signals and green points are opposite; the *p*-value results from the Breslow-Day test; label information comes from the US Food and Drug Administration (FDA) official website.

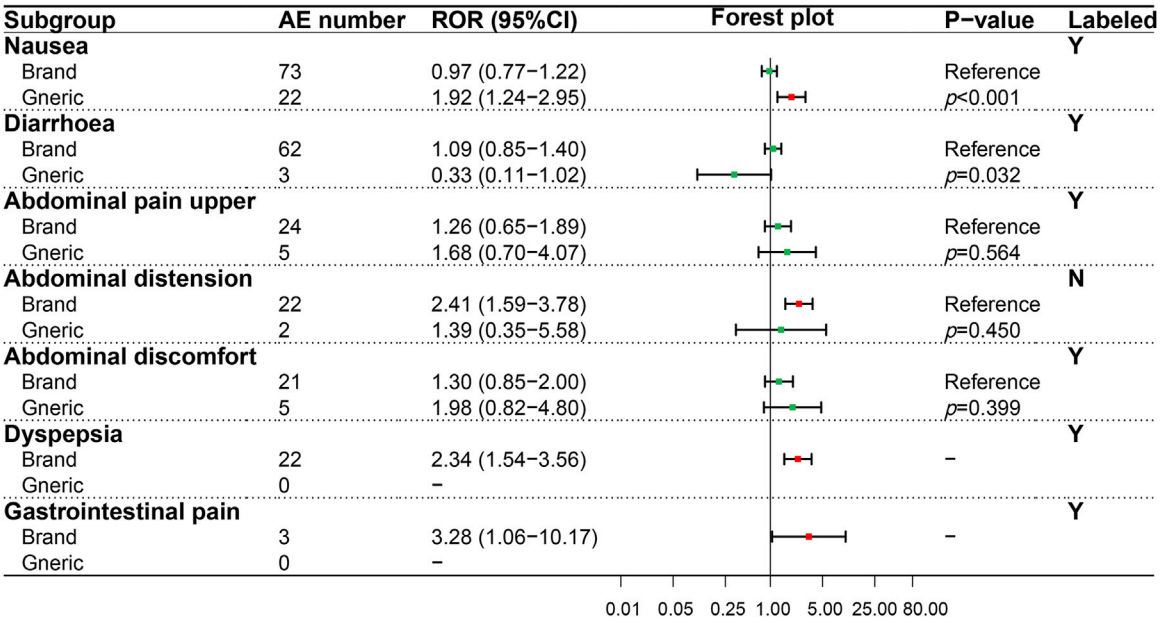

FIGURE 3
Comparison of detected AE signals for brand and generic nebivolol in the gastrointestinal system. Abbreviate: AE, adverse event; ROR, reporting odd ratio; CI, confidence interval. Note: Red points indicate positive signals and green points are opposite; the *p*-value results from the Breslow-Day test; label information comes from the US Food and Drug Administration (FDA) official website.

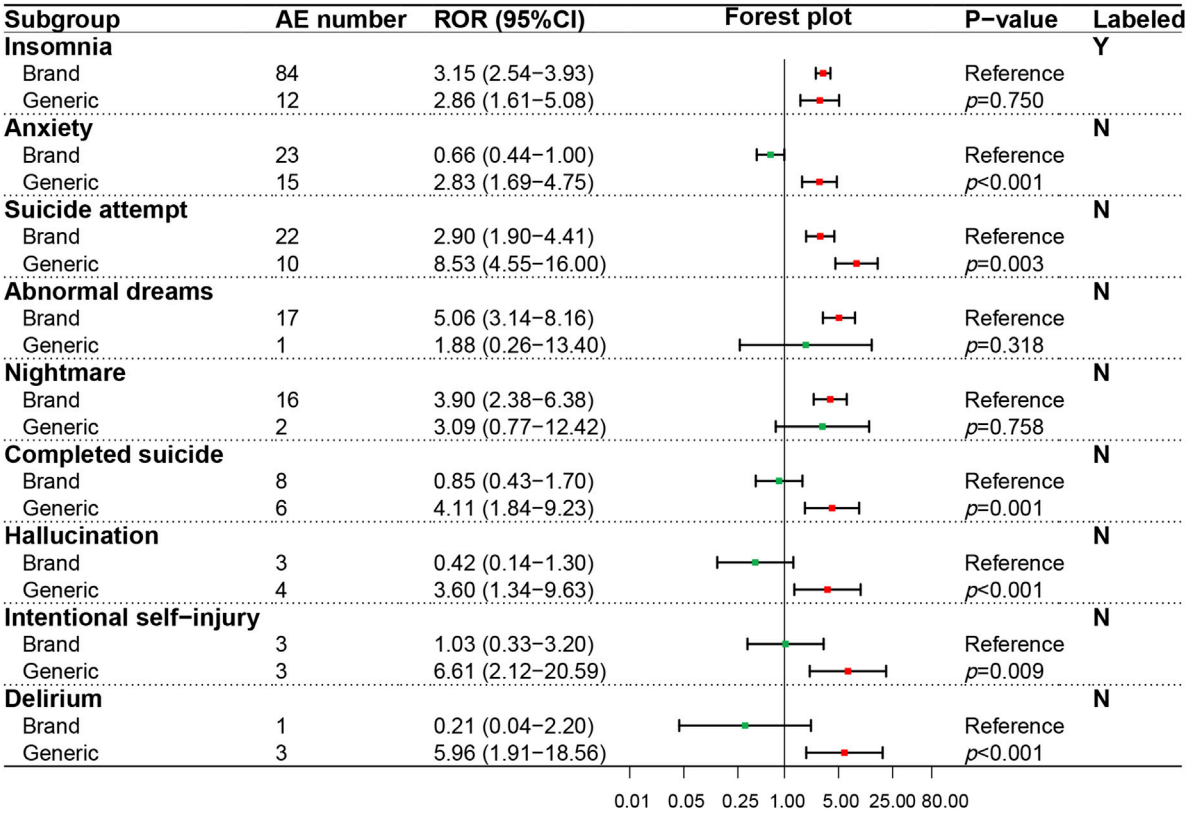

FIGURE 4
Comparison of detected AE signals for brand and generic nebivolol in the psychiatric system. Abbreviate: AE, adverse event; ROR, reporting odd ratio; CI, confidence interval. Note: Red points indicate positive signals and green points are opposite; the *p*-value results from the Breslow-Day test; label information comes from the US Food and Drug Administration (FDA) official website.

completed suicide ($p = 0.001$), hallucinations ($p < 0.001$), intentional self–injury ($p = 0.009$) and delirium ($p < 0.001$). The ADR signal results detected of 12 PTs in the neural system (SOC) were shown in Figure 5, in which five PTs were not recorded in the package insert and showed potential risk. Similar to the psychiatric system (SOC), the overall ADR risk of GN in the neural system is higher than BN and showed significant differences in dizziness ($p < 0.001$), syncope ($p < 0.001$), presyncope ($p = 0.002$), somnolence ($p = 0.007$) and decreased level of consciousness ($p < 0.001$).

4 Discussion

Generic drugs constitute a sizeable portion of the marketplace, and a long-term safety evaluation of post-marketing generic drugs cannot be ignored (White, 2020). In this study, we reviewed AE reports associated with nebivolol in the FAERS database to obtain ADR risk information of GN and BN. Meanwhile, to explore the safety profile for the GN and BN, we conducted a disproportional analysis of four SOCs. In addition, we performed the heterogeneity tests for ADR signals using the Breslow-Day test. Our results showed that some potential ADRs of nebivolol were not recorded in the package insert, and there was a difference in the safety profile between BN and GN.

PT is a detailed description of the specific clinical manifestations, site of occurrence, and disease subtype of a disease or AEs, and it is also the recommended term level for analysis of pharmacovigilance data (Brown, 2004; Bousquet et al., 2014). For the positive ADR signal recorded in the drug label, such as bradycardia (brands, ROR = 23.37, 95% CI:19.42–28.12; generics, ROR = 31.73, 95% CI: 21.12–47.67), headache (brands, ROR = 1.85, 95% CI: 1.53–2.23; generics, ROR = 1.80, 95% CI: 1.11–2.94), our results were a kind of re-verification for these ADRs of nebivolol in pharmacovigilance perspective. Moreover, for the positive AE signals not recorded in the drug label, our result showed that some potential AE risks during nebivolol use might have been previously overlooked, which deserved further attention. For example, we detected an AE signal of unstable angina (PT) in cardiac disorders, which was also described in the published literature (Akkus et al., 2012). Unstable angina requires early intervention, and its common clinical symptom is chest pain, so health professionals should pay attention to the differential diagnosis of patients with emerging chest pain on nebivolol (Kalra et al., 2008; Akkus et al., 2012). In addition, we should pay attention to the psychiatric and neurological AE risk of nebivolol. Nebivolol is a highly fat-soluble drug that is relatively easy to cross the blood-brain barrier, and its physical and chemical properties determine that it has the potential effect on neurological and psychiatric systems

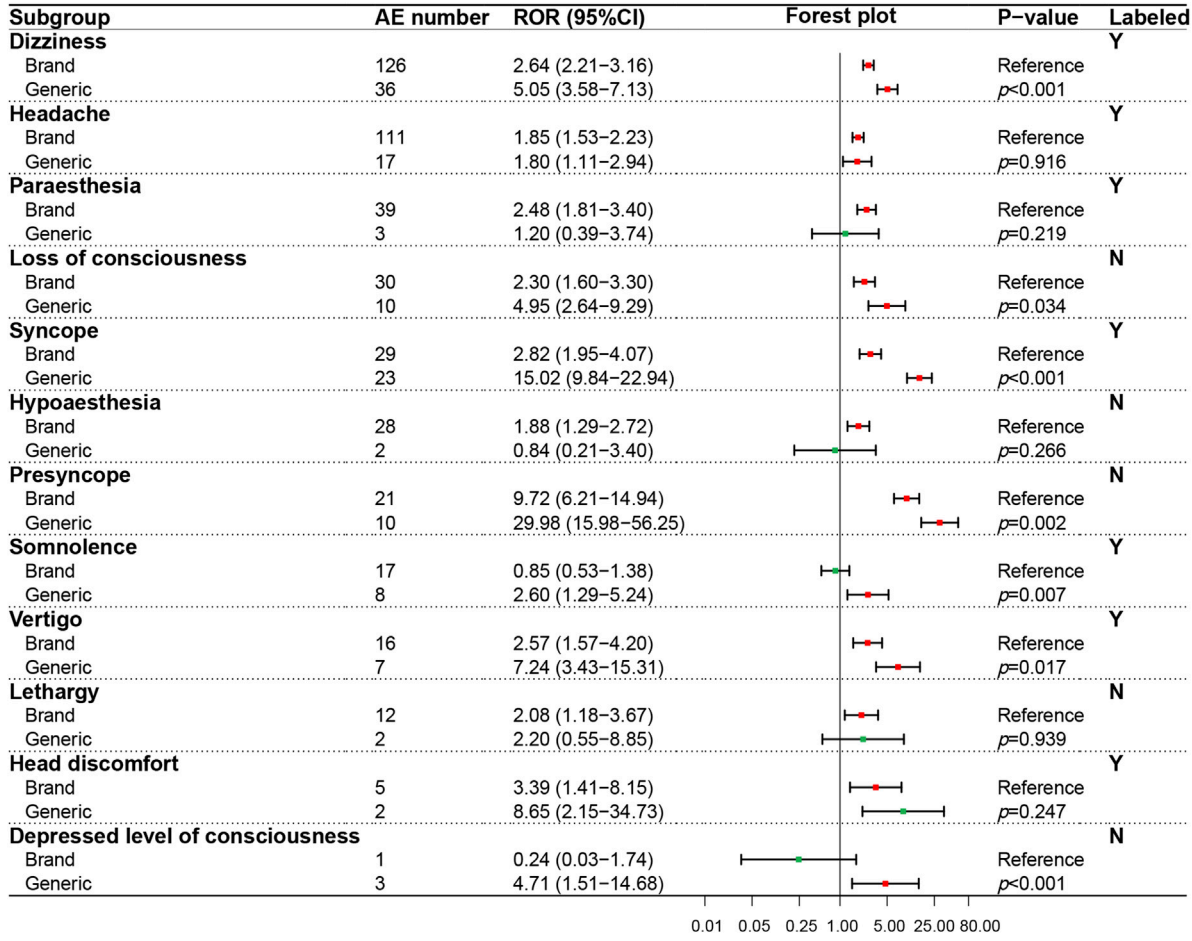

FIGURE 5
Comparison of detected AE signals for brand and generic nebivolol in the nervous system. Abbreviate: AE, adverse event; ROR, reporting odd ratio; CI, confidence interval. Note: Red points indicate positive signals and green points are opposite; the *p*-value results from the Breslow-Day test; label information comes from the US Food and Drug Administration (FDA) official website.

(Kumar et al., 2007; Cruickshank, 2010). This study detected eight unrecorded positive AE signals in the psychiatric system (SOC) and five in the neurological system (SOC), respectively. In this regard, nebivolol's high neurological and psychiatric AE risk can be partly attributed to its high lipid solubility, although further verification is needed.

In addition, to compare the AE risk difference between BN and GN, we performed the heterogeneity tests for AE signals using the Breslow-Day test. Our result showed that 15 GN-BN pairs have significant differences, which suggested that these AEs might be related to whether they are generics or brands. In these pairs, the ROR values of GN were all greater than those of BN, indicating that generic drugs were more likely to have these AEs. Although generic medications were theoretically equivalent to the originators, their actual performance in the clinical setting might not be as good as theoretical expectations (Bialer and Midha, 2010; Serebruany et al., 2019). Such a difference is explainable. On the one hand, original drugs are supported by much scientific research and safety data, while generic drugs are generally marketed based on pharmacological and bioequivalence only, lacking long-term safety and research in large samples (Meredith, 2003). On the other hand, the prescriptions of originator drugs are usually confidential, which leads to differences in the selection and dosage of excipients and the preparation process of generic drugs. As we know, excipients are chemical substances other than the active pharmaceutical ingredient (API), and they are added intentionally during the preparation of drugs to serve a specific purpose in the finished product, which have no effective pharmacological activity or impact therapeutic efficacy or safety ideally (Kalász and Antal, 2006). A study based on vitro experiments showed that the usage of excipients such as microcrystalline cellulose and starch could affect the properties of nebivolol tablets (Shaikh et al., 2010). Excipients might influence the release and (or) absorption of the API. If the increased release and (or) absorption of the API occurred in the clinical use of nebivolol, the patient may suffer from a higher risk of neurological and psychiatric disorders (Olawi et al., 2019). In addition, some excipients might even cause unexpected adverse reactions (Pifferi and Restani, 2003; Kalász and Antal, 2006; Rayavarapu et al., 2015). Therefore, it is necessary to

continuously pay attention to the post-marketing safety of generic drugs and find out the related drug risks in time.

To our knowledge, our research is the first study focusing on the safety investigation of GN and BN from the pharmacovigilance perspective, which provides additional information on the safety of nebivolol in a large sample of the population and also provides data support for clinical medication decision-making. Meanwhile, our study also provides a low-cost, reliable, and convenient strategy to compare the safety profile difference between BN and GN. However, our study has some unavoidable limitations due to the inherent nature of pharmacovigilance database. Firstly, the inconsistency in time-to-market for BN and GN may have an unknown effect on the study results. For example, brands may detect more new signals due to marketed earlier, and generics with a shorter time-to-market may be affected by Weber's effect resulting in higher values for some AE signals (Hoffman et al., 2014; Rahman et al., 2017a). Secondly, patient age, sex, comorbidities, drug dosage, and previous medical history may potentially influence the occurrence of AE. However, there is currently no well-established method that can be used to eliminate the influence of these factors on our results. Thirdly, the FAERS database runs on the basis of voluntary reporting, so underreporting, omissions, duplicate reporting, notoriety bias, and other situations may affect our results (Alatawi and Hansen, 2017; Neha et al., 2021). Fourthly, when we calculate the signal values for the BN or GN, the nebivolol data for the remaining group are grouped together to "other drugs", which may have a potential influence in the result. Fifthly, our study is conducted based on the disproportional analysis, which can only indicate a statistical association between the drug of interest and AE of interest rather than a genuine causal relationship. Finally, there are no pharmacokinetic studies or clinical studies currently to support that BN is safer than GN, so the results in our study should be interpreted cautiously and further validation is needed.

5 Conclusion

Based on the review of safety data in the FAERS database, our study conducted a disproportional analysis for GN and BN in cardiac, gastrointestinal, neurological, and psychiatric systems. Our study suggested that certain potential AE might be more likely to occur with GN rather than BN, which provides extra information for the selection and clinical use of GN and BN in the real world and may contribute to ADR monitoring of nebivolol. However, it is particularly noteworthy that the detected AE signals only represent the statistical relationship for drug-AE combination, and the actual causal relationship requires further validation.

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

HW: Data curation, Formal Analysis, Investigation, Methodology, Software, Writing–original draft, Writing–review and editing. GZ: Methodology, Writing–review and editing. HJ: Writing–review and editing. SC: Writing–review and editing. QX: Writing–review and editing. ZS: Writing–review and editing. YJ: 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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Detection of iodixanol-induced allergic reaction signals in Chinese inpatients: a multi-center retrospective database study using prescription sequence symmetry analysis

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Objective: This study aimed to explore the signal detection method for allergic reactions induced by inpatient iodixanol injection.

Methods: A database of 3,719,217 hospitalized patients from 20 large Chinese general hospitals was processed and analyzed using the prescription sequence symmetry analysis (PSSA) method.

Results: 126,680 inpatients who used iodixanol and were concurrently treated with anti-allergic drugs were analyzed. In the medical records of these patients, only 32 had documented iodixanol allergies. Statistical analysis identified 22 drugs in 4 categories—calcium preparations, adrenergic/dopaminergic agents, glucocorticoids, and antihistamines—as marker drugs. With time intervals of 3, 7, and 28 days, the adjusted sequence ratios (aSRs) for all anti-allergics and the 4 categories were greater than 1. The 7-day aSRs were 2.12 (95% CI: 2.08–2.15), 1.70 (95% CI: 1.68–1.73), 3.85 (95% confidence interval [CI]: 3.75–2.30), 2.30 (95% CI: 2.26–2.35), and 1.95 (95% CI: 1.89–2.02), respectively. The proportions of adverse drug events indicated by each signal were as follows: all anti-allergics (2.92%–3%), calcium gluconate (0.19%–0.52%), adrenergic/dopaminergic agents (2.20%–3.37%), glucocorticoids (3.13%–3.76%), and antihistamines (1.05%–1.32%).

Conclusion: This first multi-center Chinese inpatient database study detected iodixanol-induced allergy signals, revealing that reactions may be much higher than those in collected spontaneous reports. Iodixanol risk exposure was closer to actual pharmaceutical care findings. PSSA application with ≤7-day intervals appears better suited for monitoring late allergic reaction signals with these drugs.

KEYWORDS

iodixanol, allergic reactions, multi-center study, prescription sequence symmetry analysis, Chinese inpatients

1 Introduction

Iodixanol is a widely used intravenous non-ionic dimeric iodine contrast agent. Its isotonicity with plasma, high safety profile, and minimal impairment of renal function make it well suited as an adjunct for clinical diagnostic imaging, interventions, vascular stenting, and surgical treatments. In the first half of 2021, China ranked number one globally in the consumption of iodixanol injection (China Industrial Research Network, 2022). Concurrently, reported adverse drug reaction (ADR) cases caused by iodixanol have significantly increased. A total of 20,185 patients who received contrast iodixanol were recruited from 95 medical centers in China (Zhang et al., 2014). The immediate adverse reactions within 1 h of administration and the delayed adverse reactions from 1 h to 7 days after administration were recorded. The overall iodixanol-induced adverse reaction rate was 1.52%, with immediate reactions accounting for 0.58% and delayed reactions accounting for 0.97%. The major delayed reactions were mild and mostly occurred on the skin (0.68%), including rash, pruritus, and urticaria. A Korean meta-analysis found an allergic reaction rate of 0.85% (Suh et al., 2019). The majority of reports are sourced through the National ADR Monitoring Network or voluntary submissions from hospitals. When clinical adverse drug events (ADEs) occur, specifics such as allergic reactions may be documented in the electronic medical record (EMR) fields of hospital records, facilitating retrospective data analysis. Nevertheless, underreporting poses a significant challenge within voluntary systems. Systematic reviews reveal a median underreporting rate of 94% for spontaneous reporting on a global scale (Hazell and Shakir, 2006). Real-world ADEs are likely to surpass the officially reported outcomes. Meanwhile, an ongoing pharmaceutical care study, involving the simultaneous observation of 415 patients and comprehensive documentation, revealed a 30.64% overall incidence of iodixanol-induced ADEs (Zhang et al., 2022). This study found that immediate reactions accounted for 14.55%, delayed reactions accounted for 85.45%, mild reactions accounted for 73.64%, moderate reactions accounted for 25.45%, and severe reactions accounted for 0.91%. Thus, re-evaluating safety and efficacy relying solely on passively collected ADRs may not be efficient at uncovering potential risks due to extensive unreported data.

With the advent of big data, real-world study (RWS)-based drug safety re-evaluation utilizing active monitoring has become more common. RWS data sources derive mainly from collecting, processing, statistically analyzing, and scientifically interpreting EMRs. This elevates RWS to real-world evidence (RWE). Prescription sequence symmetry analysis (PSSA) is one RWS drug safety signal mining technique using large medical databases. It rapidly identifies adverse event signals and potential prescribing cascades. PSSA assumes that adverse reactions to drugs prompt prescriptions for other drugs (marker drugs). Therefore, patient records exhibit specific temporal exposure and marker drug frequency distributions (Tao and Zhan, 2012). A systematic literature review found that PSSA is widely used internationally and considered highly suitable for active adverse reaction surveillance. Recently, China has also begun utilizing PSSA on large databases while conducting methodological summaries (He et al., 2021; Lyu et al., 2021; Morris et al., 2022). Compared to traditional epidemiology, PSSA better controls time-invariant confounding factors and requires few variables to complete signal mining. This enables rapid, accurate, and low-cost detection (Zhou et al., 2019). To expand the PSSA methodology, this study mined multi-center data to uncover iodixanol allergic reaction signal characteristics and influencing factors.

2 Data and methods

2.1 Data source

Data were obtained from a large multi-center general hospital database from several Chinese provinces and cities since 2015, detailed previously (Nie et al., 2018). The top 20 hospitals by iodixanol volume were selected, with patient discharges from 1 January 2015 to 31 December 2017. The dataset contained basic inpatient demographics, clinical diagnoses per International Classification of Diseases 10th edition (ICD-10) codes, charges, standardized drug names, and Anatomical Therapeutic Chemical (ATC) classifications. As a retrospective, anonymous, non-interventional analysis, all data were only used for research. The Ethics Committee of Shanghai Fourth People's Hospital, Tongji University School of Medicine, waived review and consent.

2.2 Index and marker drugs

PSSA was applied to monitor iodixanol-induced ADEs by investigating associations between this drug and related therapeutic drugs. PSSA assumes the propensity to initiate a marker drug (e.g., thyroxine) and follows an index drug (e.g., amiodarone) (Chen et al., 2022). There is a greater tendency to start labeled drugs (marker drugs like thyroxine) after versus before index drugs (index drugs like amiodarone). The index drug purportedly causes a side effect (hypothyroidism) when treated by the marker drug. Theoretically, if the index–marker causal relationship is absent, the marker drug use would symmetrically (randomly) occur before and after the index drug. Conversely, if the index drug necessitates marker drug treatment for an ADE, the marker drug would asymmetrically initiate after more often than before the index drug. Recording inpatient drug orders chronologically allows determining the index–marker sequence by timing.

According to the Chinese Expert Consensus on Adverse Reactions Associated with Iodine Contrast Angiography Applications (Chen et al., 2014), iodine contrast adverse reaction timing is classified as acute (within 1 h), delayed (1–7 days), or late (1+ week). Like its analogs, iodixanol predominantly causes allergic reactions, with an overall rate of 0.74%–1.52%. Delayed reactions predominate over acute reactions, with most skin reactions occurring 1 h–2 days after injection and resolving within 1–7 days. However, some reactions have occurred up to 4 weeks later (Häussler, 2010; Tasker et al., 2019). Aside from treatments like oxygen and hydration, iodixanol allergy can also be treated with drugs, including epinephrine, adrenaline class of pressors, glucocorticoids, antihistamines, and calcium (Chen et al., 2014; Zhang et al., 2014). Although inpatient PSSA is less common than long-term outpatient monitoring, observed inpatient data exhibit similar temporal characteristics. Thus, this study designated iodixanol as the index drug and the above therapeutic medications as marker drugs, exploring different hospitalization lengths as the observation period. Since allergic reaction treatments

usually involve multiple and rotating drug classes, this study categorized anti-allergics by the first four or five ATC codes. Possible drugs like loratadine and diphenhydramine were aggregated by generic names, regardless of the manufacturer or dosage, as marker drugs to assess signal detection across therapeutic drug classes for potential iodixanol allergic reactions.

2.3 Interval and washout period

The PSSA methodology requires determining the index drug treatment interval and corresponding signal detection interval. This entails defining washout and interval periods. The washout period excludes previous users to select new users of index drugs. The interval is the maximum absolute time difference between index and marker drug initiation. The included patients were all inpatients, so each admission was considered a new drug user. Patients prescribed iodixanol in outpatient/emergency settings were excluded. Hence, samples with iodixanol on day 1 or 2 of hospitalization or total stays ≤3 days were excluded. Based on iodixanol-induced allergic reaction clinical occurrence and treatment patterns (Häussler, 2010; Chen et al., 2014), the washout period was 30 days before and after iodixanol use. Signal characteristics were observed at 3-, 7-, and 28-day intervals.

2.4 Calculation method of the sequence ratio

Following the PSSA summary by Morris et al. (2022), the analysis entailed four steps:

(1) The crude sequence ratio (cSR) assumed iodixanol as the index drug (I) and anti-allergy drug as the marker drug (M). I and M records were prescribed and used at different times or concurrently. Patients were grouped into "causal" and "non-causal" cohorts based on I and M chronological order. The causal cohort received the index drug I before the marker drug M, and $n_{index\to marker}$ was defined. The non-causal cohort received M before I, and $n_{marker\to index}$ was defined. The cSR was the total causal cohort samples divided by the non-causal samples:

$$cSR = \frac{n_{index\to marker}}{n_{marker\to index}}.$$

(2) The null-effect sequence ratio (neSR) was calculated. Real-world prescriptions can be impacted by various factors like insurance policies, illnesses, and other medications. To adjust for this bias, PSSA calculates the overall weighted probability P:

$$P = \frac{\sum_{m=1}^{\mu}\left[I_m \times \left(\sum_{n=m+1}^{m+d} M_n\right)\right]}{\sum_{m=1}^{\mu}\left[I_m \times \left(\sum_{n=m-d}^{m-1} M_n + \sum_{n=m+1}^{m+d} M_n\right)\right]},$$

where m is the specific iodixanol (index drug) use date; μ is the predefined hospitalization length post-iodixanol (last survey day), set as 30 days; I_m is the number of patients receiving iodixanol first on date m; d is the index–marker time interval; n is the consecutive study days; and M_n is the number of patients starting the marker drug on a given day.

After obtaining P, the approximate upper- and lower-interval probability formula for the 95% confidence interval (95% CI) of the overall binomial distribution rate when n > 200 and P × n > 15 is (Liu, 2004)

$$P_\alpha \approx \left(P \pm Z_{\alpha/2}\sqrt[2]{P(1-P)/n}\right),$$

where n is the final sample size. $Z_{\alpha/2}$ is 1.96 for a 95% two-sided alpha test.

The neSR is then obtained by the given equation:

$$neSR = \frac{P_\alpha}{1-P_\alpha}.$$

(3) The adjusted sequence ratio (aSR) was

$$aSR = \frac{cSR}{neSR}.$$

The aSR was obtained by the cSR/neSR, an adjusted sequence ratio obtained after excluding possible confounding factors. When the lower 95% CI of the aSR was greater than 1, it indicated a possible causal association between the index drug and ADR.

(4) The excess risk among exposed adjusted (ERAEA) for significant signal drugs (lower-confidence interval aSR > 1) was estimated as

$$ERAEA = \frac{n_{index\to marker} \cdot \frac{(aSR-1)}{aSR}}{n_{index}},$$

where $n_{index\to marker}$ refers to patients who used the index drug after marker drugs and n_{index} is the total index drug users.

2.5 Data processing and statistical methods

In this study, PL/SQL was used as the pre-data processing and terminal access tool, based on ORACLE 11g for pre-data processing. The post-data were developed using .net (version 2013) software, by which special software was written for data processing. Furthermore, intermediate and feature tables were constructed, and IBM SPSS 22.0 statistical software was used for statistical analysis of the study data. The count data were expressed as rates (%) expressed by the X^2 test. A statistically significant difference was considered at $p < 0.05$.

The minimum sample size estimate was

$$n = \frac{(z_{\alpha/2})^2 \times \pi(1-\pi)}{E^2},$$

where $Z_{\alpha/2}$ is the two-sided alpha test table value, π is the assumed incidence rate, and E is the tolerance error, generally half the confidence interval width. A 0.85% allergic reaction proportion meta-analysis was assumed (Suh et al., 2019). The confidence interval was 95%, making $Z_{\alpha/2}$ 1.96. Another study provided incidence bounds of 0.36%–1.95%, giving E = (0.0036 + 0.0195)/2. The minimum sample size was

$$n = (1.962) \times 0.0085 \times (1-0.0085)/(0.0036+0.0195)/2)2 \approx 243.$$

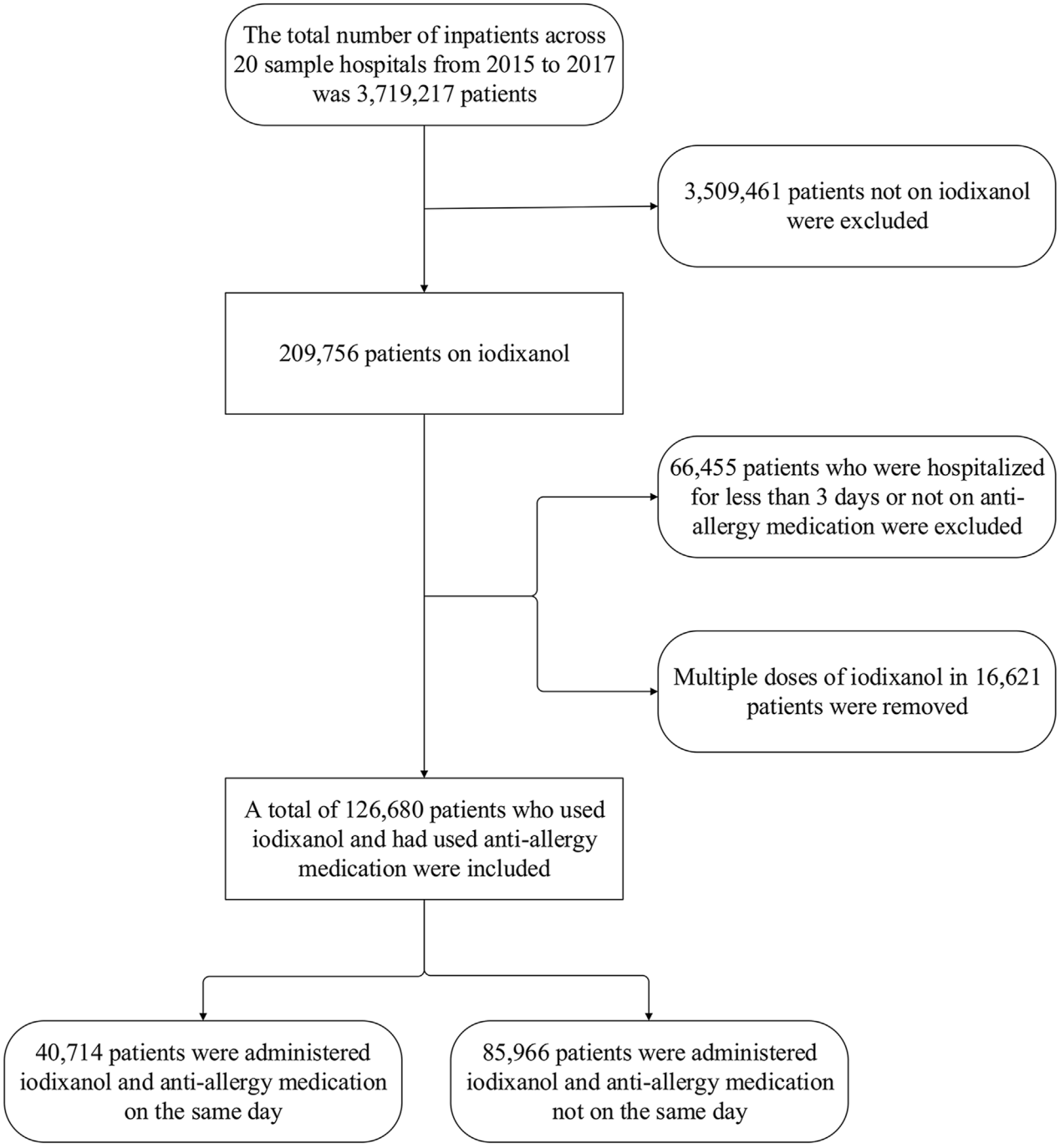

FIGURE 1
Population screening flow chart for iodixanol application with prescription sequence symmetry analysis..

3 Results

3.1 Patient inclusion and exclusion

Figure 1 displays the sample screening. The 20 hospitals had 3,719,217 inpatients during 2015–2017, with 209,756 (5.64%) using iodixanol. Of the total number of patients, 126,680 were eventually included. Then, 83,076 used iodixanol but were hospitalized <3 days or had not used anti-allergics.

Table 1 outlines the characteristics of the included patients. Among the 126,680 patients considered, 64.1% were males, representing a higher proportion than females. Examining the age distribution, adults aged 18–65 years accounted for 62.16%, the elderly over 65 years old constituted 36.79%, and minors under 18 years comprised only 1.05%. The top five primary diagnoses among inpatients collectively made up 55.96% of the entire enrolled population. These diagnoses, in descending order, were ischemic heart disease, cerebrovascular disease, gallbladder, biliary tract and

TABLE 1 Characteristics of inpatients receiving iodixanol included in this study (n = 126,680).

Category	Characteristics	Study population	Constituent ratio (%)	p-value
Gender	Male	81,199	64.1	<0.001
	Female	45,481	35.9	
Age (years)	<18	1,327	1.05	<0.001
	≥18 and <65	78,744	62.16	
	≥65	46,609	36.79	
Top 5 rankings of major diagnoses	Ischemic heart disease (I20–I25)	36,373	28.71	<0.001
	Cerebrovascular disease (I60–I69)	17,152	13.54	
	Gallbladder, biliary tract, and pancreatic disorders (K80–K87)	6,386	5.04	
	Malignant neoplasm of the digestive organs (C15–C26)	5,722	4.52	
	Special operations and healthcare (Z40–Z54)	5,253	4.15	
To operate or not	Surgery	102,295	80.75	<0.001
	Non-surgical	14,764	11.65	
	Missing data	9,621	7.59	
Allergy records	No history of allergies	116,441	91.92	<0.001
	History of allergies	10,239	8.08	
	History of allergies to iodine preparations or contrast media	199	0.16	0.381
	Iodixanol	32	0.03	

Notes: *Pearson's chi-square test (X^2) using two-sided test results.

pancreatic disorders, malignant neoplasm of the digestive organs, and special operations and healthcare. Notably, surgical patients accounted for 80.75% of this subset. In the medical record home pages, only 8.08% of patients had a documented history of allergies or allergic reactions. Specifically, regarding allergy records, 0.16% showed documented iodine contrast allergy, although the specific preparation was not clear. Only 32 cases of documented iodixanol allergy were recorded, constituting 0.03% of the total patient population.

3.2 Marker drug use

Further analysis was performed on marker drugs treating allergic reaction symptoms. Iodixanol users had 31 anti-allergic drug varieties. Ketotifen, levocetirizine, cyproheptadine, tretinoin, imipramine, midodrine, fexofenadine, beclomethasone, and Avastin ranked in the bottom 9 by usage, with <235 users each. Table 2 shows the ranking, number of hospitals, and usage proportions for the other 22 varieties. Among the anti-allergic drugs, the availability of different preparations varied across the 20 hospitals. Some formulations, such as dimenhydrinate and methoxamine, were less commonly used. Notably, the most frequently utilized preparations included dexamethasone, methylprednisolone, dopamine, promethazine, and noradrenaline. The data showed that over 50% of patients received prescriptions for methylprednisolone or noradrenaline concurrently with iodixanol on the same day. Following these, the next most commonly administered drugs were dexamethasone and metaramine, both of which are available in injectable formulations.

Figure 2 illustrates the distribution of these drugs by ATC classification (A12AA, C01CA, H02AB, R06A, and all combined) before and after the administration of iodixanol, simulating the normal distribution map of the various classes. In general, a right skew was evident both before and after the use of iodixanol, with a gradual downward trend observed on days 3–7. Notably, the use of glucocorticoids, adrenergic, and dopaminergic agents did not experience a sharp decrease until approximately day 7.

3.3 Individual marker drug-adjusted sequence ratios

Using the anti-allergics given in Table 2 as marker drugs, adjusted sequence ratios were calculated for treating potential iodixanol-induced allergic reactions. The results are presented in Table 3, indicating that, among potential iodixanol allergic reactions, only prednisone (3-day, aSR < 1) showed a sequence ratio below 1. For all four drug classes—calcium channel blockers, adrenergic/dopaminergic agents, glucocorticoids, and antihistamines—the aSR exceeded 1, irrespective of the category or individual drug.

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TABLE 2 Ranking of inpatients who received anti-allergic medication and iodixanol (*n* = 126,680).

No.	Anti-allergic drug	Hospitals	Users (n/%)	Same-day usage (n/%)	Injections (%)
1	Dexamethasone	20	39,205 (30.95)	12,334 (31.46)	97.36
2	Methylprednisolone	20	14,293 (11.28)	8,208 (57.43)	100
3	Dopamine	20	13,466 (10.63)	3,561 (26.44)	100
4	Promethazine	20	9,361 (7.39)	1,507 (16.10)	98.99
5	Noradrenaline	20	9,108 (7.19)	4,759 (52.25)	100
6	Calcium gluconate	20	7,969 (6.29)	638 (8.01)	100
7	Phenylephrine	16	6,803 (5.37)	1,168 (17.17)	100
8	Adrenaline	19	5,331 (4.21)	886 (16.62)	100
9	Prednisolone	14	4,047 (3.19)	975 (24.09)	100
10	Loratadine	16	2,221 (1.75)	212 (9.55)	0
11	Metaradrine	20	2,026 (1.6)	729 (35.98)	100
12	Prednisone	20	1,630 (1.29)	123 (7.55)	0
13	Isoprenaline	20	1,576 (1.24)	247 (15.67)	100
14	Hydrocortisone	20	1,110 (0.88)	128 (11.53)	100
15	Dobutamine	19	1,073 (0.85)	50 (4.66)	100
16	Desloratadine	9	907 (0.72)	86 (9.48)	0
17	Diphenhydramine	8	701 (0.55)	131 (18.69)	98.75
18	Chlorpheniramine	16	555 (0.44)	62 (11.17)	0
19	Cetirizine	11	473 (0.37)	47 (9.94)	0
20	Ebastine	12	446 (0.35)	31 (6.95)	0
21	Dimenhydrinate	4	439 (0.35)	34 (7.74)	0
22	Methoxamedrine	6	278 (0.22)	29 (10.43)	0

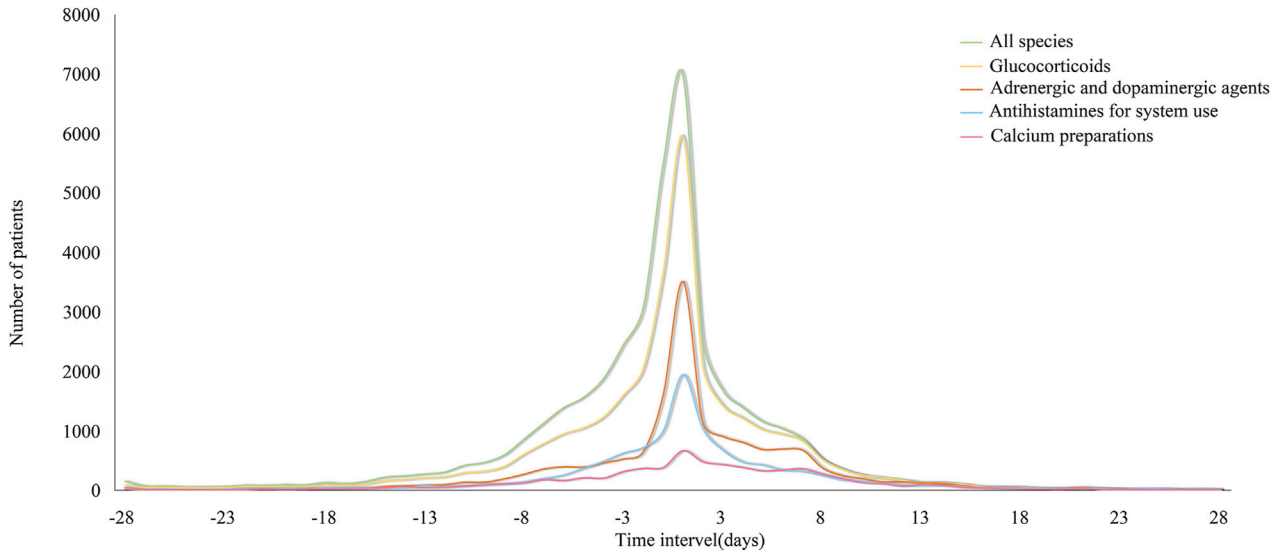

FIGURE 2
Distribution of inpatients' anti-allergic drugs count by category before and after iodixanol.

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TABLE 3 Results of prescription sequence symmetry analysis on marker drugs for allergic reactions induced by iodixanol.

Category	Marking of drugs/ interval	Iodixanol pre-/post-medication (N)			aSR (95% CI)		
		3 d	7 d	28 d	3 d	7 d	28 d
Overall		11,913/ 16,019	15,916/ 19,681	17,890/ 21,528	2.12 (2.08–2.15)	1.70 (1.68–1.73)	1.51 (1.49–1.54)
A12AA, calcium preparations	Calcium gluconate	1,663/1,832	3,047/2,369	4,372/2,839	1.31 (1.25–1.37)	1.39 (1.33–1.45)	1.32 (1.27–1.39)
C01CA, adrenergic and dopaminergic agents		5,701/3,486	8,527/4,831	10,311/ 5,839	5.22 (5.08–5.38)	3.85 (3.75–3.95)	3.18 (3.10–3.26)
	Dopamine	3,496/2,363	5,248/2,943	6,445/3,334	3.44 (3.31–3.57)	2.90 (2.80–3.00)	2.57 (2.48–2.66)
	Noradrenaline	1,362/588	2,146/930	3,019/1,227	12.1 (11.5–12.8)	7.55 (7.19–7.93)	5.60 (5.36–5.86)
	Phenylephrine	2,363/175	3,737/434	4,819/760	21.6 (20.6–22.7)	9.09 (8.67–9.54)	5.38 (5.13–5.65)
	Adrenaline	1,038/886	1,987/1,150	2,995/1,346	3.34 (3.14–3.56)	2.64 (2.50–2.79)	2.27 (2.15–2.40)
	Metaradrine	209/319	468/461	667/603	3.08 (2.76–3.47)	2.77 (2.51–3.06)	2.31 (2.11–2.54)
	Isoprenaline	337/124	761/178	1,086/229	5.50 (4.95–6.12)	4.07 (3.68–4.49)	3.25 (2.94–3.60)
	Dobutamine	248/104	531/163	788/208	2.70 (2.39–3.05)	2.54 (2.25–2.87)	2.20 (1.94–2.49)
	Methoxamedrine	71/28	116/51	171/69	5.87 (4.58–7.74)	3.66 (2.88–4.73)	2.75 (2.17–3.51)
H02AB, glucocorticoids		9,916/ 1,0405	13,700/ 12,993	15,764/ 14,624	2.95 (2.89–3.01)	2.30 (2.26–2.35)	2.00 (1.96–2.03)
	Dexamethasone	9,177/8,315	12,697/ 10,477	14,827/ 11,859	3.11 (3.04–3.19)	2.43 (2.38–2.48)	2.09 (2.05–2.13)
	Methylprednisolone	1,475/1,735	2,396/2,349	3,079/2,886	4.55 (4.35–4.77)	3.48 (3.34–3.62)	2.93 (2.83–3.05)
	Prednisolone	957/271	1,906/418	2,406/630	8.05 (7.53–8.61)	5.54 (5.21–5.90)	3.92 (3.69–4.17)
	Prednisone	311/441	609/496	931/527	0.97 (0.88–1.07)	1.30 (1.18–1.43)	1.35 (1.22–1.49)
	Hydrocortisone	259/161	426/244	616/343	2.99 (2.64–3.39)	2.39 (2.12–2.70)	1.90 (1.69–2.14)
R06A, antihistamines for system use		3,777/3,035	5,281/4,050	6,593/4,626	2.39 (2.30–2.48)	1.95 (1.89–2.02)	1.72 (1.66–1.78)
	Promethazine	2,270/2,098	3,296/2,938	4,305/3,425	2.74 (2.62–2.87)	2.08 (2.00–2.17)	1.78 (1.71–1.86)
	Loratadine	990/322	1,316/388	1,547/429	3.09 (2.84–3.36)	2.82 (2.59–3.06)	2.60 (2.39–2.83)
	Desloratadine	394/214	493/233	555/248	1.97 (1.73–2.25)	1.94 (1.70–2.21)	1.86 (1.62–2.12)
	Diphenhydramine	125/160	207/228	274/272	2.66 (2.24–3.21)	2.09 (1.78–2.48)	1.75 (1.50–2.06)
	Chlorpheniramine	204/109	285/129	333/146	2.41 (2.04–2.87)	2.34 (1.98–2.78)	2.18 (1.84–2.58)
	Cetirizine	186/103	237/122	283/136	2.08 (1.73–2.50)	1.98 (1.65–2.38)	1.85 (1.54–2.22)

(Continued on following page)

TABLE 3 (*Continued*) Results of prescription sequence symmetry analysis on marker drugs for allergic reactions induced by iodixanol.

Category	Marking of drugs/ interval	Iodixanol pre-/post-medication (N)			aSR (95% CI)		
		3 d	7 d	28 d	3 d	7 d	28 d
	Ebastine	155/99	237/110	289/119	1.61 (1.34–1.95)	1.74 (1.44–2.10)	1.70 (1.40–2.05)
	Dimenhydrinate	109/118	169/150	241/161	1.56 (1.29–1.91)	1.32 (1.09–1.60)	1.28 (1.06–1.55)

Note: aSR, adjusted sequence ratio.

TABLE 4 Excess risk among the exposed adjusted and estimated population of drugs used in the treatment of allergic reactions to iodixanol (*n* = 209,756).

Category and time interval	Adjusted percentage of additional risk exposure	Adjusted number of additional risk exposure	Percentage of the total population (%)
Overall			
3 d	0.10	6,294	3.00
7 d	0.10	6,607	3.15
28 d	0.09	6,108	2.91
A12AA, calcium preparation			
3 d	0.05	396	0.19
7 d	0.11	864	0.41
28 d	0.14	1,085	0.52
C01CA, adrenergic and dopaminergic agents			
3 d	0.18	4,611	2.20
7 d	0.24	6,313	3.01
28 d	0.27	7,075	3.37
H02AB, glucocorticoids			
3 d	0.13	6,557	3.13
7 d	0.15	7,766	3.70
28 d	0.16	7,894	3.76
R06A, antihistamines for system use			
3 d	0.17	2,198	1.05
7 d	0.20	2,585	1.23
28 d	0.21	2,777	1.32

3.4 Excess risk among exposed adjusted

Table 4 provides the excess risk among exposed adjusted extrapolated for all drugs and categories.

4 Discussion

Approximately 75 million CT scans are conducted each year in the United States, and half of them include the use of iodinated contrast media (ICM). In Korea, it is estimated that more than 4 million CT scans involve ICM, but the proportion of iodixanol used in large sample databases and the rate of spontaneous reporting of ADRs are unclear (Cha et al., 2019). Based on the results of this study, we can calculate that the proportion of iodixanol used was 5.64% (209,756/3,719,217). Therefore, it can be inferred that among the 92.98 million patients admitted to 2,548 tertiary Chinese hospitals in 2018 (Ministry of Health of China, 2022), over 5 million inpatients may receive iodixanol annually.

Since the occurrence of allergic reactions and subsequent treatment drugs following iodixanol are unclear, we included potential reaction treatment drug categories and varieties according to the literature and guidelines as index medications. Glucocorticoids have anti-inflammatory, immunosuppressive, anti-

shock, and other effects and are widely used clinically, but they lack specificity for allergic reactions. Antihistamines are commonly used allergy drugs exhibiting strong specificity and having a sufficient sample size. Calcium agents are commonly used adjuvant drugs for allergic reactions, showing some specificity. Epinephrine is mainly used for severe allergic reactions and can serve as a marker for such reactions (Chen et al., 2014; Chen et al., 2014; Kuna et al., 2016; Kuna et al., 2016; Huang et al., 2022; Huang et al., 2022). Resulting allergy therapies encompassed systemic glucocorticoids like dexamethasone and methylprednisolone; adrenergic/dopaminergic agents such as dopamine, noradrenaline, and phenylephrine; calcium gluconate; and antihistamines, including promethazine and loratadine. These are commonly hospital-administered. Methylprednisolone, noradrenaline, and iodixanol have high same-day application rates (Table 2). We presume that iodixanol is primarily used for cardiovascular/cerebrovascular diagnosis, often paired with prompt surgery and multidrug treatment. Some patients may also receive glucocorticoids like dexamethasone with iodixanol to prevent reactions, as per early guidelines and the literature (Chen et al., 2014; He, 2017). Figure 1 shows anaphylactic treatments given with the iodixanol concentrate within 7 days. This conforms to most allergic reactions arising within 7 days, especially acute reactions within 1 h. It should be noted that PSSA does not account for index and marker drugs administered concurrently, which could miss signals for acute and severe reactions like shock, which are more often treated with epinephrine. However, including the index–marker sequential order on the same day would confer the same bias.

This demonstrates allergy signal detection capacity. Three-day signal detection exceeded 7 or 28 days, reflecting reaction patterns. Phenylephrine, noradrenaline, and prednisolone have relatively high aSRs, fitting their emergency acute reaction treatment use. However, considering that the typical medical administration of iodixanol within days does not match acute reaction timing, signal interference from illness or other treatments is also plausible. Adding a matched blank control cohort could improve this. Antihistamines also showed the strongest detection with the highest aSR for loratadine. This conforms to their oral preparations and delayed reaction treatment applications.

Although most literature records suggest that immediate and non-immediate hypersensitivity reactions to ICM occur at a frequency of 0.5%–3% in patients receiving non-ionic ICM (Torres et al., 2021), ADRs are highly likely to be underreported. From 2009 to 2017, only 2,469 cases of ADRs were collected from nearly 200 hospitals in the region, of which iodixanol ADRs ranked first (533, 42.30%), with rash, pruritus, and flushing as the top 3 reactions. Furthermore, 90.48% of ADRs occurred within 24 h (Xu et al., 2020). Thus, the proportion of spontaneous reporting records was only 0.035%, consistent with this study. Although active pharmacological care can detect missed adverse events (Hu et al., 2022), it is less efficient and labor-intensive. Table 4 shows that the ADE proportion estimates based on excess risk among exposed adjusted were 3.00%–2.92% for all anti-allergics combined, 0.19%–0.52% for calcium gluconate, 2.20%–3.37% for adrenergic/dopaminergic agents, 3.13%–3.76% for glucocorticoids, and 1.05%–1.32% for antihistamines. These results are closer to the ADE rates reported through active pharmaceutical care (Hu et al., 2022) and suggest reduced actual occurrence versus spontaneously reported iodixanol-induced allergic reaction proportions. Therefore, analyzing adverse reaction signals in drugs after exposure using PSSA-like medical big data technology can better reveal real-world adverse reaction rates.

5 Limitations and strengths

Some assumptions were made to facilitate the methodology, including patients using iodixanol for the first time and only once. However, approximately 8% actually used it more than twice but were excluded, implying the theoretical ability to have reactions. Furthermore, adrenergic/dopaminergic agents and glucocorticoids have many clinical indications. Applying PSSA alone to ascertain allergic reactions, particularly acute ones, and inferring post-intervention adverse event proportions like drugs and surgery may be inappropriate. In this study, it was difficult to distinguish the reasons for drug use when processing big data. Since the prescription date accuracy in the Medicare database is only at the day level, the first prescription dates of the labeled drugs and indicator drugs could not be definitively determined as the same date. In classical PSSA, patients prescribed both drugs on the same day are usually excluded. For inpatient exposed drug adverse event monitoring, later reaction signal tracking like delayed hypersensitivity with ≤7-day intervals is more suitable. Adding a matched blank cohort without iodixanol exposure would improve this, comparing those receiving anti-allergics without iodixanol. This is the next step for further study and refinement.

6 Conclusion

To the best of our knowledge, this first multi-center Chinese inpatient database study detected iodixanol allergy signals, elucidating the applicability of different anti-allergic drug classes for signal detection and associated parameter settings. Meanwhile, inpatient iodixanol allergic reactions likely occur at substantially higher frequencies than those reported in collected spontaneous reports. We calculated the real-world iodixanol risk exposure and obtained results more closely aligned with actual pharmaceutical care findings. We also found that due to inpatient recording and reaction traits, PSSA is better suited for monitoring delayed hypersensitivity signals at intervals ≤7 days.

Data availability statement

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

Ethics statement

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

guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

DZ: writing–original draft and data curation. XY: writing–review and editing and data curation. ZY: conceptualization, writing–review and editing, and data curation. WS: writing–review and editing, formal analysis, and visualization. SC: visualization, writing–review and editing, project administration, and supervision. LX: methodology, validation, and 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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A disproportionality analysis of FDA adverse event reporting system (FAERS) events for ticagrelor

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Background: Ticagrelor is a commonly used antiplatelet agent, but due to the stringent criteria for trial population inclusion and the limited sample size, its safety profile has not been fully elucidated.

Method: We utilized OpenVigil 2.1 to query the FDA Adverse Event Reporting System database and retrieved reports by the generic name "ticagrelor" published between 1 October 2010 and 31 March 2023. Adverse drug events (ADEs) were classified and described according to the preferred terms and system organ classes in the Medical Dictionary of Regulatory Activity. Proportional reporting ratio (PRR), reporting odds ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) were used to detect signals.

Results: The number of ADE reports with ticagrelor as the primary suspect drug was 12,909. The top three ADEs were dyspnea [1824 reports, ROR 7.34, PRR 6.45, information component (IC) 2.68], chest pain (458 reports, ROR 5.43, PRR 5.27, IC 2.39), and vascular stent thrombosis (406 reports, ROR 409.53, PRR 396.68, IC 8.02). The highest ROR, 630.24, was found for "vascular stent occlusion". Cardiac arrest (137 reports, ROR 3.41, PRR 3.39, IC 1.75), atrial fibrillation (99 reports, ROR 2.05, PRR 2.04, IC 1.03), asphyxia (101 reports, ROR 23.60, PRR 23.43, IC 4.51), and rhabdomyolysis (57 reports, ROR 2.75, PRR 2.75, IC 1.45) were suspected new adverse events of ticagrelor.

Conclusion: The FAERS database produced potential signals associated with ticagrelor that have not been recorded in the package inserts, such as cardiac arrest, atrial fibrillation, asphyxia, and rhabdomyolysis. Further clinical surveillance is needed to quantify and validate potential hazards associated with ticagrelor-related adverse events.

KEYWORDS

ticagrelor, adverse events, FDA adverse event reporting system, disproportionality analysis, data mining

1 Introduction

P2Y12 inhibitors, such as clopidogrel, prasugrel, and ticagrelor, have emerged as pivotal in mitigating adverse cardiovascular outcomes following revascularization in coronary artery disease (CAD). Among them, ticagrelor is a third-generation P2Y12 receptor antagonist that reversibly binds to the P2Y12 receptor and almost completely inhibits

ADP-induced platelet aggregation *in vitro* (Husted et al., 2006). Ticagrelor was approved for marketing by the European Medicines Agency (EMA) on 3 December 2010, followed by the US Food and Drug Administration (FDA) on 20 July 2011. A genetic sub-study in the Platelet inhibition and patient Outcomes (PLATO) trial showed that CYP2C19 or ABCB1 gene diversity did not affect the efficacy of ticagrelor in reducing major cardiovascular events compared to clopidogrel (Wallentin et al., 2010). Several guidelines recommend ticagrelor as the first-line or preferred antiplatelet agent for patients with acute coronary syndrome (ACS) (Amsterdam et al., 2014; Collet et al., 2021). A study based on the United States databases showed that clopidogrel is the most used P2Y12 inhibitor, accounting for 60.9% of the prescription share, followed by ticagrelor (25.1%) and prasugrel (13.6%). For patients less than or equal to 65 years, ticagrelor use increased from 13.7% in 2013 to 45.6% in 2018 and exceeded clopidogrel use in the third quarter of 2018 (Kumar et al., 2023). As the usage rate of ticagrelor increases their long-term safety profiles remain incompletely evaluated, posing potential risks to an increasing number of users.

Although the safety evaluation of ticagrelor has been conducted in clinical trials, due to the stringent criteria for trial population inclusion and the limited sample size, serious adverse drug events (ADEs) with low incidence and long-term medication safety issues cannot be clarified during the clinical trial phase. With the expansion of the user base of ticagrelor after its launch, the FDA has requested revisions and updates to the drug safety information of ticagrelor. In October 2019, the FDA approved a revision of the package insert for ticagrelor, which added new safety information about thrombotic thrombocytopenic purpura (TTP) (FDA, 2019). TTP is a serious condition which can occur after a brief drug exposure (<2 weeks) and requires prompt treatment (George, 2022). Furthermore, new safety information about central sleep apnea (CSA) and Cheyne-Stokes respiration was added in September 2020, and a new section about CSA and Cheyne-Stokes respiration was added to the "WARNINGS AND PRECAUTIONS" section in August 2021 (FDA, 2020; FDA, 2021). Over the past years, several case reports have emerged showing the possibility of serious ticagrelor-induced bradyarrhythmia (Al-Bayati et al., 2021; Aranganathan et al., 2021; Kotaru and Kalavakunta, 2021). A sub-study of the PLATO trial showed that more patients treated with ticagrelor had ventricular pauses compared to clopidogrel-treated patients, but there were no apparent clinical consequences related to the increase in ventricular pauses in patients receiving ticagrelor (Scirica et al., 2011). To date, the risk of bradyarrhythmia in patients treated with ticagrelor is still incompletely evaluated. A meta-analysis showed that ticagrelor increased the risk of bradyarrhythmia or severe bradyarrhythmia; however, due to missing outcome data in two-thirds of eligible studies, the evidence was low to moderate (Pujade et al., 2020). A pharmacovigilance study compared the adverse drug reaction signals of ticagrelor and clopidogrel, but did not summarize ADEs related to arrhythmia (Tang et al., 2022). With the increase in the number of users of ticagrelor, it is still necessary to conduct post-market reassessment to characterize new and serious ADEs.

Our study aimed to conduct a pharmacovigilance analysis for ticagrelor and ADEs using the FDA Adverse Event Reporting System (FAERS) database to explore the post-marketing safety profile of ticagrelor.

2 Materials and methods

2.1 Data sources and collection

The FAERS database is a publicly available database that collects ADE reports spontaneously reported by healthcare professionals, patients, pharmaceutical manufacturers, etc., in different regions, and reflects the real-world occurrence of ADEs (Wei et al., 2023). Data mining algorithms have been used for safety monitoring and re-evaluation of drugs post-marketing from FAERS databases (Shu et al., 2022; Tian et al., 2022; Jiang et al., 2024). Therefore, we evaluated the safety of ticagrelor by analyzing the proportional imbalance of ADEs in the FAERS database since its launch.

Data for this study were obtained from the FAERS database. The AEs in the FAERS database were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (https://www.meddra.org/). OpenVigil is a novel web-based pharmacovigilance analysis tool which uses the openFDA online interface of the FDA to access US pharmacovigilance data from the FAERS database (Böhm et al., 2012). OpenVigil 2.1 is an AE data extraction and cleaning, mining, and analysis tool specifically designed for the FAERS database, which currently includes the FAERS data from 1 January 2004 to 31 March 2023. OpenVigil relies on the U.S. Adopted Name (USAN) scheme, only valid reports with an unambiguous mapping of the free-text drug name to a USAN drug name were included in the analysis. In the FAERS database, there are numerous updates on cases, which means an entire case may include many unique reports. In this study, entire cases were used for analysis, a case contributes to the result if at least one of its reports includes the ticagrelor-event relationship.

We used OpenVigil 2.1 to query the FAERS database and retrieve reports on the generic name "ticagrelor" from 1 October 2010 to 31 March 2023. In each AE report from the FAERS database, the reporters assigned role codes for each reported drug. In our study, we selected cases defined as AE reports, in which the reporter referred to ticagrelor as a "Primary Suspect." AEs were classified and described according to the preferred terms (PTs) and the system organ classes (SOCs) in the international MedDRA, version 24.0. Because it is impossible to identify individual patients, ethical approval was not required in our hospital.

2.2 Statistical analysis

Proportional reporting ratio (PRR), reporting odds ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) methods are commonly used to detect ADE signals in pharmacovigilance (Noguchi et al., 2021). PRR can be used to estimate the relative risk, but the PRR method is sensitive and prone to false positive signals, especially when the number of reported cases is low, while ROR is a consistent estimate of the rate ratio or hazard ratio and is less biased than other indices. The advantage of BCPNN is that it is relatively stable even when the number of reports is small. Therefore, we combined ROR, PRR and BCPNN method to mine the ADE signals of ticagrelor, and when the results of the three methods were positive, the signal was judged to be a suspected ADE signal. The criteria of disproportionate

TABLE 1 Formulas and signal detection criterias for reporting odds ratio (ROR), proportional reporting ratio (PRR) and bayesian confidence propagation neural network (BCPNN) (Shu et al., 2022; Jiang et al., 2024).

Algorithms	Equation	Criteria
ROR	$ROR = (a/c)/(b/d)$	a>3; the lower limit of 95%Cl > 1
	$SE(\ln ROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	
	$95\%CI = e^{\ln(ROR)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	
PRR	$PRR = [a/(a+b)]/[c/(c+d)]$	a>3; $PRR > 2\chi^2 > 4$
	$\chi^2 = \frac{(ad-bc)^2 \times (a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}$	
BCPNN	$IC = log_2\frac{p(x,y)}{p(x)p(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$	a>3; IC025 > 0
	$E(IC) = log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(\ln 2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right]+\left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right]+\left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\right\}$	
	$\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$IC-2SD = E(IC)-2\sqrt{V(IC)}$	
	$\alpha 1 = \beta 1 = 1, \alpha = \beta = 2, \gamma 11 = 1$	

Equation: *a*, number of reports containing both ticagrelor and the suspect adverse drug reaction; *b*, number of reports containing the suspect adverse drug reaction with other medications (except ticagrelor); *c*, number of reports containing ticagrelor with other adverse drug reactions (except the event of interest); *d*, number of reports containing other medications and other adverse drug reactions. ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ^2, chi-squared; BCPNN, bayesian confidence propagation neural network; IC, information component; IC025, the lower limit of 95%CI, of the IC.

measure and standard of signal detection were shown in (Table 1) (Bate et al., 1998; Evans et al., 2001; van Puijenbroek et al., 2003). In order to better demonstrate the strength of ADE signals, we defined the judgment criteria for signal intensity shown in Supplementary Table S1. The higher the PRR/ROR/IC value, the higher the strength of the signal.

3 Results

3.1 ADE reports and clinical information

A total of 9,699,440 ADE reports were identified from FAERS database from 1 October 2010 to 31 March 2023. There were 12,909 ADE reports with ticagrelor as the primary suspect drug, involving 2,229 PTs. The number of reports was much higher in males (7,421 reports, 57.49%) than in females (4,310 reports, 33.39%); the main age group was 65–84 years (3,302 reports, 25.58%); most reports were submitted in 2016 (3,203 reports, 24.81%); and the main reporting country was the US (8,058 reports, 62.42%) (Supplementary Table S2).

3.2 Signal ADE mining

In this study, ROR, PRR and BCPNN were used to analyze ADE signals, and 263 risk signals were detected. Furthermore, 22 invalid signals were eliminated including non-reference value ADEs (e.g., inability to afford medication, insurance issues), ADEs related to primary diseases (e.g., acute myocardial infarction, unstable angina pectoris, ACS), and drug use error events (e.g., product name confusion, intentional product misuse), shown in Supplementary Table S3. Finally, 241 positive signals by three methods were included (Figure 1).

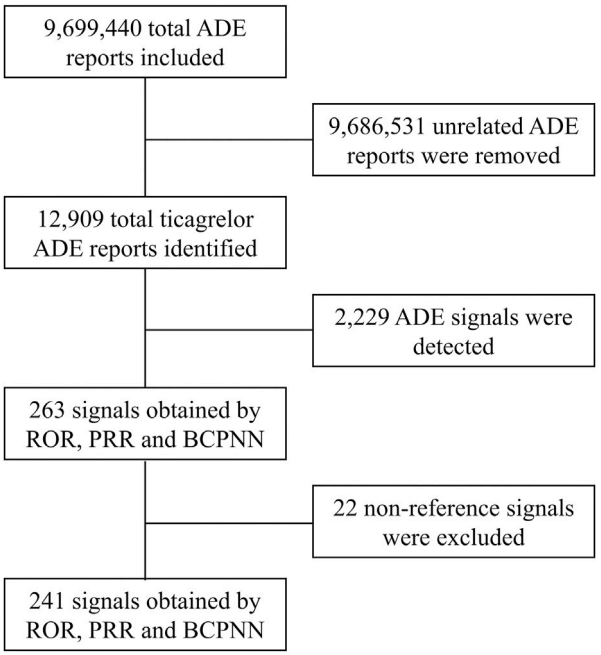

FIGURE 1
Flow chart for ticagrelor ADE identification from the FAERS database between 1 October 2010 and 31 March 2023. ADE, adverse drug event; ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, bayesian confidence propagation neural network.

TABLE 2 PT signal detection results of the top 50 ADEs based on the number of reports about ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)
Dyspnea	1824	7.34(6.99–7.72)	6.45(8,505.60)	2.68(2.60)
Chest pain[a]	458	5.43(4.94–5.96)	5.27(1,579.28)	2.39(2.24)
Vascular stent thrombosis	406	409.53(362.66–462.45)	396.68(104,579.20)	8.02(7.14)
Contusion	399	8.63(7.81–9.54)	8.39(2,571.97)	3.06(2.88)
Hemorrhage	399	6.56(5.93–7.25)	6.39(1,800.29)	2.66(2.50)
Feeling abnormal[a]	326	2.34(2.09–2.61)	2.30(241.32)	1.20(1.03)
Chest discomfort[a]	283	6.09(5.41–6.86)	5.98(1,164)	2.57(2.37)
Epistaxis	270	6.98(6.18–7.88)	6.86(1,336.38)	2.77(2.56)
Gastrointestinal hemorrhage	270	5.00(4.43–5.64)	4.91(835.45)	2.29(2.09)
Anemia	250	2.81(2.48–3.19)	2.78(283.63)	1.47(1.28)
Cerebral hemorrhage	169	8.43(7.24–9.82)	8.33(1,073.04)	3.04(2.76)
Hemoglobin decreased	152	3.31(2.82–3.89)	3.29(239.22)	1.71(1.46)
Cardiac arrest[a]	137	3.41(2.88–4.04)	3.39(227.59)	1.75(1.48)
Thrombosis[a]	132	3.00(2.53–3.56)	2.98(171.44)	1.57(1.30)
Intracranial hemorrhage	123	12.42(10.38–14.85)	12.31(1,247.09)	3.60(3.21)
Bradycardia	123	4.35(3.64–5.20)	4.32(309.49)	2.10(1.81)
Melaena	108	9.31(7.69–11.26)	9.24(776.16)	3.19(2.81)
Syncope	105	2.06(1.70–2.50)	2.05(55.66)	1.04(0.74)
Asphyxia[a]	101	23.60(19.35–28.80)	23.43(2,081.81)	4.51(3.94)
Atrial fibrillation[a]	99	2.05(1.68–2.50)	2.04(51.51)	1.03(0.72)
Hypoacusis[a]	94	2.85(2.33–3.50)	2.84(110.11)	1.50(1.18)
Rectal hemorrhage	83	4.02(3.24–4.99)	4.00(182.89)	1.99(1.63)
Hematuria	81	4.43(3.56–5.51)	4.41(209.04)	2.13(1.75)
Stress[a]	81	2.17(1.74–2.70)	2.16(49.50)	1.11(0.77)
Vascular stent occlusion	71	630.24(459.67–864.11)	626.78(23,830.40)	8.42(5.48)
Vascular stent stenosis	68	185.18(141.95–241.56)	184.21(9,801.84)	7.21(5.18)
Faces discolored	68	6.64(5.22–8.43)	6.61(315.45)	2.71(2.25)
Blood pressure decreased[a]	64	2.09(1.63–2.67)	2.08(34.84)	1.05(0.67)
Exertional dyspnea	63	3.94(3.07–5.05)	3.92(133.75)	1.97(1.54)
Hematochezia	61	2.40(1.86–3.08)	2.39(47.79)	1.25(0.85)
Hematemesis	58	4.73(3.65–6.13)	4.71(165.07)	2.23(1.76)
Nervousness[a]	58	2.06(1.59–2.67)	2.05(30.31)	1.04(0.63)
Rhabdomyolysis[a]	57	2.75(2.12–3.57)	2.75(61.38)	1.45(1.03)
Cardio-respiratory arrest[a]	55	2.61(2.00–3.4)	2.60(52.50)	1.38(0.95)
Hematoma	52	3.93(2.99–5.16)	3.92(109.55)	1.96(1.49)
Hemoptysis	52	3.88(2.96–5.1)	3.87(107.43)	1.95(1.47)
Pulmonary edema[a]	52	2.45(1.87–3.22)	2.45(43.03)	1.29(0.85)
Upper gastrointestinal hemorrhage	51	5.49(4.16–7.23)	5.47(180.63)	2.44(1.92)

(Continued on following page)

TABLE 2 (*Continued*) PT signal detection results of the top 50 ADEs based on the number of reports about ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)
Complete atrioventricular block[a]	48	14.73(11.06–19.61)	14.68(586.83)	3.85(3.08)
Gastric ulcer[a]	47	5.01(3.76–6.68)	5.00(145.33)	2.31(1.78)
Hemorrhagic stroke	46	10.76(8.04–14.41)	10.73(390.71)	3.40(2.71)
Subdural hematoma	46	5.64(4.22–7.54)	5.62(168.99)	2.48(1.92)
Gout	46	5.15(3.85–6.88)	5.13(147.98)	2.35(1.81)
Visual acuity reduced[a]	45	2.51(1.88–3.37)	2.51(39.23)	1.32(0.85)
Atrioventricular block[a]	44	10.70(7.94–14.42)	10.67(370.73)	3.40(2.69)
Skin discoloration[a]	44	2.02(1.50–2.71)	2.01(21.36)	1.01(0.54)
Gastric hemorrhage	43	5.74(4.25–7.76)	5.73(161.97)	2.51(1.93)
Cardiogenic shock[a]	42	5.86(4.32–7.94)	5.84(162.51)	2.54(1.94)
Sleep apnea syndrome	42	4.49(3.31–6.08)	4.48(109.30)	2.16(1.60)
Sinus arrest[a]	41	58.67(42.68–80.66)	58.49(2,096.27)	5.76(4.12)

[a]ADE, not recorded in the drug labels/datasheets; ADE, adverse drug event; PTs, preferred terms; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95%CI, of the IC.

3.3 SOCs of ADE signals

The 241 positive ADE signals were classified using MedDRA for the involved organs and systems. A total of 18 SOCs were involved in ticagrelor ADE signals. The common SOCs were respiratory, thoracic, and mediastinal disorders (2,637 reports, 23 signals), general disorders and administration site conditions (1,688 reports, 13 signals), gastrointestinal disorders (1,131 reports, 39 signals), and cardiac disorders (1,050 reports, 45 signals) (Supplementary Table S4).

3.4 ADE frequency analysis

The top 50 ADEs of ticagrelor based on the number of reports are shown in Table 2. The main ticagrelor-related ADEs were dyspnea-related, bleeding-related, and bradycardia-related ADEs. Dyspnea and hemorrhage were the most serious ADEs with high signal strength mentioned in the package insert. Some ADEs not mentioned in the package insert, such as chest pain, feeling abnormal, chest discomfort, cardiac arrest, and thrombosis, were found to be possible new ADE signals.

The top 50 ADEs of ticagrelor based on risk strength are shown in Table 3. The ADEs with high signal intensity are mainly bradycardia-related ADEs. Among them, ventricular asystole [16 reports, ROR 218.56, 95% confidence interval (CI) 125.22–381.48], Cheyne-Stokes respiration (8 reports, ROR 87.05, 95% CI 41.86–181.05), and sinoatrial block (19 reports, ROR 63.74, 95% CI 39.89–101.85) had strong ADE signals. In addition, ADEs such as ventricular asystole, sinoatrial block, sinus arrest, idioventricular rhythm, and a feeling of suffocation were not mentioned in the package insert.

3.5 Bleeding-related PT

In this study, we found bleeding-related ADEs of ticagrelor distributed to 14 SOCs (Supplementary Table S5). The highest numbers of reports and signals were found for gastrointestinal disorders (849 reports, 22 signals), followed by injury, poisoning, and procedural complications (548 reports, 10 signals) and vascular disorders (520 reports, 4 signals). The PT distribution of the top 20 ADEs based on the number of reports of ticagrelor-related hemorrhage is shown in Table 4.

3.6 PTs in respiratory, thoracic and mediastinal disorders

PTs related to respiratory, thoracic, and mediastinal disorders are shown in Table 5. We identified new ADEs added to FDA-approved drug instructions, such as sleep apnea syndrome (42 reports, ROR 4.49, 95% CI 3.31–6.08) and Cheyne-Stokes respiration (8 reports, ROR 87.05, 95% CI 41.86–181.05) which have extremely high signal strength. Asphyxia, a feeling of suffocation, tachypnea, bronchospasm, orthopnea, hyperventilation, abnormal respiration, apnea, and acute pulmonary edema were found as possible new ADE risk signals.

3.7 PTs in cardiac disorders

PTs related to cardiac disorders are shown in Table 6. We identified new ADEs added to the FDA-approved drug instructions, such as bradycardia (123 reports, ROR 4.35, 95% CI 3.64–5.20), which had an extremely high signal strength. Cardiac arrest, atrial fibrillation, cardio-respiratory arrest, atrioventricular block complete, atrioventricular block, and cardiogenic shock were found as possible new ADE risk signals.

4 Discussion

In this study, bleeding, dyspnea, and bradycardia-related ADEs were the main ADEs of ticagrelor. Due to differences in the

TABLE 3 PT signal detection results of top 50 ADEs based on signal strength about ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)
Vascular stent occlusion	71	630.24(459.67–864.11)	626.78(23,830.40)	8.42(5.48)
Vascular stent thrombosis	406	409.53(362.66–462.45)	396.68(104,579.20)	8.02(7.14)
Arterial restenosis	18	375.71(213.31–661.74)	375.19(4,231.97)	7.97(3.38)
Restenosis	4	250.20(80.68–775.88)	250.12(569.05)	7.55(0.82)
Ventricular asystole[a]	16	218.56(125.22–381.48)	218.29(2,514.95)	7.40(3.18)
Vascular stent stenosis	68	185.18(141.95–241.56)	184.21(9,801.84)	7.21(5.18)
Coronary artery restenosis	27	143.99(95.36–217.42)	143.69(3,092.17)	6.92(3.93)
Coronary artery reocclusion	5	125.11(48.53–322.51)	125.06(426.34)	6.75(1.24)
Platelet function test abnormal	12	106.03(57.92–194.11)	105.94(1,002.89)	6.54(2.67)
Cheyne-stokes respiration	8	87.05(41.86–181.05)	87.00(534.71)	6.29(2.01)
Sinoatrial block[a]	19	63.74(39.89–101.85)	63.65(1,022.97)	5.88(3.24)
Sinus arrest[a]	41	58.67(42.68–80.66)	58.49(2,096.27)	5.76(4.12)
Idioventricular rhythm[a]	9	52.80(26.85–103.81)	52.76(379.95)	5.63(2.13)
Vascular occlusion	35	36.02(25.65–50.59)	35.93(1,101.09)	5.10(3.66)
Vascular stenosis	5	32.36(13.22–79.22)	32.34(117.06)	4.96(1.16)
A feeling of suffocation[a]	34	31.46(22.31–44.36)	31.38(930.99)	4.91(3.54)
Spinal cord hematoma	5	30.27(12.38–74.02)	30.26(109.27)	4.86(1.15)
Bleeding time prolonged	17	28.51(17.56–46.29)	28.47(408.10)	4.78(2.78)
Gastrointestinal angiodysplasia[a]	6	28.33(12.54–64.02)	28.32(127.14)	4.77(1.41)
Cardiac ventricular thrombosis	13	25.36(14.59–44.09)	25.34(270.88)	4.62(2.41)
Asphyxia[a]	101	23.60(19.35–28.80)	23.43(2,081.81)	4.51(3.94)
Coronary artery stenosis	38	22.73(16.45–31.40)	22.67(743.10)	4.46(3.37)
Occult blood	5	19.25(7.92–46.77)	19.24(67.43)	4.23(1.05)
Microcytic anemia	16	17.97(10.94–29.51)	17.95(233.77)	4.13(2.44)
Vascular pseudoaneurysm[a]	15	16.14(9.68–26.93)	16.13(193.79)	3.98(2.31)
Cardiac aneurysm[a]	7	15.55(7.35–32.87)	15.54(79.58)	3.93(1.42)
Traumatic intracranial hemorrhage	8	15.36(7.63–30.94)	15.35(91.58)	3.91(1.58)
Erosive duodenitis[a]	6	15.32(6.83–34.39)	15.31(65.25)	3.91(1.22)
Complete atrioventricular block[a]	48	14.73(11.06–19.61)	14.68(586.83)	3.85(3.08)
Coronary artery dissection[a]	7	13.94(6.60–29.45)	13.93(70.28)	3.78(1.37)
Orthopnea[a]	19	13.52(8.59–21.29)	13.50(203.94)	3.73(2.39)
Paroxysmal nocturnal dyspnea	4	12.78(4.76–34.33)	12.77(31.87)	3.65(0.62)
Intracranial hemorrhage	123	12.42(10.38–14.85)	12.31(1,247.09)	3.60(3.21)
Nocturnal dyspnea	7	12.31(5.83–25.98)	12.30(60.81)	3.60(1.31)
Myocardial necrosis marker increased	12	12.28(6.94–21.73)	12.27(111.35)	3.60(1.90)
Subcutaneous hematoma	8	12.18(6.06–24.50)	12.18(70.12)	3.58(1.46)
Gastrointestinal polyp hemorrhage	4	12.11(4.51–32.52)	12.10(29.90)	3.58(0.60)
Retroperitoneal hematoma	14	11.92(7.03–20.22)	11.91(127.21)	3.55(2.02)

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TABLE 3 (*Continued*) PT signal detection results of top 50 ADEs based on signal strength about ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)
Atrioventricular block second degree[a]	18	11.73(7.36–18.69)	11.71(163.30)	3.53(2.22)
Irregular breathing[a]	4	11.46(4.27–30.77)	11.46(28.00)	3.50(0.58)
Ear hemorrhage	11	11.25(6.20–20.42)	11.25(91.31)	3.47(1.75)
Cerebral mass effect[a]	6	11.20(5.00–25.09)	11.20(45.31)	3.47(1.08)
Cerebellar hemorrhage	9	11.02(5.71–21.29)	11.02(71.20)	3.44(1.53)
Acute left ventricular failure[a]	4	10.92(4.07–29.30)	10.91(26.40)	3.43(0.56)
Hemorrhagic stroke	46	10.76(8.04–14.41)	10.73(390.71)	3.40(2.71)
Bradyarrhythmia	9	10.71(5.55–20.68)	10.70(68.77)	3.40(1.51)
Atrioventricular block[a]	44	10.70(7.94–14.42)	10.67(370.73)	3.40(2.69)
Brain death[a]	16	10.67(6.52–17.49)	10.66(128.78)	3.40(2.05)
Dyspnea at rest	13	10.38(6.00–17.94)	10.37(99.47)	3.36(1.85)
Iron deficiency anemia	37	10.01(7.23–13.85)	9.98(286.31)	3.30(2.53)

[a]ADE, not recorded in the drug labels/datasheets; ADE, adverse drug event; PTs, preferred terms; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95%CI, of the IC.

TABLE 4 PT signal detection results of top 20 ADEs related to hemorrhage induced by ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)	Intensity
Contusion	399	8.63(7.81–9.54)	8.39(2,571.97)	3.06(2.88)	+
Hemorrhage	399	6.56(5.93–7.25)	6.39(1,800.29)	2.66(2.50)	+
Gastrointestinal hemorrhage	270	5.00(4.43–5.64)	4.91(835.45)	2.29(2.09)	+
Epistaxis	270	6.98(6.18–7.88)	6.86(1,336.38)	2.77(2.56)	+
Anemia	250	2.81(2.48–3.19)	2.78(283.63)	1.47(1.28)	+
Cerebral hemorrhage	169	8.43(7.24–9.82)	8.33(1,073.04)	3.04(2.76)	+
Hemoglobin decreased	152	3.31(2.82–3.89)	3.29(239.22)	1.71(1.46)	+
Intracranial hemorrhage	123	12.42(10.38–14.85)	12.31(1,247.09)	3.60(3.21)	+ +
Melaena	108	9.31(7.69–11.26)	9.24(776.16)	3.19(2.81)	+
Rectal hemorrhage	83	4.02(3.24–4.99)	4.00(182.89)	1.99(1.63)	+
Hematuria	81	4.43(3.56–5.51)	4.41(209.04)	2.13(1.75)	+
Faces discolored	68	6.64(5.22–8.43)	6.61(315.45)	2.71(2.25)	+
Hematochezia	61	2.40(1.86–3.08)	2.39(47.79)	1.25(0.85)	+
Hematoma	52	3.93(2.99–5.16)	3.92(109.55)	1.96(1.49)	+
Hemoptysis	52	3.88(2.96–5.10)	3.87(107.43)	1.95(1.47)	+
Upper gastrointestinal hemorrhage	51	5.49(4.16–7.23)	5.47(180.63)	2.44(1.92)	+
Subdural hematoma	46	5.64(4.22–7.54)	5.62(168.99)	2.48(1.92)	+
Hemorrhagic stroke	46	10.76(8.04–14.41)	10.73(390.71)	3.40(2.71)	+ +
Gastric hemorrhage	43	5.74(4.25–7.76)	5.73(161.97)	2.51(1.93)	+
Internal hemorrhage	39	4.32(3.16–5.93)	4.31(95.51)	2.10(1.53)	+

PTs, preferred terms; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95%CI, of the IC; intensity, the judgment criteria of signal intensity was shown in Supplementary Table S1.

TABLE 5 PT signal detection results of top 20 ADEs related to respiratory, thoracic, and mediastinal disorders induced by ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)	Intensity
Dyspnea	1824	7.34(6.99–7.72)	6.45(8,505.6)	2.68(2.60)	+
Epistaxis	270	6.98(6.18–7.88)	6.86(1,336.38)	2.77(2.56)	+
Asphyxia[a]	101	23.60(19.35–28.80)	23.43(2081.81)	4.51(3.94)	+ +
Exertional dyspnea	63	3.94(3.07–5.05)	3.92(133.75)	1.97(1.54)	+
Hemoptysis	52	3.88(2.96–5.10)	3.87(107.43)	1.95(1.47)	+ +
Pulmonary edema	52	2.45(1.87–3.22)	2.45(43.03)	1.29(0.85)	+
Sleep apnea syndrome	42	4.49(3.31–6.08)	4.48(109.30)	2.16(1.60)	+
A feeling of suffocation[a]	34	31.46(22.31–44.36)	31.38(930.99)	4.91(3.54)	+ +
Pulmonary hemorrhage	32	8.40(5.93–11.91)	8.38(198.53)	3.05(2.26)	+
Tachypnea[a]	29	4.52(3.13–6.51)	4.51(75.31)	2.17(1.48)	+
Bronchospasm[a]	20	3.39(2.19–5.27)	3.39(31.22)	1.76(0.97)	+
Orthopnea[a]	19	13.52(8.59–21.29)	13.5(203.94)	3.73(2.39)	+ +
Hyperventilation[a]	14	5.17(3.06–8.75)	5.17(42.69)	2.36(1.26)	+
Dyspnea at rest	13	10.38(6.00–17.94)	10.37(99.47)	3.36(1.85)	+ +
Pulmonary alveolar hemorrhage	12	4.44(2.52–7.83)	4.44(28.42)	2.14(1.00)	+
Respiration abnormal[a]	12	3.32(1.88–5.85)	3.31(17.06)	1.72(0.69)	+
Apnea[a]	12	3.15(1.79–5.55)	3.15(15.43)	1.65(0.63)	+
Cheyne-stokes respiration	8	87.05(41.86–181.05)	87.00(534.71)	6.29(2.01)	+ + +
Acute pulmonary edema[a]	8	3.74(1.87–7.49)	3.74(13.34)	1.90(0.55)	+
Nocturnal dyspnea	7	12.31(5.83–25.98)	12.30(60.81)	3.60(1.31)	+ +

[a]ADE, not recorded in the drug labels/datasheets; PTs, preferred terms; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95%CI, of the IC; intensity, the judgment criteria of signal intensity was shown in Supplementary Table S1.

definition of bleeding, the incidence of bleeding induced by ticagrelor reported in previous literature varies widely, fluctuating between 3% and 32% (Wang et al., 2018). The risk of bleeding of ACS patients treated with ticagrelor versus clopidogrel was analyzed in the PLATO study, which showed there was no significant increase in the overall rate of major bleeding (11.6% with ticagrelor and 11.2% with clopidogrel, respectively; p = 0.43) (Wallentin et al., 2009). The PEGASUS-TIMI 54 study reported an increased risk of major bleeding with ticagrelor compared to aspirin-backed placebo in patients with prior myocardial infarction over 1 year, but the incidence of TIMI major bleeding was similar between different dosing groups (2.60% in the 90 mg group and 2.30% in the 60 mg group), and the incidence of intracranial or fatal bleeding was 0.63% and 0.71%, which was close to 0.60% in the placebo group (Bonaca et al., 2015). The risk of bleeding is included in the black box warning on the package insert of ticagrelor, and intracranial hemorrhage is defined as the main fatal/life-threatening bleeding in the PLATO trial. This study found that risk signals in the nervous system, including cerebral hemorrhage (169 reports, ROR 8.43, 95% CI 7.24–9.82), intracranial hemorrhage (123 reports, ROR 12.42, 95% CI 10.38–14.85), and hemorrhagic stroke (46 reports, ROR 10.76, 95% CI 8.04–14.41), had a high signal strength. Ticagrelor increases the risk of bleeding while reducing the risk of ischemia, so it is necessary to optimize the balance between ischemia and bleeding risk. Therefore, the dosage and duration of ticagrelor should be evaluated individually based on the patient's risk of ischemia and bleeding, the occurrence of adverse events, complications, and combination with other drugs.

Gastrointestinal disorders had the third highest number of PT signals (1,131 reports, 39 signals), while in the subgroup analysis of bleeding-related ADEs, the highest number of reports and signals was also found for gastrointestinal disorders (849 reports, 22 signals). This is consistent with the observation in clinical studies that the increased risk of bleeding is primarily due to gastrointestinal bleeding (GIB) events, which occur more frequently than other major bleeding events. A meta-analysis showed an increased risk of GIB with third-generation P2Y12 inhibitors compared to clopidogrel (RR = 1.28, 95% CI = 1.13–1.46) and a higher risk of GIB occurring in the upper gastrointestinal tract compared with other sites; with a GIB incidence of 1.25% (216/17329) for ticagrelor, there was no increased risk of GIB compared with clopidogrel (RR = 1.15, 95% CI = 0.94–1.39) (Guo et al., 2019). The results of this study again validate that there is a higher risk of bleeding with a greater proportion originating from the gastrointestinal tract with ticagrelor, which is generally consistent with the results of other studies and the dosing cautionary information. In addition, a clinical safety review by the FDA reported a higher incidence of

TABLE 6 PT signal detection results of top 20 ADEs related to cardiac disorders induced by ticagrelor.

PTs	Reports	ROR (95% CI)	PRR (χ^2)	IC (IC025)	Intensity
Cardiac arrest[a]	137	3.41(2.88–4.04)	3.39(227.59)	1.75(1.48)	+
Bradycardia	123	4.35(3.64–5.20)	4.32(309.49)	2.10(1.81)	+
Atrial fibrillation[a]	99	2.05(1.68–2.50)	2.04(51.51)	1.03(0.72)	+
Cardio-respiratory arrest[a]	55	2.61(2.00–3.40)	2.60(52.50)	1.38(0.95)	+
Complete atrioventricular block[a]	48	14.73(11.06–19.61)	14.68(586.83)	3.85(3.08)	+ +
Atrioventricular block[a]	44	10.70(7.94–14.42)	10.67(370.73)	3.40(2.69)	+ +
Cardiogenic shock[a]	42	5.86(4.32–7.94)	5.84(162.51)	2.54(1.94)	+
Sinus arrest[a]	41	58.67(42.68–80.66)	58.49(2,096.27)	5.76(4.12)	+ +
Coronary artery stenosis	38	22.73(16.45–31.40)	22.67(743.1)	4.46(3.37)	+ + +
Pericardial effusion[a]	32	2.87(2.03–4.06)	2.86(36.80)	1.51(0.93)	+
Ventricular fibrillation[a]	28	5.52(3.81–8.01)	5.51(98.29)	2.45(1.71)	+
Myocardial ischemia[a]	26	4.50(3.06–6.62)	4.49(66.79)	2.16(1.43)	+
Ventricular tachycardia[a]	26	3.37(2.29–4.96)	3.37(40.80)	1.75(1.07)	+
Sinoatrial block[a]	19	63.74(39.89–101.85)	63.65(1,022.97)	5.88(3.24)	+ + +
Atrioventricular block second degree[a]	18	11.73(7.36–18.69)	11.71(163.30)	3.53(2.22)	+ +
Sinus bradycardia[a]	18	3.73(2.34–5.92)	3.72(32.99)	1.89(1.03)	+
Ventricular asystole[a]	16	218.56(125.22–381.48)	218.29(2,514.95)	7.40(3.18)	+ + +
Cardiac ventricular thrombosis	13	25.36(14.59–44.09)	25.34(270.88)	4.62(2.41)	+ +
Cardiac tamponade[a]	13	4.90(2.84–8.46)	4.90(36.31)	2.29(1.16)	+
Cardiac failure acute[a]	13	4.15(2.41–7.16)	4.15(27.81)	2.05(0.98)	+ +

[a]ADE, not recorded in the drug labels/datasheets; PTs, preferred terms; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; $\chi 2$. chi-squared; IC, information component; IC025, the lower limit of 95%CI, of the IC; intensity, the judgment criteria of signal intensity was shown in Supplementary Table S1.

gastrointestinal AEs with ticagrelor compared to clopidogrel, including overall gastrointestinal or anal bleeding events, spontaneous GIB events, and nausea, vomiting, dyspepsia, diarrhea, and the presence of *Helicobacter pylori*, and a higher incidence of constipation with clopidogrel (Serebruany et al., 2013). This study found risk signals such as gastrointestinal hemorrhage (270 reports, ROR 5.00, 95% CI 4.43–5.64), melaena (108 reports, ROR 9.31, 95% CI 7.69–11.26), and rectal hemorrhage (83 reports, ROR 4.02, 95% CI 3.24–4.99), but the number of reports of nausea, vomiting, dyspepsia, and diarrhea was low, and no signal was detected. This may be because these digestive ADE symptoms are mild and non-specific in patients on multiple medications, and they may be underreported, leading to confounding bias. For patients with a history of GIB and an increased risk of bleeding, ticagrelor should be prescribed with caution, and antiplatelet therapy with clopidogrel or the addition of a proton pump inhibitor for GIB prophylaxis is recommended.

In addition, dyspnea (1824 reports, ROR 7.34, 95% CI 6.99–7.72) was the most reported with strong signal values. The incidence of dyspnea in clinical trials is reported in the package insert as approximately 14%–21%. Adverse reactions of dyspnea (including dyspnea, dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea, and nocturnal dyspnea) were reported in 13.8% and 7.8% of patients in the ticagrelor and clopidogrel groups, respectively, in the PLATO study (Wallentin et al., 2009). This study revealed dyspnea-related PTs that were generally consistent with the ADEs reported in the PLATO study, in addition to ADEs not included in the package insert, such as asphyxia, a feeling of suffocation, and tachypnea. The PEGASUS-TIMI 54 study reported more frequent dyspnea in both ticagrelor dose groups compared with the aspirin-backed placebo group, with a slightly lower incidence in the low-dose group than in the high-dose group (18.93% in the 90 mg group and 15.84% in the 60 mg group). Most episodes of dyspnea were mild (58.1%) or moderate (36.9%) in severity, mostly single episodes early after treatment initiation, which resolved spontaneously or after discontinuation of the drug (Bonaca et al., 2015). The PLATO study showed that, compared with patients in the clopidogrel group, patients with dyspnea in the ticagrelor group were more likely to have onset of dyspnea within 7 days, with a median duration of 23 days (Storey et al., 2011). The mechanism of ticagrelor-related dyspnea remains to be confirmed, and current studies suggest that dyspnea is most often seen with reversible P2Y12 inhibitors. Moreover, by analyzing the ADEs of ticagrelor associated with the respiratory system, we identified risk signals for sleep apnea syndrome (42 reports, ROR 4.49, 95% CI 3.31–6.08), apnea (12 reports, ROR 3.15, 95% CI 1.79–5.55), and Cheyne-Stokes respiration (8 reports, ROR 87.05, 95% CI 41.86–181.05). A previous study using the VigiBase database found 28 cases of sleep apnea in ADE reports associated with ticagrelor, and through a proportional imbalance analysis, sleep apnea

was identified as a risk signal for ticagrelor (ROR = 4.16, 95% CI = 2.87–6.03) (Revol et al., 2018). A single-center prospective clinical trial was conducted to assess the association between CSA hypoventilation syndrome (CSAHS) and ticagrelor administration; a high prevalence of CSA after ACS was found (22.3%), and a much higher incidence was found in patients treated with ticagrelor than in those who were not (30% vs. 7.3%), confirming the association between ticagrelor and CSA (Meurin et al., 2021). As a result, the US FDA approved a new safety statement about CSA and Cheyne-Stokes respiration in September 2020 (FDA, 2020). Current hypotheses of underlying mechanisms of dyspnea related adverse reactions caused by ticagrelor include the antagonism of microglial P2Y12 receptors (Revol et al., 2018), the inhibition of the type 1 equilibrative nucleoside transporter (ENT1) protein and its effects on tissue adenosine levels or the inhibition of P2Y12 receptors located on C fibres of sensory neurons (Parodi and Storey, 2015). Therefore, caution is advised in patients with a history of asthma/chronic obstructive pulmonary disease; if dyspnea occurs during dosing, first assess its severity, whether it worsens, and whether it is due to the original disease or other causes; if the symptoms are mild and tolerated by the patient, continue to use ticagrelor and monitor the patient closely; if dyspnea worsens or is not tolerated by the patient and is suspected to be caused by ticagrelor, a switch to clopidogrel can be made.

The present study revealed many PTs that were positively related to arrhythmia; PTs related to bradycardia include cardiac arrest (137 reports, ROR 3.41, 95% CI 2.88–4.04), bradycardia (123 reports, ROR 4.35, 95% CI 3.64–5.20), complete atrioventricular block (48 reports, ROR 14.73, 95% CI 11.06–19.61), atrioventricular block (44 reports, ROR 10.70, 95% CI 7.94–14.42), and sinus arrest (41 reports, ROR 58.67, 95% CI 42.68–80.66). Among them, bradycardia is mentioned in the drug labels/datasheets. There are multiple case reports about bradycardia-related ADEs caused by ticagrelor and serious bradyarrhythmia, both as early effects or in a delayed fashion (Al-Bayati et al., 2021; Aranganathan et al., 2021; Kotaru and Kalavakunta, 2021). The EMA identified ticagrelor-related bradyarrhythmia as a potential safety issue and included it in the European Risk Management Plan in 2011 (Pujade et al., 2020). In the DISPERSE-2 clinical trial (Cannon et al., 2007), ventricular pauses were observed in patients receiving ticagrelor treatment. Therefore, the PLATO, PEGASUS, THEMIS, and THALES trials excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, second or third-degree AV block, or bradycardia-related syncope and are not protected with a pacemaker) (Scirica et al., 2011; Steg et al., 2019; Johnston et al., 2020; Bergmark et al., 2021). The electrocardiographic (ECG) sub-study of PLATO showed that ticagrelor compared to clopidogrel did not increase arrhythmic events even in subjects with ACS who present with mild conduction abnormalities on their baseline ECG (Scirica et al., 2018). However, a current meta-analysis of randomized controlled trials found an increased risk of both bradyarrhythmia and severe bradyarrhythmia; the latter seems mostly due to ventricular pauses of >2.5 s, but due to the lack of outcome data in two-thirds of eligible studies, the evidence is low to moderate (Pujade et al., 2020). The mechanism underlying ticagrelor-induced bradycardia is incompletely understood. On the one hand, ticagrelor may increase adenosine levels by inhibiting cellular adenosine uptake through the ENT1 transporter, causing bradycardia and heart block. On the other hand, ticagrelor may have a direct effect on automaticity and cardiac conduction (Cattaneo et al., 2014). In addition, ticagrelor seems to also increase the risk of tachycardia. Atrial fibrillation (99 reports, ROR 2.05, 95% CI 1.68–2.50), ventricular fibrillation (28 reports, ROR 5.52, 95% CI 3.81–8.01), and ventricular tachycardia (26 reports, ROR 3.73, 95% CI 2.29–4.96) were positive signals related with tachycardia. At present, there is no consensus on whether ticagrelor can cause tachycardia. A case report described a patient with unstable angina pectoris and a history of paroxysmal atrial fibrillation developed recurrent atrial fibrillation following the use of ticagrelor (Zhang et al., 2016). Ticagrelor could increase the adenosine half-life and plasma concentration levels and enhance the biological effects of adenosine, which has the potential to cause atrial fibrillation(Akkaif et al., 2021). However, a cross-sectional study did not find any difference in detailed ECG and echocardiographic parameters as atrial fibrillation predictors between ticagrelor and clopidogrel groups in ACS patients (Algül et al., 2019). Therefore, it is necessary to be aware that bradycardia may be related to the use of ticagrelor. Patients with bradycardia risk factors should be cautious when using ticagrelor. In addition, after the start of ticagrelor treatment, ACS patients should undergo careful ECG monitoring.

In addition, rhabdomyolysis (57 reports, ROR 2.75, 95% CI 2.12–3.57), which is not mentioned in the package insert, was reported in a high number. After reviewing individual cases, it was found that 52 of the reports received combination therapy with statins. Current national and international guidelines recommend dual antiplatelet therapy and long-term administration of statins for secondary prevention of cardiovascular events for the management of patients with ACS (Amsterdam et al., 2014; Collet et al., 2021). This ADE is most likely the result of a drug-drug interaction (DDI) between ticagrelor and statins because ticagrelor is a CYP3A4 substrate and a weak inhibitor of CYP3A4, which may lead to increased concentrations of statins such as simvastatin, leading to rhabdomyolysis. A pharmacokinetic study in healthy volunteers showed a significant increase in exposure when combined with simvastatin (80 mg) and atorvastatin (80 mg), which are metabolized by CYP3A4, and it is recommended that during treatment with ticagrelor, simvastatin should not be administered at doses greater than 40 mg (Teng et al., 2013). Although the increase in exposure to atorvastatin was modest, the first case of a ticagrelor-atorvastatin interaction was reported. A 62-year-old female patient was diagnosed with rhabdomyolysis after 2 months of treatment with ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol 25 mg twice daily, and aspirin. Kido et al. considered it might be related to the use of ticagrelor (Kido et al., 2015). Although Rosuvastatin is mainly metabolized by CYP2C9, there are reports of rhabdomyolysis caused by the DDI of rosuvastatin and ticagrelor. Vrkić Kirhmajer et al. reported 8 cases of rhabdomyolysis caused by the combination of rosuvastatin and ticagrelor as of early 2018 in the WHO Adverse Drug Reaction Database (VigiBase). Three potential mechanisms of action for the occurrence of DDI with ticagrelor and rosuvastatin are also summarized (Vrkić Kirhmajer et al., 2018): (i) renal impairment caused by ticagrelor, leading to reduced renal excretion of rosuvastatin, (ii) competition in the levels of transporter proteins (OATP1B1, P-glycoprotein, ABCG2, MRP2), leading to reduced biliary and renal excretion of rosuvastatin, and (iii) genetic polymorphisms in metabolic enzymes (CYPs, UGTs) and drug transporter proteins, leading to increased competition between drugs. It has been shown that risk

factors for rhabdomyolysis include renal impairment, hypertension, diabetes, and older age (Nguyen et al., 2018). For patients with the above risk factors, a combination of lower dose of statins and other lipid-lowering agents may be considered when using ticagrelor or replaced with other antiplatelet agents (Roule et al., 2023). During the initial phase of ticagrelor treatment, close monitoring is required. If rhabdomyolysis occurs, the drug should be stopped immediately, and the antiplatelet drug regimen should be changed.

The following limitations exist in this study. First, we found the top number of reports for "vascular disorders" and "general disorders and administration site conditions" according to SOC classification, including many ADEs that may be related to the progression of primary diseases such as vascular stent occlusion, vascular stent thrombosis, arterial restenosis, and restenosis. It is important to highlight that patients using ticagrelor face an elevated risk of encountering symptoms such as respiratory distress, stent thrombosis, or chest pain attributed to potential disease effects. These symptoms may be documented as ADEs and result in positive signals. Our study, however, only establishes statistical associations, as the FAERS database lacks a causal relationship between a drug and an ADE. When symptoms associated with the primary disease manifest, it is crucial to provide a meticulous explanation. In addition, FAERS is a self-reporting system, the quality of the reports were unable to be guaranteed and the overall population size using ticagrelor is unknown, underreporting may occur in the ADE reporting process, making it difficult to calculate the incidence of ADEs.

5 Conclusion

Our study, analyzing real-world data from the FAERS database, identified 18 System Organ Classes (SOCs) affected by ticagrelor ADEs, predominantly in respiratory, thoracic, and mediastinal systems. Common ADEs like bleeding, dyspnea, and bradycardia were consistent with package insert reports, with notable findings in gastrointestinal bleeding and rare ADEs such as sleep apnea syndrome and Cheyne-Stokes respiration. Additionally, we identified new ADEs including cardiac arrest, atrial fibrillation, asphyxia, and rhabdomyolysis.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Independent Ethics Committee (IEC) for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University [Application ID: (2022)448]. 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

YP, YW, and JL participated in the study design. YP and YW were responsible for data collection and data analysis. YP and YW wrote the first draft of the manuscript. YZ, JC, and JL made appropriate revisions. 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

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1251961/full#supplementary-material

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