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Application of data mining in pharmaceutical research

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Application of data mining in pharmaceutical research

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Editorial: Application of data mining in pharmaceutical research

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Editorial on the Research Topic
Application of data mining in pharmaceutical research

Big data from medical public databases and data-mining techniques are pivotal to advancing various healthcare fields, particularly epidemiology, public health, and clinical research. These databases provide a wealth of information on health indicators, disease prevalence, and patient outcomes, and applying data-mining techniques to them can reveal trends, correlations, and patterns for informing public health policies and clinical practices (Yang et al., 2020; Wu et al., 2021). For example, researchers can analyze data on disease incidence and mortality rates to identify risk factors and develop targeted interventions for reducing disease burdens. In clinical research, mining data obtained from medical databases aids in identifying potential drug targets, evaluating treatment efficacy, and predicting patient outcomes. This can lead to the development of new therapies and the optimization of existing treatments, ultimately improving patient care and outcomes. However, relatively few studies have applied data-mining techniques to various medical databases with a focus on pharmacy. Therefore, this Research Topic focuses on the application of data mining in pharmaceutical research. Below we introduce and comment on the 11 research articles comprising this Research Topic.

Chen et al. investigated the relationships of low- and high-dose aspirin use with the risks of death from all causes, cardiovascular disease (CVD), and cancer among US adults aged 40 years and older using data from the NHANES (National Health and Nutrition Examination Survey). The study found that low-dose aspirin did not significantly reduce the risk of death from any cause, whereas high-dose aspirin use was associated with an increased risk of CVD death. The study highlights the need for caution in recommending high-dose aspirin for the primary prevention of CVD, especially in older adults, due to the potential increased risk of adverse outcomes.

Fang et al. conducted a real-world disproportionality analysis of apalutamide, a drug used to treat prostate cancer, using data from the FDA Adverse Event Reporting System. The analysis aimed to identify the safety of apalutamide in real-world settings, and yielded valuable evidence for the safety profile of apalutamide in clinical practice. Wang et al.

conducted a retrospective pharmacovigilance analysis using the same database to identify drugs associated with tooth discoloration. The authors concluded that caution is needed when using these drugs, especially during pregnancy and early childhood. However, they also stated that further investigations are needed to confirm their findings and fully understand the mechanisms underlying tooth discoloration.

Li et al. analyzed the adverse drug reactions (ADRs) of five anti-TNFα agents using data from the WHO-VigiAccess database. The analysis identified common ADRs and their proportion. The findings suggest the importance of monitoring and the rational use of these drugs due to their potential for serious ADRs.

Del Fiol et al. analyzed the sales trends of psychotropic drugs in Brazil during the COVID-19 pandemic in order to identify any changes in consumption patterns. Using data from the National System of Controlled Products Management, the researchers found that sales of certain psychotropics increased significantly during the pandemic. The findings suggest that the pandemic has had a significant negative impact on mental health that has led to an increased use of these medications.

Three articles by Zhu et al., Wu et al., and Yang et al. used the Medical Information Mart for Intensive Care database. Zhu et al. aimed to determine the association between glucocorticoid use and all-cause mortality in critically ill patients with heart failure. The authors recommended that glucocorticoids should not be given to critically ill patients with heart failure, but also stated that further prospective studies or randomized controlled trials are needed for validation. Wu et al. analyzed the impact of ondansetron on acute pancreatitis patients in the ICU, and produced findings supporting the use of ondansetron as an antiemetic in ICU patients with acute pancreatitis. Yang et al. investigated the association between thiamine administration and prognosis in critically ill patients with heart failure, with the findings suggesting that thiamine supplementation can improve the prognosis of critically ill patients with heart failure.

Bu et al. analyzed global trends in the incidence rates of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) from 2010 to 2019 using data from the Global Burden of Disease Study 2019. The study found that the age-standardized incidence rate (ASR) of MDR-TB decreased over the analyzed period, while that of XDR-TB remained stable. The incidence trends varied by region, with most regions showing a decrease in MDR-TB but an increase in XDR-TB. People aged 35–44 and 55–64 years had the highest incidence rates of both MDR-TB and XDR-TB. Regions with a higher sociodemographic index (SDI) tended to have lower ASRs of MDR-TB. The authors concluded that current efforts to curb MDR-TB and XDR-TB are insufficient, and hence new strategies are needed, especially in high-risk regions and age groups as well as low-SDI regions.

Zhang et al. analyzed the risk factors and developed predictive models for acute kidney injury (AKI) in hospitalized patients treated with cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium using multivariate logistic regression analysis. The findings suggest that evaluating risk factors before administering these antibiotics can reduce the incidence of AKI and emphasize the need for increased awareness among medical staff and patients regarding AKI.

Luo et al. developed and validated a nomogram for predicting pulmonary infection (PI) in patients receiving immunosuppressive drugs based on the LASSO (least absolute shrinkage and selection operator) and multivariate Cox regression analyses. The study concluded that the nomogram could aid in predicting the PI risk in individual patients receiving immunosuppressive treatment and assist in personalized clinical decision-making. This suggests that the nomogram model has potential for widespread implementation in clinical practice to reduce the occurrence of PI.

In summary, the application of big data and data mining in pharmaceutical research supplements and adds practical evidence that can support decision-makers and clinicians. This Research Topic presents recent evidence and new perspectives for this.

Author contributions

QB: Writing–original draft. JL: Writing–review and editing. LZ: Writing–review and editing. SC: Writing–review and editing. DJ: Writing–review and editing. ZP: 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.

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Association between glucocorticoid use and all-cause mortality in critically ill patients with heart failure: A cohort study based on the MIMIC-III database

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Background: Heart failure (HF) is the terminal stage of various heart diseases. Conventional treatments have poor efficacy, and diuretic resistance can present. Previous studies have found that the use of glucocorticoids can enhance the diuretic effect of patients with heart failure and reduce heart failure symptoms. However, the relationship between glucocorticoid use and mortality in patients with heart failure in intensive care units is unclear.

Objectives: The aim of this study was to determine the association between glucocorticoid use and all-cause mortality in critically ill patients with heart failure. Methods: The information on patients with heart failure in this study was extracted from the MIMIC-III (Medical Information Mart for Intensive Care-III) database. Patients in the glucocorticoid and non-glucocorticoid groups were matched using propensity scores. The Kaplan-Meier method was used to explore the difference in survival probability between the two groups. A Cox proportional-hazards regression model was used to analyze the hazard ratios (HRs) for the two patient groups. Subgroup analyses were performed with prespecified stratification variables to demonstrate the robustness of the results.

Results: The study included 9,482 patients: 2,099 in the glucocorticoid group and 7,383 in the non-glucocorticoid group. There were 2,055 patients in each group after propensity-score matching. The results indicated that the non-glucocorticoid group was not significantly associated with reduced mortality in patients with heart failure during the 14-day follow-up period [HRs = .901, 95% confidence interval (CI) = .767–1.059]. During the follow-up periods of 15–30 and 15–90 days, the mortality risk was significantly lower in the non-glucocorticoid group than in the glucocorticoid group (HRs = .497 and 95% CI = .370–.668, and HRs = .400 and 95% CI = .310–.517, respectively). Subgroup analyses indicated no interaction among each stratification variable and glucocorticoid use.

Conclusion: Glucocorticoid use was associated with an increased mortality risk in critically ill patients with heart failure.

KEYWORDS

glucocorticoids, heart failure, all-cause mortality, retrospective cohort study, MIMIC-III database

Introduction

Heart failure (HF) is caused by abnormalities in heart structure and function, is characterized by water and sodium retention, often manifests as congestive pulmonary edema or vena cava congestion, and has typical symptoms of dyspnea, edema, and fatigue (Ponikowski et al., 20162016). It has become one of the most common causes of death worldwide, and has gradually become a serious public health problem due to the aging population and its increasing prevalence in the elderly (Vergaro et al., 2019). However, in addition to the aggravation of physiological symptoms, severe HF can also be accompanied by oliguria, electrolyte imbalance, and renal function deterioration. Conventional treatments often fail to significantly relieve symptoms, which increases the difficulty of treatment and the mortality risk.

The relationship between glucocorticoids and the cardiovascular system is well known to be complex. Studies have found that in the treatment of patients with acute decompensated heart failure (ADHF) and diuretic resistance, glucocorticoid use can enhance the effect of diuresis, increase urine output, and improve renal function (Massari et al., 2012). One study assessed a case of a diuretic-resistant patient with ADHF treated using methylprednisolone as a conventional treatment. After 3 days of glucocorticoid treatment the HF symptoms were significantly relieved, and the level of brain natriuretic peptide had decreased by 46% (Massari et al., 2012). A study by Bayliss found that glucocorticoids can promote urinary sodium excretion in patients with congestive HF and induce serum sodium to return to normal levels (Bayliss, 1966). The mechanism of the aforementioned beneficial effects may be related to a 30%–50% increase in renal blood flow and improved renal function (Raisz et al., 1957; Pechet et al., 1959). Studies of HF by Liu et al. found that patients in the glucocorticoid group had an increased urine output and glomerular filtration rate (GFR) compared with those in the placebo group, and these effects were observed after 3 days of glucocorticoid use (Liu et al., 2006a). There are a few studies that have suggested that glucocorticoids can be used safely in the short term and can lead to improvements in the clinical treatment of patients with ADHF (Liu and Liu, 2014). The results of a large, randomized, controlled clinical trial of methylprednisolone for treating acute myocardial infarction indicated that glucocorticoid use reduced the mortality risk in patients with new myocardial infarction by 50% (Stubbs, 1986). However, using glucocorticoids for HF also has certain adverse effects, such as increasing the risk of nosocomial infection, which makes this intervention controversial (Dec, 2007; Mosterd and Hoes, 2007). Glucocorticoids are the drugs most frequently associated with adverse drug events in hospitalized patients in the United States (AHRQ, 2006). Metabolic and cardiovascular adverse events are among the most common and serious adverse events caused by glucocorticoids (Fardet and Fève, 2014).

Research on the association between glucocorticoid use and all-cause mortality in patients with HF in intensive care units has produced unclear results. The aim of this study was to determine the associations of glucocorticoid use with 30- and 90-day all-cause mortality risk in patients with HF.

Materials and methods

Data collection

The data analyzed in this study were extracted from the Medical Information Mart for Intensive Care-III (MIMIC-III) database. This large database was established in 2003 by the Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. The latest version (version 1.4) of the MIMIC-III database collects admission data on more than 40,000 patients during 2001–2012. The database contains detailed patient information, including basic patient demographics, laboratory test results, imaging data, comorbidities, and other medical information (Yang et al., 2020). The database also includes times of admission, discharge, and death. Information on patients who died after discharge can be obtained from the social security database. We completed the relevant courses and passed the examination to obtain a certificate to access the database (certificate number: 45848365).

Patients are fully deidentified in the MIMIC-III database, and so this study did not require approval from the ethics committees of the hospitals. We used Structured Query Language to extract information on variables from the MIMIC-III database. Variables for which the proportion of missing data exceeded 10% were excluded, and missing values for the remaining variables were calculated using the multiple imputation method. The variables in this study included basic patient demographics, laboratory test results, comorbidities, and vital-sign variables (Wu et al., 2021). Demographic information included age and sex. Laboratory test results included potassium, sodium, hemoglobin, lymphocyte, platelet count, activated partial thromboplastin time (APTT), white blood cell (WBC) count, oxygen saturation (SpO2), and glucose. Vital signs included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (Rr), and body temperature (T). Comorbidities included congestive HF, hypertension, chronic pulmonary disease, diabetes, renal failure, liver disease, peptic ulcer, obesity, and anemia.

Inclusion and exclusion criteria

Patients diagnosed with HF according to the disease codes of the ninth revision of the International Classification of Diseases were included in the study. Exclusion criteria were as follows: 1) age < 18 years, 2) age > 90 years, and 3) not the first hospitalization.

Patient outcomes

The outcomes of this study were 30- and 90-day all-cause mortality in patients with HF after admission.

Statistical analysis

The study population was divided into glucocorticoid and non-glucocorticoid groups. Normally distributed continuous variables are expressed as mean ± standard-deviation values, and non-normally distributed continuous variables are expressed as quartiles. Student's

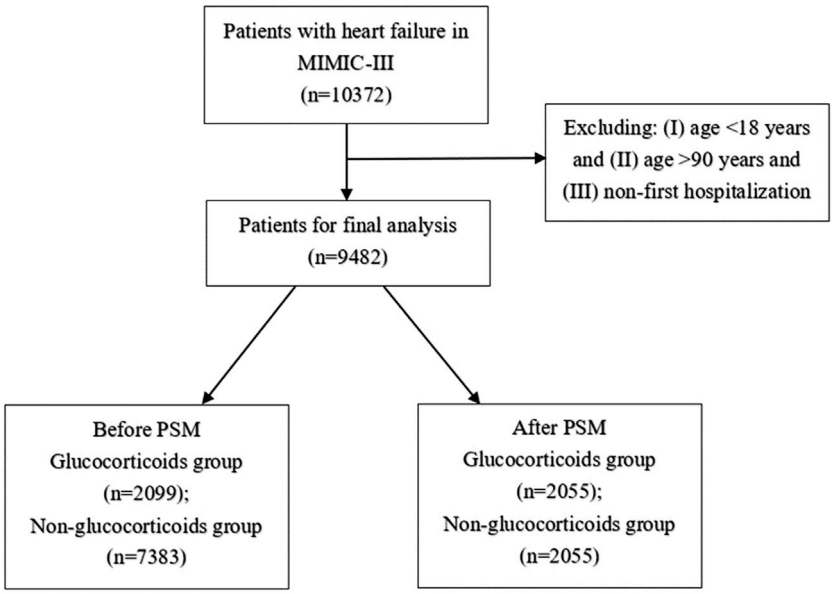

FIGURE 1
Selection of study population from MIMIC-III database.

t-test and Kruskal–Wallis test were used to assess the significance of differences between the glucocorticoid and non-glucocorticoid groups. Categorical variables are expressed as frequencies and percentages, and the chi-square test was used to compare differences between groups. Propensity-score matching (PSM) was used to address the imbalance of baseline characteristics between the glucocorticoid and non-glucocorticoid groups. Patients were matched at a 1:1 ratio using estimated propensity scores with a .05 caliper width. The standardized mean difference (SMD) was used to assess whether baseline characteristics were balanced, with SMD < .1 indicating that they were. Multicollinearity among covariates was tested using the variance inflation factor (VIF), with VIF < 5 indicating that there was no multicollinearity.

We counted the number of outcome events at different follow-up periods and compared the differences between the two groups. The Kaplan-Meier (K-M) method was used to estimate the 30- and 90-day survival probabilities of patients in the glucocorticoid and non-glucocorticoid groups, and the log-rank test was used to compare differences in survival probabilities between the two groups. According to the intersection of the survival curves between the glucocorticoid and non-glucocorticoid groups, combined with our clinical experience, we divided the 30-day follow-up period into 1–14 and 15–30 days, and the 90-day period into 1–14 and 15–90 days. We performed landmark analyses for endpoints at different follow-up periods, and differences between the glucocorticoid and non-glucocorticoid groups were compared using the log-rank test.

Cox proportional-hazards regression was used to determine the differences in the risk of death between patients in the glucocorticoid and non-glucocorticoid groups, and results were expressed using hazard ratios (HRs) and 95% confidence intervals (95% CIs). We selected the population of the glucocorticoid group as a reference and established three Cox proportional-hazards regression models: 1) Model I, unadjusted model; 2) Model II, included age, sex, HR, SBP, DBP, Rr, T, and SpO2; and 3) Model III, Model II plus potassium, sodium, hemoglobin, lymphocyte, platelet count, APTT, WBC count, glucose, congestive HF, hypertension, chronic pulmonary disease, diabetes, renal failure, liver disease, peptic ulcer, obesity, and anemia. The performance of each model was evaluated by calculating the C statistic.

We also identified prespecified age, sex, congestive HF, diabetes, hypertension, chronic lung disease, renal failure, liver disease, peptic ulcer, obesity, and anemia. Patients were divided into two groups based on age, with the cutoff of 65 years. In each subgroup, Cox proportional-hazards regression analysis was performed after establishing Model III, and the results were presented using forest plots. We also assessed whether each variable interacted with glucocorticoid exposure to impact all-cause mortality in each follow-up period.

A probability value of p-value < .05 was considered significant. We used R software (version 4.2.0) for statistical analyses. The R packages used included gtsummary, tableone, dplyr, remotes, jskm, survival, MatchIt, foreign, forestplot, tidyverse, ISwR, car, lattice, MASS, nnet, mice, and cobalt.

Results

As shown in Figure 1, 10,372 patients with HF were extracted from the MIMIC-III database. After excluding those aged < 18 and > 90 years and who had previously been hospitalized, 9,482 patients were included in the final analysis. Before PSM, 2,099 patients who had used glucocorticoids were assigned to the glucocorticoid group and 7,383 patients who had not used glucocorticoids were assigned to the non-glucocorticoid group. Table 1 lists the baseline characteristics of the glucocorticoid and non-glucocorticoid groups before matching. Supplementary Table S1 lists the VIFs for each covariate in the three follow-up periods, all of which were < 5, indicating no multicollinearity among the variables. The mean ages of the

TABLE 1 Baseline characteristics of population before PSM.

Variables	GCS (*n* = 2099)	Non-GCS (*n* = 7383)	*p*-value	SMD
Potassium (mmol/L)	4.47 ± .79	4.42 ± .71	.011	.061
Sodium (mmol/L)	137.91 ± 4.46	138.15 ± 4.14	.022	.056
Hemoglobin (g/dl)	11.30 ± 1.83	11.50 ± 1.85	<.001	.107
Lymphocyte (%)	12.69 ± 8.58	14.02 ± 7.56	<.001	.165
Platelet count (k/μl)	249.35 ± 112.50	245.18 ± 95.43	.090	.040
APTT (s)	36.06 ± 16.95	38.31 ± 20.67	<.001	.119
WBC, (k/μl)	13.06 ± 20.53	11.76 ± 9.66	<.001	.081
Heart rate (beats/min) (Hr)	87.08 ± 16.34	83.86 ± 15.32	<.001	.203
SBP (mmHg)	116.36 ± 16.48	116.12 ± 16.91	.564	.014
DBP (mmHg)	58.09 ± 10.36	57.24 ± 10.22	.001	.083
Respiration rate (beats/min)	20.30 ± 4.35	19.38 ± 3.95	<.001	.220
Body temperature (°C)	36.72 ± .67	36.76 ± .62	.024	.055
Oxygen saturation, %	96.51 ± 2.84	96.90 ± 2.73	<.001	.142
Glucose, mg/dl	152.10 ± 49.73	140.47 ± 44.04	<.001	.248
Age (years)	71.28 ± 13.62	73.01 ± 13.76	<.001	.127
Gender			<.001	.161
Man	979 (46.6)	4035 (54.7)		
Female	1120 (53.4)	3348 (45.3)		
Congestive heart failure,n (%)			<.001	.104
Yes	2048 (97.6)	7066 (95.7)		
No	51 (2.4)	317 (4.3)		
Hypertension, n (%)			.002	.078
Yes	1215 (57.9)	4556 (61.7)		
No	884 (42.1)	2827 (38.3)		
Chronic pulmonary disease, n (%)			<.001	.356
Yes	960 (45.7)	2127 (28.8)		
No	1139 (54.3)	5256 (71.2)		
Diabetes, n (%)			.028	.055
Yes	715 (34.1)	2710 (36.7)		
No	1384 (65.9)	4673 (63.3)		
Renal failure, n (%)			.325	.025
Yes	571 (27.2)	1927 (26.1)		
No	1528 (72.8)	5456 (73.9)		
Liver disease, n (%)			<.001	.148
Yes	225 (10.7)	486 (6.6)		
No	1874 (89.3)	6897 (93.4)		
Peptic ulcer, n (%)			.908	.006
Yes	17 (.8)	64 (.9)		
No	2082 (99.2)	7319 (99.1)		

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics of population before PSM.

Variables	GCS (*n* = 2099)	Non-GCS (*n* = 7383)	*p*-value	SMD
Obesity, n (%)			.257	.029
Yes	147 (7.0)	464 (6.3)		
No	1952 (93.0)	6919 (93.7)		
Anemia, n (%)			<.001	.087
Yes	157 (7.5)	395 (5.4)		
No	1942 (92.5)	6988 (94.6)		

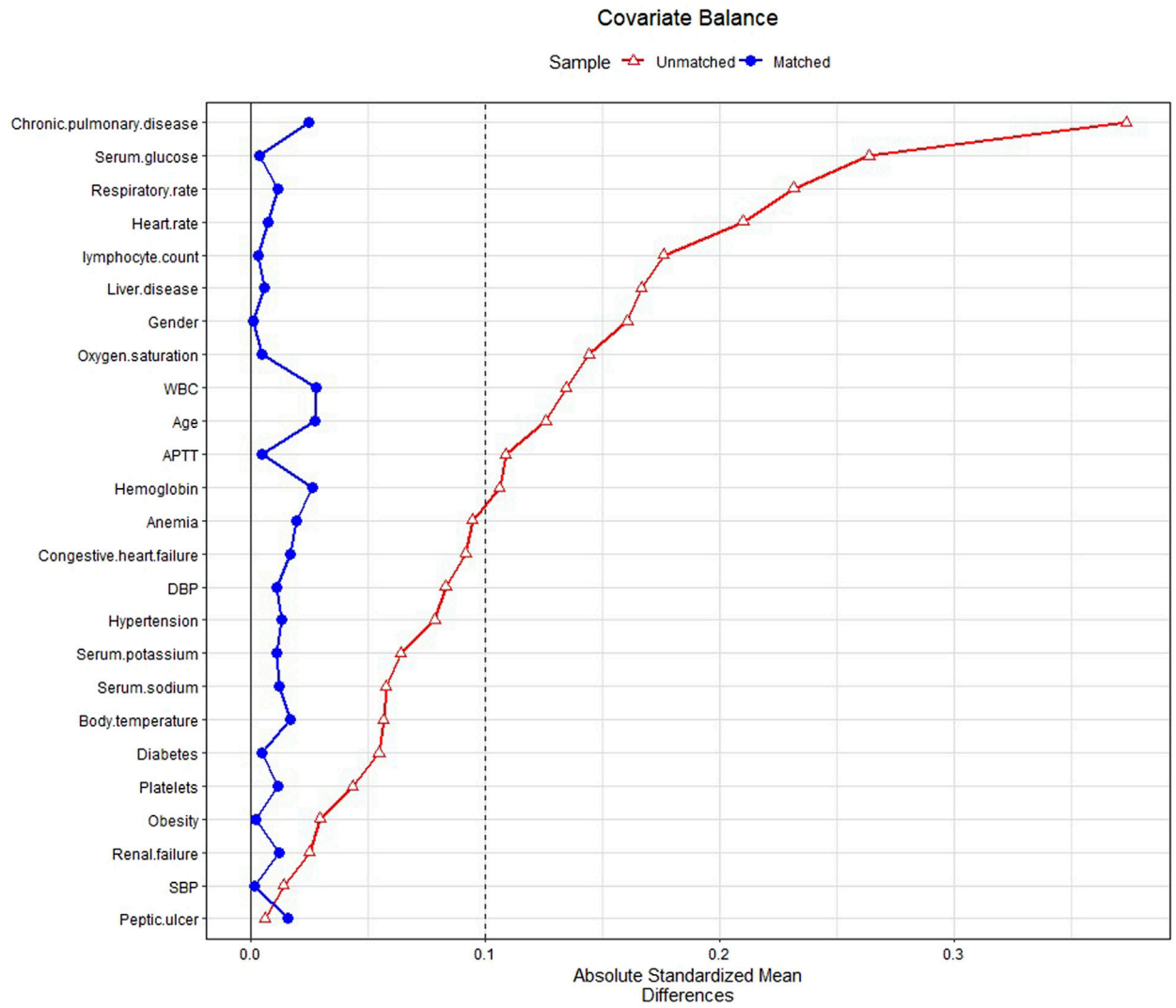

FIGURE 2
Standardized mean difference (SMD) of variables before and after propensity score matching.

glucocorticoid and non-glucocorticoid groups were 71.28 and 73.01 years, respectively. The numbers of males and females were 979 and 1,120 in the glucocorticoid group, respectively, and 4,035 and 3,348 in the non-glucocorticoid group. The numbers of patients with congestive HF in the glucocorticoid and non-glucocorticoid groups were 2,048 (97.6%) and 7,066 (95.7%), respectively. The WBC and lymphocyte counts were significantly higher in the glucocorticoid group than in the non-glucocorticoid group. Overall, the baseline characteristics of the two groups of patients were unbalanced for most variables.

TABLE 2 Mortality rates in patients with heart failure in the glucocorticoids group and non-glucocorticoids groups.

	Before PSM			After PSM		
	GCS	Non-GCS	*p*-value	GCS	Non-GCS	*p*-value
Mortality, n (%)						
1–14 day mortality	325 (15.5)	860 (11.6)	.001	314 (15.3)	301 (14.6)	.599
15–30 day mortality	137 (7.7)	192 (2.9)	<.001	133 (7.6)	68 (3.8)	<.001
15–90 day mortality	211 (11.8)	242 (3.7)	<.001	205 (11.7)	85 (4.8)	<.001

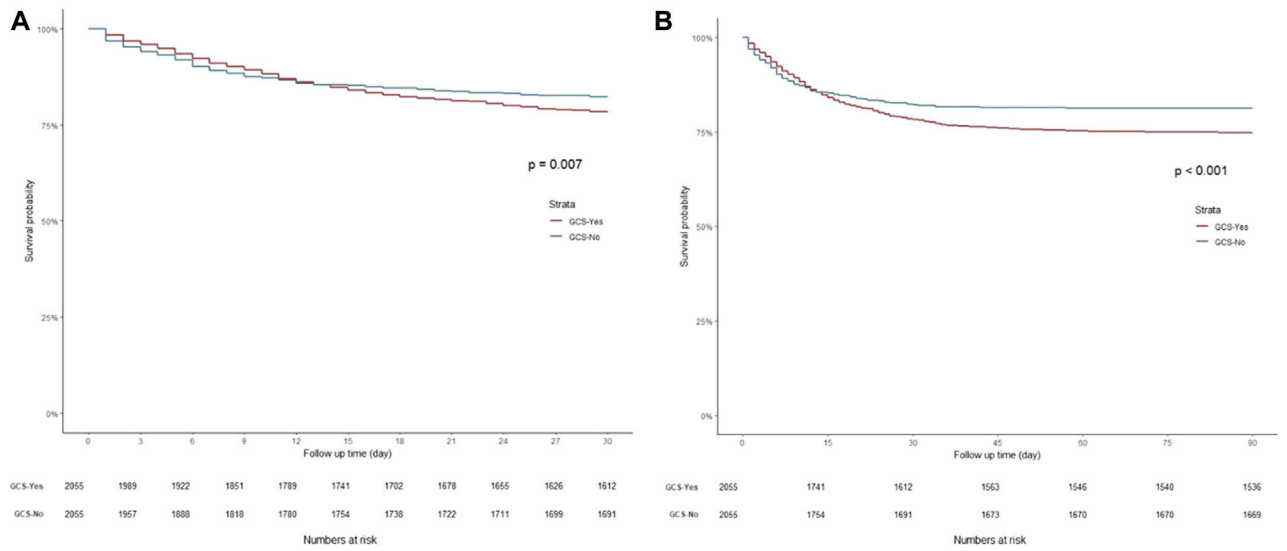

FIGURE 3
Kaplan-Meier survival curves of non-glucocorticoids group and non-glucocorticoids group after PSM. **(A)** 30-day mortality; **(B)** 90-day mortality.

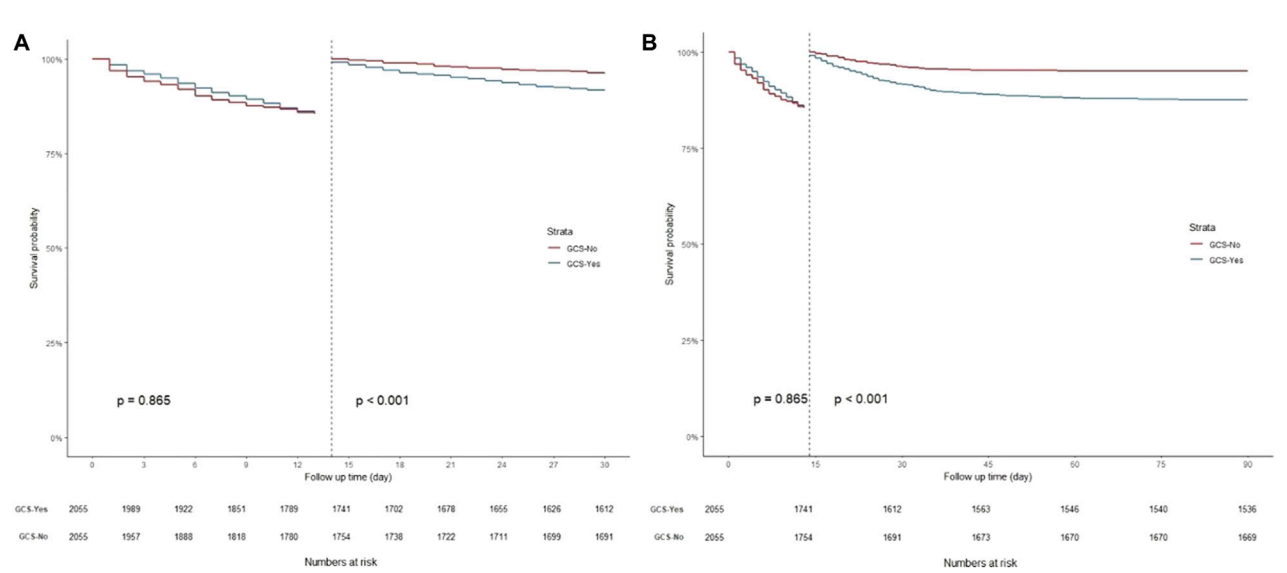

FIGURE 4
Landmark analysis discriminating between survival probability before and after 14 day of follow-up. **(A)** Landmark analysis during 30-day follow-up; **(B)** Landmark analysis during 90-day follow-up.

TABLE 3 Association between the non-glucocorticoid group and all-cause mortality.

	Before PSM			After PSM		
	GCS	Non-GCS	*p*-value	GCS	Non-GCS	*p*-value
1–14 day mortality		HR (95% CI)				
Events/total n	325/2099	860/7383		314/2055	301/2055	
Model I	References	.747 (.657–.848)	.001	References	.972 (.830–1.139)	.728
Model II	References	.822 (.722–.936)	.003	References	.921 (.785–1.081)	.316
Model III	References	.898 (.786–1.027)	.118	References	.901 (.767–1.059)	.209
15–30 day mortality						
Events/total n	137/1774	192/6523		133/1741	68/1754	
Model I	References	.371 (.298–.462)	<.001	References	.496 (.370–.665)	<.001
Model II	References	.405 (.324–.507)	<.001	References	.502 (.374–.672)	<.001
Model III	References	.472 (.374–.595)	<.001	References	.497 (.370–.668)	<.001
15–90 day mortality						
Events/total n	211/1774	242/6523		205/1741	85/1754	
Model I	References	.300 (.250–.361)	<.001	References	.398 (.309–.513)	<.001
Model II	References	.331 (.274–.400)	<.001	References	.401 (.311–.517)	<.001
Model III	References	.372 (.306–.452)	<.001	References	.400 (.310–.517)	<.001

In PSM, 2,055 patients with glucocorticoids were matched with the same number of patients in the non-glucocorticoid group. The baseline characteristics of patients in the glucocorticoid and non-glucocorticoid groups after PSM are listed in Supplementary Table S2. Figure 2 presents the SMD of each covariate before and after PSM. All covariates had SMD < .1 after matching, with *p*-value > .05, indicating that the covariates in the two groups had been balanced.

We assessed differences in all-cause mortality between the glucocorticoid and non-glucocorticoid groups during different follow-up periods. Before PSM, in all follow-up periods (14, 15–30, and 15–90 days), the mortality rate was significantly higher in the glucocorticoid group than in the non-glucocorticoid group (*p*-value < .05). Similarly, the mortality rate was significantly higher in the glucocorticoid group than in the non-glucocorticoid group after PSM; however, there was no significant difference between the two groups during the 14-day follow-up period after PSM (*p*-value > .05). The results are listed in Table 2.

K-M curves were used to plot the 30- and 90-day survival probabilities of the glucocorticoid and non-glucocorticoid groups after PSM, which are shown in Figure 3, respectively. Figure 4 present the results of the landmark analysis for 30- and 90-day survival probabilities, respectively. The 30- and 90-day survival probabilities differed significantly between the two patient groups (*p*-value < .05). The survival curves of the glucocorticoid and non-glucocorticoid groups intersected at 14 days. After 14 days, the mortality risk was slightly higher in the non-glucocorticoid group than in the glucocorticoid group, but the difference was not significant (*p*-value > .05). After 15–30 and 15–90 days of follow-up, the mortality risk was significantly lower in the non-glucocorticoid group than in the glucocorticoid group (*p*-value < .05).

In the Cox proportional-hazards regression analysis, we calculated the C statistic for Model III. Before and after PSM, the C statistics for Model III were .739 and .746 for 14 days, respectively, .769 and .760 for 15–30 days, and .775 and .758 for 15–90 day, indicating that the adopted model had good accuracy; the results are listed in Supplementary Table S3. After PSM, within the 14-day follow-up period and with the glucocorticoid group as a reference, the HRs (95% CI) values of the non-glucocorticoid group were .972 (.830–1.139) for Model I, .921 (.785–1.081) for Model II, and .901 (.767–1.059) for Model III. The difference between the two groups for Model III was not significant (*p*-value > .05). During the 15–30 day follow-up period, the risk of death was significantly lower in the non-glucocorticoid group than in the glucocorticoid group (*p*-value < .05); the HRs (95% CI) values of the non-glucocorticoid group were .496 (.370–.665) for Model I, .502 (.374–.672) for Model II, and .497 (.370–.668) for Model III. Similarly, during the 15–90 day follow-up period, the HRs (95% CI) values of the non-glucocorticoid groups were .398 (.309–.513) for Model I, .401 (.311–.517) for Model II, and .400 (.310–.517) for Model III, respectively, and the differences between the risks of death were significant (*p*-value < .05). The results of the Cox proportional-hazards regression analysis are presented in Table 3.

The subgroup analysis results indicated that stratification variables and glucocorticoid exposure did not interact (P for interaction > .05). Supplementary Figures S1–S3 show the subgroup analysis results. Within 14 days, there were no significant differences in the risk of death between the glucocorticoid and non-glucocorticoid groups for each stratification variable (*p*-value > .05), which was consistent with the overall risk of death, indicating that the results were robust. In the 15–30 and 15–90 day follow-up periods, the risk of death differed significantly between the glucocorticoid and non-glucocorticoid groups (*p*-value < .05) for all stratification variables except for

obesity and anemia, which was consistent with the overall risk of death, indicating that the results were robust.

Discussion

HF is a complex clinical syndrome caused by abnormal changes in cardiac structure and/or function *via* various mechanisms, which results in ventricular systolic and/or diastolic dysfunction. It is a severe manifestation or terminal stage of various heart diseases. In the early stage of HF, the stress response significantly increases the levels of epinephrine, glucagon, and glucocorticoids to above the physiological ranges (Luger et al., 1987). In the later stage, due to low cardiac output, the adrenal cortex is ischemic and hypoxic due to hypoperfusion, so its function of synthesizing corticosteroids is impaired, resulting in decreased blood cortisol.

Glucocorticoids are steroid compounds secreted by the zona fasciae in the adrenal cortex and is mostly regulated by the hypothalamic-pituitary-adrenal axis (Liu et al., 2019a). Physiological doses of glucocorticoids can regulate substance metabolism in the body and maintain its life activities. Supraphysiological doses of glucocorticoids have anti-inflammatory, anti-infective, antishock, and immunosuppressive effects, so they are widely used in clinical practice. The effects of standard treatment drugs are often less strong in the late stage of HF than in the early stage. The adrenal glands are often in an excited state due to repeated acute HF attacks, which eventually leads to a decrease in glucocorticoid secretion, especially in elderly patients with HF accompanied by adrenal insufficiency and infection.

Various animal experiments have found that glucocorticoids can enhance myocardial contractility, which occurs *via* numerous mechanisms. First, the increased release or enhanced effect of endogenous catecholamines indirectly leads to increased myocardial contractility (Tecklenberg et al., 1973; Jain et al., 2004). Second, it may also be caused by β-adrenergic receptor upregulation in the myocardium (Nishimura et al., 1997). Glucocorticoids can also protect kidney function. Previous studies have found that glucocorticoids dilate renal blood vessels, enhance the sensitivity of nephrons to diuretics, and increase the GFR (Liu et al., 2007; Smets et al., 2012; Liu et al., 2016), *via* the following mechanisms: First, glucocorticoids upregulate natriuretic peptide receptor A expression in the inner medullary collecting duct cells to enhance the sensitivity of the kidneys to natriuretic peptides and promote the diuretic effect in patients with HF (Gardner et al., 1986; Damjancic and Vierhapper, 1990a; Liu et al., 2010; Liu et al., 2011). Second, glucocorticoids reduce the production and secretion of vasopressin, and downregulate arginine vasopressin receptor expression (Erkut et al., 1998; Liu et al., 2006b; Greenwood et al., 2015; Zhu et al., 2020); the production of prostaglandins, nitric oxide, and dopamine is also increased, resulting in improved renal blood flow and GFR (Gong et al., 2008; Tokudome et al., 2009; Butts and Phillips, 2013; Liu et al., 2019b). Third, an animal study found that glucocorticoids somewhat affected the synthesis and release of atrial natriuretic peptide (ANP) (Garcia et al., 1985), up-regulating ANP receptors in vascular endothelial cells (Lanier-Smith and Currie, 1990). Likewise, studies have found that glucocorticoids may modulate ANP-mediated natriuresis and diuresis in humans (Damjancic and Vierhapper, 1990b). Glucocorticoids also enhance pulmonary edema clearance. Glucocorticoids can adjust the activity of alveolar epithelial Na+ channel and Na+-K+ ATPase, increase the tension in pulmonary blood vessels, and reduce the permeability of capillaries, so it can increase alveolar fluid clearance and accelerate the curing of pulmonary edema (Barquin et al., 1997; Ingbar et al., 1997).

However, excessive cortisol secretion and the use of various synthetic glucocorticoids increase the incidence rates of diabetes and cardiovascular disease (Plotz et al., 1952). Glucocorticoid use in non-diabetic patients increases their risk of developing diabetes by two-to fourfold (Conn and Poynard, 1994; Gurwitz et al., 1994; Blackburn et al., 2002; Gulliford et al., 2006). The mechanism of glucocorticoid-induced diabetes involves increasing insulin resistance, thereby affecting the glucose metabolism process, which is similar to the mechanism of type 2 diabetes. In the liver, increased insulin resistance can increase basal glucose production. Insulin also promotes intracellular glucose utilization by stimulating glucose transporter type 4, but glucocorticoids interfere with these signaling pathways and with glycogen synthesis. The above two mechanisms may lead to abnormal glucose metabolism and increase blood glucose levels (Ruzzin et al., 2005; Burén et al., 2008). An observational study found that low-density lipoprotein (LDL) was elevated after glucocorticoid therapy in patients with asthma, heart transplant, kidney transplant, and rheumatoid arthritis, which led to abnormal lipid metabolism (Sholter and Armstrong, 2000). An *in vitro* study found that hydrocortisone and dexamethasone alter LDL degradation in fibroblasts and macrophages, which may contribute to atherosclerosis (Henze et al., 1983; Hirsch and Mazzone, 1986).

Dexamethasone is also known to cause cardiotoxicity (de Salvi Guimarães et al., 2017a). Studies have found that long-term dexamethasone use may lead to cardiac fibrosis, increased norepinephrine-induced vasoconstriction, increased apoptosis, and decreased angiogenesis (Qi and Rodrigues, 2007; de Salvi Guimarães et al., 2017a). Dexamethasone can also cause cphy, which is an adaptive ardiac hypertrochange in response to dexamethasone-induced hypertension (Walker, 2007; Stahn and Buttgereit, 2008; Bal et al., 2009). Bézard et al. (2021) assessed the effect of dexamethasone on cardiac function using the Langendorff perfused heart model in healthy rats. The model is free from other confounding factors, allowing for precise studies of how the heart responds to dexamethasone (Sutherland and Hearse, 2000). Their study found that dexamethasone significantly reduced overall left ventricle (LV) function, as well as being caused LV systolic and diastolic dysfunction to various degrees. It is particularly interesting that the above-mentioned changes were also observed in healthy rats (Bézard et al., 2021). Similarly, de Salvi Guimarães et al. (2017b) found that dexamethasone-treated rats also developed multiple circulatory complications, including increased blood pressure, myocardial fibrosis, and cardiomyocyte apoptosis, which led to myocardial remodeling and diastolic dysfunction. That study also confirmed that the mechanisms underlying these changes included impaired calcium handling and activation of the calcineurin signaling pathway. It has also been found that systemic glucocorticoid use may increase the risk of deep-vein thrombosis, especially in patients with pulmonary embolism (Johannesdottir et al., 2013). Despite the effects of glucocorticoids on sodium excretion, diuresis, and increased GFR, glucocorticoid use increased the likelihood of non-acute complications such as diabetes, dyslipidemia, cardiotoxicity, and deep-vein thrombosis, which will be detrimental to the prognosis of patients with HF.

In this study, the WBC count was higher in the glucocorticoid group than in the non-glucocorticoid group (13.06 ± 20.53 vs. 11.76 ± 9.66 k/μl), as was the proportion of patients with chronic respiratory disease (45.7% vs. 28.8%). This suggests that the higher risk of death in the glucocorticoid group is caused by glucocorticoid-use-related diseases, such as chronic respiratory disease and infection. Some studies also found that serum inflammatory markers were associated with the incidence of cardiovascular events, and disease activity was directly related to the occurrence of cardiovascular events (Ross, 1999). We found that the association between glucocorticoid use and increased mortality in patients with HF persisted after adjusting for chronic respiratory disease and WBC counts.

We performed subgroup analyses of age, sex, congestive HF, diabetes, hypertension, chronic lung disease, kidney failure, liver disease, peptic ulcer, obesity, and anemia. The results indicated that there was no interaction between stratification variables and glucocorticoid exposure. The results of each subgroup analysis and the overall results also remained consistent at different follow-up times, indicating that our results were robust.

The highlight of our study was the division of follow-up into two time periods to more precisely account for the occurrence of outcome events. This study had some limitations. First, database limitations meant that we did not perform a subgroup analysis of total glucocorticoid dosage and administration duration. Second, the left ventricle ejection fraction was not analyzed in the study because it had more than 40% missing values. In addition, our study is a single-center study, and we hope that in future studies, multi-center studies can be conducted to obtain more information.

In conclusion, this retrospective study of a large database found that glucocorticoid use was associated with increased all-cause mortality in critically ill patients with HF. Our findings suggest that the use of glucocorticoids should not be recommended for critically ill patients with HF, but this requires further validation in prospective studies or randomized controlled trials.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://mimic.mit.edu/.

Author contributions

J-LZ and LH contributed equally to the work. J-RW and H-YY contributed to the study concept and study design and contributed equally. J-LZ performed statistical analysis and data interpretation. J-LZ were responsible for the quality control of data and algorithms. S-QY, LH, and X-MX performed literature research and data extraction. All authors contributed to writing of the manuscript and approved the final 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.2023.1118551/full#supplementary-material

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Low- or high-dose preventive aspirin use and risk of death from all-cause, cardiovascular disease, and cancer: A nationally representative cohort study

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Background and aim: For a long time, aspirin has been recommended for the prevention of cardiovascular disease (CVD). However, results of long-term effects of aspirin use on the risk of CVD and all-cause death as well as cause-specific mortality are not consistent. This study aims to investigate the relationship between low- or high-dose preventive aspirin use and the risk of death from all-cause, CVD, and cancer among US adults aged 40 years and older.

Methods: A prospective cohort study was conducted by utilizing four cycles of the National Health and Nutrition Examination Survey (NHANES) and linked 2019 mortality files. Cox proportional hazard models accounting for multiple covariates were used to calculate hazard ratio (HR) and 95% confidence interval (CI) for the associations between low- or high-dose aspirin use and risk of death.

Results: A total of 10,854 individuals (5,364 men and 5,490 women) were enrolled in the study. During a median follow-up of 4.8 years, 924 death events including 294 CVD death and 223 cancer death were documented. We found no evidence that taking low-dose aspirin decreased the chance of dying from any cause (HR: 0.92, 95% CI: 0.79–1.06), CVD (HR: 1.03, 95% CI: 0.79–1.33), or cancer (HR: 0.80, 95% CI: 0.60–1.08). High-dose aspirin users had a higher risk of CVD death compared to participants who had never used aspirin (HR: 1.63, 95% CI: 1.11–2.41).

Conclusion: Using low-dose aspirin has no effect on the risk of death from any causes, whereas taking high doses of aspirin increases the risk of CVD death.

KEYWORDS

aspirin, cardiovascular diseases, cancer, mortality, cohort study

Introduction

For a long time, people who have one or more risk factors for cardiovascular disease (CVD) have been recommended to take aspirin, one of the most often used drugs, to prevent CVD (Ittaman et al., 2014). According to estimates, 46.7% of US individuals aged 60 or older reported using aspirin to prevent CVD events (Liu et al., 2021). However, no consensus was established between the various guidelines committees on whether or how to use aspirin for primary prevention (Patrono and Baigent, 2019). According to the 2019 American College of Cardiology/American Heart Association Guidelines on the Primary Prevention of CVD,

persons aged 40 to 70 who have a higher risk of developing CVD but not a higher risk of bleeding may benefit from using low-dose (75–100 mg/d) aspirin (Arnett et al., 2019). In contrast, the routine use of aspirin for the primary prevention of CVD in people without known CVD risk is not advised by the 2021 European Guidelines for Cardiovascular Disease Prevention in Clinical Practice (Visseren et al., 2022). The most recent recommendation statement from the US Preventive Services Task Force (USPSTF) indicates that persons aged 40 to 59 who have a 10% or greater 10-year CVD risk should consider taking low-dose aspirin as their primary method of preventing CVD, but that low-dose aspirin use is not recommended for adults 60 years of age or older (Davidson et al., 2022). The guidelines differ because there is limited or conflicting information about the benefits of using aspirin for primary prevention. There is a dearth of evidence in community-based general populations covering a wide age range, despite the fact that low-dose aspirin use was compared to placebo for its effectiveness in preventing CVD in particular populations. In addition to CVD events, the relationship between preventive aspirin use and mortality risk has also been widely concerned. However, no consensus was established between the various studies on this issue. For example, some studies found that low-dose aspirin use was associated with a lower risk of mortality (Chan et al., 2007; Skriver et al., 2019) and other studies have found that aspirin has no effect or even harmful effect on the risk of death (Del et al., 2022; Shahrivar et al., 2022). By utilizing the National Health and Nutrition Examination Survey (NHANES) and linked mortality data, this study aims to investigate the relationship between low- or high-dose preventive aspirin use and the risk of all-cause, CVD, and cancer deaths among US adults 40 years of age and older.

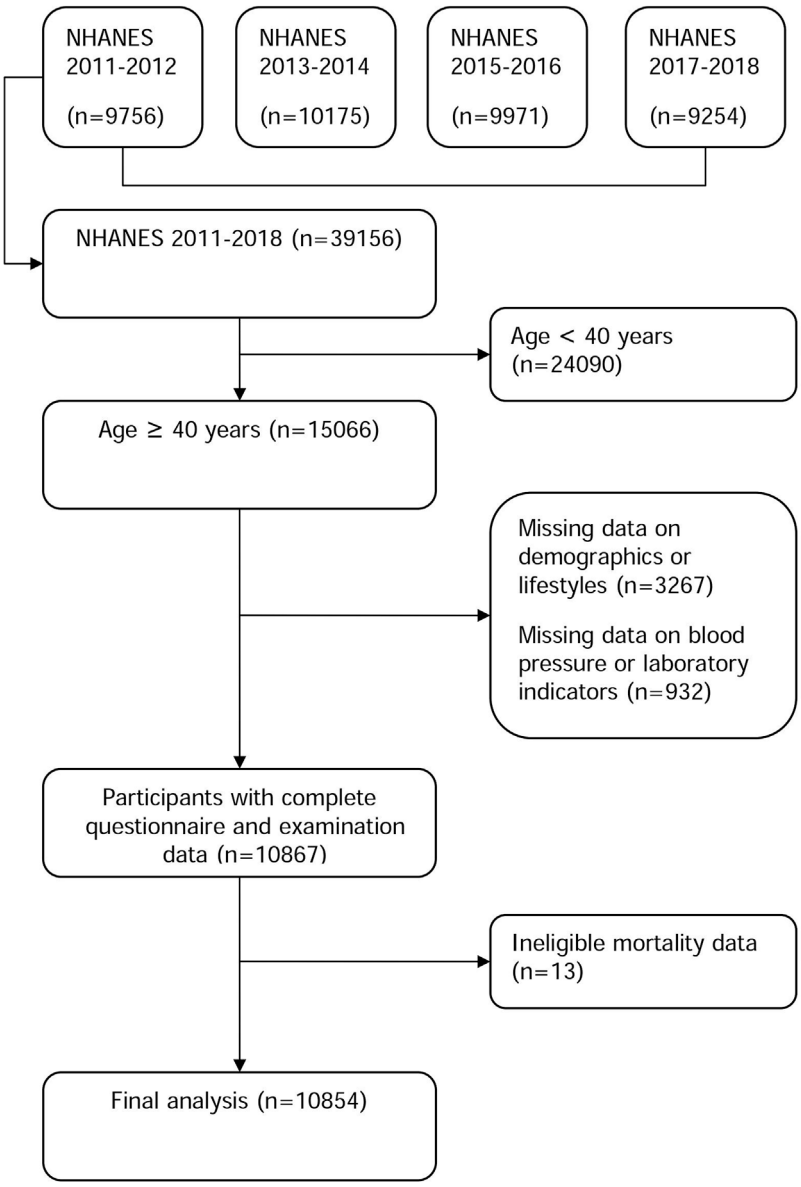

FIGURE 1
Flowchart of the study population selection.

Methods

Study population

Four NHANES cycles (2011-12, 2013-14, 2015-16, and 2017-18) were used to identify participants in this study. NHANES is a cohort of US residents who reside in communities and is nationally representative. A detailed description of the study population and sample design can be found elsewhere (Centers for Disease Control and Prevention, 2014). Within four cycles of the NHANES, 39,156 people nationwide were enrolled in the study (9,756 in the 2011-12 cycle, 10,175 in the 2013-14 cycle, 9,971 in the 2015-16 cycle, and 9,254 in the 2017-18 cycle). We only included individuals in this study who were 40 years of age or older (n = 15,066), as the questions about preventive aspirin use were relevant to this age group. In addition, we excluded 4,212 persons missing demographic or lifestyle information (n = 3,267), anthropometric results or laboratory markers (n = 932), or mortality information (n = 13). This resulted in the final analysis including 10,854 participants. Figure 1 shows a flowchart outlining the process of participant selection step-by-step. The study protocol was approved by the National Center for Health Statistics (NCHS) institutional review board (Protocol #2011-17 and Protocol #2018-01), and written informed consent was provided by all participants. The data used in this study is available to the public through https://www.cdc.gov/nchs/nhanes/. The data mining technology can be found in previous studies (Yang et al., 2020; Wu et al., 2021).

Preventive aspirin use

The preventive aspirin use questions were asked by trained interviewers in the participants' homes. Participants were questioned about whether their doctors had ever advised them to take aspirin for preventive. The participant's actual aspirin dosage was recorded in the preventative aspirin use questionnaire. The aspirin doses ranged from 25 mg to 500 mg, despite the fact that the majority of survey participants were taking 81 mg or 325 mg. We used ≤100 mg/d as low-dose aspirin use in accordance with prior studies and recommendations (McNeil et al., 2018a; Davidson et al., 2022). As a result, we defined high-dose aspirin use in the analysis as aspirin dosage >100 mg/d.

Assessment of mortality

The NCHS has linked data collected from a number of its population surveys, such as NHANES, with records of deaths from the National Death Index (NDI). For this study, the 2019 NCHS Public-Use Linked Mortality Files were used to obtain mortality data, including mortality status, cause of death, and follow-up duration for all included persons from the date of survey participation until death or 31 December 2019. The participant's principal cause of death is stated on their death certificate as one of nine cause-specific death categories based on the International Classification of Diseases, 10th Revision (ICD-10) code. (Centers for Disease Control and Prevention, 2019). In the current study, cancer mortality was recorded as ICD-10 code C00-C97, while cardiovascular mortality included deaths from heart disease (ICD-10 code I00-I09, I11, I13, and I20-I51) or cerebrovascular diseases (ICD-10 code I60-I69). Additionally, all-cause mortality was used to describe deaths for any reason (Zhou et al., 2022).

Measurement of covariates

In-person interviews with participants were conducted by qualified interviewers to collect information on their lifestyles and demographics. The participants' ethnicity was divided into four groups (i.e., Hispanic, White, Black, and others). There are three levels of education (i.e., <high school, high school, and ≥high school). The original marital status variable contains never married, married, living with a partner, separated, widowed, and divorced. We combined the categories of married and cohabiting into one to simplify the analysis. The categories of divorced, widowed, and separated people were also combined for the same purpose. The family monthly poverty level index, which measures the ratio of monthly income to poverty, was adopted to reflect family economics. According to NCHS-recommended analytical procedures, this indicator was divided into three categories: 1.30, 1.31–1.85, and >1.85. Drinkers were defined as participants who had ingested alcohol at least 12 times in the year prior. Sedentary time is defined as all time spent seated, excluding time spent sleeping, and is a reflection of sedentary behavior.

Body weight (in kilograms) and height (in centimeters) were measured by trained staff using standard devices. Body mass index (BMI) is derived as weight in kilograms divided by height in meters squared. BMI ≥30 kg/m^2 was used by the World Health Organization (WHO) Expert Consultation to define obesity (WHO Expert Consultation, 2004). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with a mercury sphygmomanometer. The analysis used the average of three blood pressure values. Hypertension was considered as SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or using antihypertensive medications (Zhou et al., 2019).

Blood samples were obtained and kept frozen (−20°C) until they were sent to the University of Minnesota for analysis. On a Roche Modular P chemistry analyzer, the enzymatic approach was used to detect total cholesterol (TC). Hypercholesterolemia was defined as TC ≥6.2 mmol/L and/or current drug use. High-performance liquid chromatography (HPLC) Glycohemoglobin Analyzer was used to measure hemoglobin A1c. Hemoglobin A1c ≥6.5% and/or ongoing insulin or hypoglycemic drug use were used to diagnose diabetes.

Statistical analysis

For continuous variables that do not conform to the normal distribution, descriptive data on participant characteristics were shown as weighted median (p25-p75), and for categorical variables, frequency (weighted percentages) was used. Participants were divided into three groups based on how they had previously taken aspirin for preventive (i.e., no use, low-dose, high-dose). To compare the between-group differences in characteristics, we used Kruskal-Wallis method for continuous variables and a χ^2 test for categorical variables. The hazard ratio (HR) and 95% confidence

TABLE 1 Characteristics of the study population (*n* = 10,854).

Characteristics	Aspirin use			*p* values
	No use (*n* = 7,404)	Low-dose (*n* = 2,970)	High-dose (*n* = 480)	
Age, years	54.0 (46.0–63.0)	64.0 (57.0–72.0)	63.0 (56.0–72.0)	<0.0001
Men, n(%)	3,495 (46.2)	1,561 (50.6)	308 (65.6)	<0.0001
Ethnicity, n(%)				<0.0001
Hispanic	1,826 (12.4)	618 (8.3)	52 (3.8)	
White	2,887 (70.2)	1,365 (77.1)	284 (82.3)	
Black	1,617 (9.7)	681 (9.1)	100 (7.5)	
Asian or others	1,074 (7.7)	306 (5.6)	44 (6.4)	
Education, n(%)				<0.0001
Less than high school	1,656 (13.6)	676 (12.6)	116 (14.4)	
High school	1,645 (21.9)	701 (23.4)	128 (29.6)	
More than high school	4,103 (64.5)	1,593 (64.0)	236 (56.0)	
Family monthly poverty levels				<0.0001
≤1.30	2,428 (21.0)	891 (17.8)	152 (18.9)	
1.31–1.85	1,079 (11.1)	469 (12.0)	78 (12.1)	
>1.85	3,897 (68.0)	1,610 (70.2)	250 (69.0)	
Marital status, n(%)				<0.0001
Married/cohabitation	4,619 (67.8)	1775 (67.2)	282 (68.7)	
Divorced/widowed	2,073 (24.2)	981 (26.9)	162 (24.5)	
Never married	712 (8.0)	214 (6.0)	36 (6.8)	
Smoking status, n(%)				<0.0001
Current	1,405 (18.4)	454 (14.0)	106 (17.5)	
Former	1,954 (27.7)	1,084 (36.6)	197 (43.4)	
Never	4,045 (53.9)	1,432 (49.4)	177 (39.1)	
Drinker, n(%)	4,761 (71.6)	1852 (69.8)	320 (73.6)	<0.0001
Sedentary time, hours/d	6.0 (4.0–9.0)	6.0 (4.0–9.0)	7.0 (4.0–9.0)	<0.0001
Obesity, n(%)	2,946 (39.3)	1,348 (45.4)	235 (56.3)	<0.0001
Hypertension, n(%)	3,206 (37.4)	2,117 (65.5)	339 (69.7)	<0.0001
Diabetes, n(%)	1,195 (11.5)	1,100 (28.6)	143 (31.1)	<0.0001
Hypercholesterolemia, n(%)	2,387 (31.8)	1,843 (61.7)	283 (61.5)	<0.0001

Values are presented as weighted median (p25-p75) or frequency (weighted percentage) when appropriate.

interval (CI) for the risks of dying from any cause, CVD, or cancer were calculated using Cox proportional hazards models. Age, sex, ethnicity, education levels, family poverty rates, marital status, smoking, drinking, time spent sitting down, obesity, hypertension, diabetes, and hypercholesterolemia were adjusted in the model. Additionally, we conducted a number of subgroup analyses based on age, sex, ethnicity, drinking, smoking, weight, diabetes, hypertension, and hypercholesterolemia. Considering that those with cardiovascular disease at baseline are more likely to take aspirin, we additionally eliminated participants who had ever received a diagnosis of heart failure, coronary heart disease, angina, heart attack, or stroke for the purposes of the sensitivity analysis. All analyses were performed using SAS 9.4 from the SAS Institute in Cary, North Carolina. The threshold for statistical significance was a two-tailed *p*-value of 0.05. The forest plot of the subgroup analysis was created using the R package "forestplot" in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 2 Multivariable-adjusted hazard ratio (HR) and 95% confidence interval (CI) of aspirin use associated with deaths from all-cause, cardiovascular disease (CVD), and cancer.

	Aspirin use		
	No use	Low-dose	High-dose
Person-years of follow-up	36,244	14,115	2,342
All-cause death			
No. of deaths	494	348	82
Mortality, per 1,000 person-years	13.6	24.7	35.0
Age- and sex-adjusted HR	1 (Reference)	0.96 (0.84–1.11)	1.33 (1.05–1.69)
Multivariable-adjusted HR	1 (Reference)	0.92 (0.79–1.06)	1.18 (0.93–1.50)
CVD death			
No. Of deaths	141	119	34
Mortality, per 1,000 person-years	3.9	8.4	14.5
Age- and sex-adjusted HR	1 (Reference)	1.09 (0.85–1.39)	1.80 (1.23–2.63)
Multivariable-adjusted HR	1 (Reference)	1.03 (0.79–1.33)	1.63 (1.11–2.41)
Cancer death			
No. Of deaths	129	75	19
Mortality, per 1,000 person-years	3.6	5.3	8.1
Age- and sex-adjusted HR	1 (Reference)	0.81 (0.60–1.08)	1.20 (0.74–1.96)
Multivariable-adjusted HR	1 (Reference)	0.80 (0.60–1.08)	1.10 (0.67–1.80)

Adjusted for age, sex, ethnicity, education levels, family monthly poverty levels, marital status, smoking status, drinking, sedentary time, obesity, hypertension, diabetes, and hypercholesterolemia.

Results

In our study, 10,854 participants (5,364 men and 5,490 women) with a median (range) age of 60.0 (50.0, 69.0) years were enrolled in the analysis. The study population's characteristics based on its prior use of preventive aspirin are shown in Table 1. Overall, participants who have used aspirin for prevention tended to be older, more likely to be men, to be of the white race, to drink, to spend more time sedentary, and to have cardiometabolic diseases like obesity, hypertension, diabetes, and hypercholesterolemia than participants who have never used aspirin.

The effects of aspirin use at low or high doses on the risk of mortality from any cause, cardiovascular disease, and cancer are shown in Table 2. High-dose aspirin users had a higher risk of dying from a CVD (HR: 1.63, 95% CI: 1.11–2.41) than those who had never used aspirin, even after controlling for age, sex, ethnicity, education levels, family monthly poverty levels, marital status, smoking, drinking, and sedentary behavior. High-dose aspirin use was not significantly linked with all-cause mortality (HR: 1.18, 95% CI: 0.93–1.50) or cancer mortality (HR: 1.10, 95% CI: 0.67–1.80). Aside from that, there was no proof that taking low-dose aspirin reduced the risk of dying from any cause (HR: 0.92, 95% CI: 0.79–1.06), CVD (HR: 1.03, 95% CI: 0.79–1.33), or cancer (HR: 0.80, 95% CI: 0.60–1.08).

We conducted a subgroup analysis by age group because the USPSTF provided various recommendations to those 40–59 years old and 60 years or older. While high-dose aspirin usage was linked to a greater risk of CVD death among participants aged 60 years and older (HR: 1.65, 95% CI: 1.10–2.47), low-dose aspirin use had no significant effects on all-cause and cause-specific mortality among any age group (Table 3).

Figure 2 shows the results of additional stratified analyses we conducted by various factors to determine if low- or high-dose aspirin use is associated with CVD mortality. We found that low-dose aspirin use did not alter CVD mortality in any subgroups, which is consistent with our main finding. However, we found that using high doses of aspirin increased CVD mortality in male participants, those who were Black, Asian, or of other races, those who had never smoked, and those who were of normal weight, had diabetes, or had hypertension.

Results of sensitivity analysis by excluding those with CVD at baseline are shown in Table 4. Low- or high-dose aspirin use was not linked to cancer or all-cause death, which is consistent with our main findings. Low-dose aspirin use was not linked to CVD death, but high-dose aspirin use was positively associated with the hazard of dying from a CVD (HR: 2.04, 95% CI: 1.10–3.79).

Discussion

In this 4.8-year median follow-up community-based prospective cohort study, we found that among participants aged 40 or older, high-dose aspirin use was linked to an increased risk of CVD death, whereas low-dose aspirin use was not linked to the risk of deaths from all causes, CVD, or cancer.

Aspirin's role in the primary prevention of CVD has been the topic of heated discussion for many years. In 2018, the results of three fairly large randomized clinical trials (RCTs) with diverse populations and endpoints were published. In the ASPREE trial, 19,114 healthy older individuals (70 years of age or older) were enrolled. They were randomized to receive either a placebo (n = 9,589) or 100 mg of enteric-coated aspirin (n = 9,525). During a

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TABLE 3 Stratified analysis for the association between aspirin use and risk of death by age.

	Aspirin use		
	No use	Low-dose	High-dose
Age between 40 to 59 years			
Person-years of follow-up	22,443	4,075	794
All-cause death			
No. of deaths	106	35	8
Mortality, per 1,000 person-years	4.7	8.6	10.1
Age- and sex-adjusted HR	1 (Reference)	1.41 (0.95–2.08)	1.63 (0.79–3.36)
Multivariable-adjusted HR	1 (Reference)	1.16 (0.77–1.75)	1.15 (0.55–2.39)
CVD death			
No. of deaths	20	12	2
Mortality, per 1,000 person-years	0.9	2.9	2.5
Age- and sex-adjusted HR	1 (Reference)	2.77 (1.31–5.85)	2.31 (0.53–10.04)
Multivariable-adjusted HR	1 (Reference)	1.61 (0.73–3.53)	1.31 (0.29–5.86)
Cancer death			
No. of deaths	28	6	4
Mortality, per 1,000 person-years	1.2	1.5	5.0
Age- and sex-adjusted HR	1 (Reference)	0.76 (0.31–1.86)	2.66 (0.92–7.68)
Multivariable-adjusted HR	1 (Reference)	0.86 (0.34–2.20)	2.51 (0.85–7.45)
60 years or older			
Person-years of follow-up	13,801	10,040	1,548
All-cause death			
No. of deaths	388	313	74
Mortality, per 1,000 person-years	28.1	31.2	47.8
Age- and sex-adjusted HR	1 (Reference)	0.93 (0.80–1.08)	1.30 (1.01–1.67)
Multivariable-adjusted HR	1 (Reference)	0.89 (0.77–1.04)	1.18 (0.92–1.53)
CVD death			
No. of deaths	121	107	32
Mortality, per 1,000 person-years	8.8	10.7	20.7
Age- and sex-adjusted HR	1 (Reference)	1.00 (0.77–1.30)	1.74 (1.17–2.57)
Multivariable-adjusted HR	1 (Reference)	0.97 (0.74–1.27)	1.65 (1.10–2.47)
Cancer death			
No. of deaths	101	69	15
Mortality, per 1,000 person-years	7.3	6.9	9.7
Age- and sex-adjusted HR	1 (Reference)	0.80 (0.59–1.09)	1.02 (0.59–1.76)
Multivariable-adjusted HR	1 (Reference)	0.80 (0.58–1.09)	0.93 (0.54–1.63)

Adjusted for age, sex, ethnicity, education levels, family monthly poverty levels, marital status, smoking status, drinking, sedentary time, obesity, hypertension, diabetes, and hypercholesterolemia.

median follow-up of 4.7 years, the aspirin group had a higher risk of dying from any cause (HR: 1.14, 95% CI: 1.01–1.29) and dying from cancer (HR: 1.31, 95% CI: 1.10–1.56) than the placebo group. Aspirin use, however, had no discernible impact on CVD death when compared to placebo (HR: 0.82, 95% CI: 0.62–1.08) (McNeil et al., 2018b). In the ASCEND trial, 15,480 individuals with diabetes who were 40 years of age or older were randomized assigned to receive either a placebo or aspirin daily doses of 100 mg. After an average follow-up of 7.4 years, the aspirin group had a lower incidence of major vascular events than the placebo group (HR: 0.88, 95% CI: 0.79–0.97), including myocardial infarction, non-hemorrhagic stroke, and death from any vascular cause. However, the aspirin group experienced more serious bleeding episodes (HR: 1.29, 95% CI: 1.09–1.52) than the placebo group (Bowman et al., 2018). The ARRIVE trial enrolled 12,546 patients who were 55 or older in age and had a baseline moderate risk of CVD. A dose of 100 mg of aspirin (n = 6,270) or a placebo (n = 6,276) was given to participants, who were randomly selected. Time up to the first occurrence of cardiovascular mortality, myocardial infarction, unstable angina, stroke, or transient ischemic attack was the primary endpoint. After a median follow-up of 60 months, there was

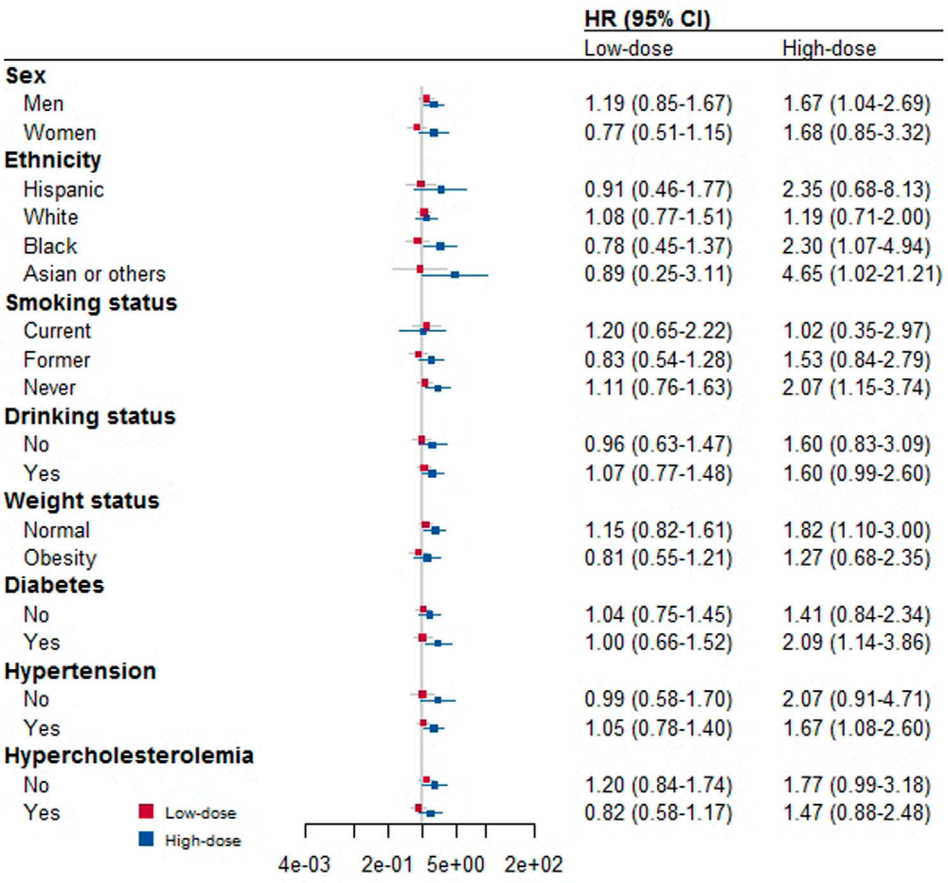

FIGURE 2
Stratified analysis for the association between aspirin use and risk of death by other covariates.

TABLE 4 Sensitivity analysis for the association between aspirin use and risk of death by excluding participants who had cardiovascular diseases at baseline (*n* = 9,155).

	Aspirin use		
	No use (*n* = 6,769)	Low-dose (*n* = 2,106)	High-dose (*n* = 280)
All-cause death			
No. of deaths	349	189	35
Age- and sex-adjusted HR	1 (Reference)	0.95 (0.80–1.14)	1.38 (0.97–1.96)
Multivariable-adjusted HR	1 (Reference)	0.94 (0.78–1.14)	1.29 (0.90–1.83)
CVD death			
No. of deaths	79	57	12
Age- and sex-adjusted HR	1 (Reference)	1.20 (0.85–1.70)	2.00 (1.08–3.68)
Multivariable-adjusted HR	1 (Reference)	1.28 (0.89–1.83)	2.04 (1.10–3.79)
Cancer death			
No. of deaths	101	50	12
Age- and sex-adjusted HR	1 (Reference)	0.88 (0.62–1.24)	1.63 (0.89–2.99)
Multivariable-adjusted HR	1 (Reference)	0.89 (0.62–1.26)	1.53 (0.83–2.80)

Adjusted for age, sex, ethnicity, education levels, family monthly poverty levels, marital status, smoking status, drinking, sedentary time, obesity, hypertension, diabetes, and hypercholesterolemia.

no discernible difference between the aspirin and placebo groups in the occurrence of the primary endpoint (HR: 0.96, 95% CI: 0.81–1.13) (Gaziano et al., 2018).

Aspirin use and the risk of death in individuals with cancer or hypertension have also been the topic of several observational studies. Per a *post hoc* analysis of the Systolic Blood Pressure Intervention Trial

(SPRINT), aspirin use had no impact on the risk of all-cause death in hypertensive patients (HR: 0.84, 95% CI: 0.53–1.30) (Del et al., 2022). According to a cohort study using the Colorectal Cancer Data Base Sweden (CRCBaSe), aspirin use during follow-up was linked to an increased risk of all-cause mortality (HR: 1.09, 95% CI: 1.04–1.15) but not colorectal cancer (CRC) mortality (HR: 0.98, 95% CI: 0.91–1.06) among patients who were diagnosed with CRC (Shahrivar et al., 2022). In Denmark, after a prostate cancer diagnosis, the usage of low-dose aspirin was compared to death in a large cohort research. According to the findings, taking low-dose aspirin during exposure periods of 5 years (HR: 0.91, 95% CI: 0.83–1.00) and 7 years (HR: 0.84, 95% CI: 0.72–0.97) was associated with a slight reduction in prostate cancer mortality (Skriver et al., 2019). The Nurses' Health Study found that women who reported low-to-moderate aspirin use had a decreased risk of death from all causes (HR: 0.75, 95% CI: 0.71–0.81), CVD (HR: 0.62, 95% CI: 0.55–0.71), and cancer (HR: 0.88, 95% CI: 0.81–0.96) during the course of a 24-year follow-up compared to those who never took aspirin (Chan et al., 2007).

As previously mentioned, aspirin use and the risks of cardiovascular events, overall mortality, and cause-specific death are still being debated. Previous RCTs and observational studies were mainly conducted in selected populations and there is a lack of studies conducted in community-based general populations. For the first time, our study provides a special perspective on aspirin's primary preventive effect in the generally representative national population. We found that taking low-dose aspirin had no beneficial effect on the risk of dying due to any cause while high-dose aspirin use might increases the risk of CVD death, especially for those aged 60 years and older.

Bleeding is the most frequent aspirin side effect, which may cancel out any positive effects. For example, taking aspirin increased gastrointestinal bleeding incidents substantially (HR: 2.11, 95% CI: 1.36–3.28) compared with placebo in the ARRIVE trial (Gaziano et al., 2018). An earlier study found that aspirin users who are 70 years of age or older have a dramatically increased risk of bleeding events (Patrono et al., 2005). Aspirin's positive and negative effects have the same underlying mechanism. The primary metabolite of arachidonic acid, thromboxane A2 (TXA2), can be inhibited by aspirin. Aspirin's therapeutic effectiveness in reducing the risk of atherothrombosis and its side effect of bleeding can be explained by the fact that TXA2 is a potent inducer of platelet aggregation (Patrono, 2015; Petrucci et al., 2022). Controversial recommendations made by European and US guidelines reflect the uncertainty over the relative benefits and risks of using aspirin for the primary prevention of CVD.

Our study comes with a number of limitations. First, the usage of aspirin use was recorded only based a one-time questionnaire, which may lead to recall bias and inaccurate estimate of dose intensity. Second, although it is based on the fact that preventive drugs are generally taken regularly for a long time, the NHANES preventive aspirin use questionnaire did not collect participants' drug duration, which should be taken into account when interpreting the results. Third, there is a lack of data on the incidence of CVD or bleeding events during follow-up because this analysis linked NHANES with death records of NDI Fourth, the observational study design makes it impossible to establish a causal link between aspirin use and risk of death.

In conclusion, using low-dose aspirin has no effect on the risk of death from any causes, whereas taking high dosage of aspirin use increases the risk of CVD death, especially for those aged 60 years and older.

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 US National Center for Health Statistics (NCHS) institutional review board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ and GL contributed to the study conception and design. LZ and YC contributed to the material preparation, data collection and analysis. The first draft of the manuscript was written by LZ, YC, and FC. JL, HH, and GL contributed to the review and editing the manuscript. All authors read and approved the final manuscript.

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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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Global trends in the incidence rates of MDR and XDR tuberculosis: Findings from the global burden of disease study 2019

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Purpose: The study aimed to quantify the global trends of the incidence rates of multidrug-resistant (MDR) tuberculosis (MDR-TB) and extensively drug-resistant (XDR) tuberculosis (XDR-TB).

Methods: Cases, age-standardized rates (ASRs), and incidence rates of MDR-TB and XDR-TB during 2010–2019 were obtained from the Global Burden of Disease Study 2019. The incidence trends of MDR-TB and XDR-TB were evaluated using the estimated annual percentage changes (EAPCs) in ASRs. The relationships among the ASRs of MDR-TB and XDR-TB, the MDR rate, the XDR rate, and socio-demographic index (SDI) were assessed using locally weighted regression and Pearson's correlation coefficient.

Results: The global ASR of MDR-TB on average decreased by 1.36% (EAPC = −1.36, 95% confidence interval [CI] = −2.19 to −0.52) per year whereas that of XDR-TB was stable (EAPC = 0.69, 95% CI = −0.15–1.54) during 2010–2019. The incidence trends of MDR-TB in most regions and countries were decreasing, but those of XDR-TB were increasing. People aged 35–44 and 55–64 years had the highest incidence rates for MDR-TB and XDR-TB. The MDR and XDR rates both peaked in those aged 35–44 years. Areas with higher SDI tended to have lower ASRs of MDR-TB ($p < 0.001$, $\rho = -0.43$).

Conclusion: The current achievements for the incidence trends of MDR-TB and XDR-TB are insufficient. More strategies and tools need to be developed to further curb MDR-TB and XDR-TB, especially in high-risk areas and age groups, and in low SDI regions.

KEYWORDS

tuberculosis, incidence, trend, MDR, XDR

Introduction

Tuberculosis is a chronic infectious disease seriously endangering human health that has become a major global public health and social problem (Kazempour Dizaji et al., 2018; World Health Organization, 2021a), with 1.3 million deaths due to TB in 2020 alone (World Health Organization, 2021a). One of the main reasons is that the drug resistance of TB continues to evolve. Standard treatment involving the two most-effective drugs (isoniazid and rifampicin) can achieve excellent cure rates for drug-sensitive patients with TB (Seung et al., 2015). In the treatment of drug-resistant TB, that of multidrug-resistant is very difficult since MDR-TB is resistant to the two most-effective first-line anti-TB drugs (isoniazid and rifampicin) (Trisakul et al., 2022). Nevertheless, extensively drug-resistant (XDR) TB, as a kind of MDR, is more concerning, and is resistant to isoniazid and rifampicin as well as all fluoroquinolone and second-line injectable drugs (World Health Organization, 2018; Lin et al., 2022; Trisakul et al., 2022). The overall cure rates of MDR-TB and XDR-TB were only 56% and 39%, respectively (World Health Organization, 2018). For more than a decade, the proportion of MDR and rifampicin-resistant patients diagnosed with TB for the first time has remained around 3%–4%, and that of patients previously treated for TB has remained at 18%–21%. There are even countries with proportions of previously treated MDR-TB cases exceeding 50% (World Health Organization, 2021a). The proportion of XDR-TB in TB is rarely reported.

According to the End TB Strategy of the World Health Organization (WHO) and the UN Sustainable Development Goals (United Nations, 2015; World Health Organization, 2015), global TB deaths must be reduced by 95% in 2035 compared with 2015. With the current data, this goal is difficult to achieve (World Health Organization, 2021a), and so it is time for urgent action to end the global TB epidemic (Pan et al., 2020a; World Health Organization, 2021a). MDR-TB and XDR-TB increase the risk of death in patients with TB and hinder the achievement of the above goal. Studying the global incidence trends of MDR-TB and XDR-TB is helpful for preventing and treating TB, and thereby reducing deaths from TB. However, there has been no systematic summary addressing this issue. The purpose of this study was therefore to determine the global incidence trends of MDR-TB and XDR-TB using the Global Burden of Disease Study (GBD) 2019 data.

Methods

Data source

Data sources for TB within the GBD 2019 data can be explored using the online GBD Results Tool (https://vizhub.healthdata.org/gbd-results/). The ICD-10 codes for TB are A10–A19.9, B90–B90.9, K67.3, K93.0, M49.0, and P37.0, while the ICD 9 codes are 010–019.9, 137–137.9, 138.0, 138.9, 139.9, 320.4, and 730.4–730.6. The GBD Results Tool is a data set developed and supported by the Institute for Health Metrics and Evaluation, which is an independent global health research center based at the University of Washington. This database provides epidemiological information on 369 diseases and injuries during 1990–2019 for 23 age groups; for males, females, and both sexes combined; and for 204 countries and territories that were grouped into 21 regions and 7 superregions. Previous studies have described the method of estimating TB incidence from the GBD database in detail (GBD 2019 Diseases and Injuries Collaborators, 2020; GBD 2019 Risk Factors Collaborators, 2020). Briefly, the TB data were derived from population-based surveys on tuberculin and cohort studies that examined the risk of developing active TB disease as a function of induration size. An updated systematic review was performed on the GBD 2019 which included routine surveillance and surveys reported to the WHO and the risk of MDR-TB (Mesfin et al., 2014; GBD 2019 Diseases and Injuries Collaborators, 2020). From the GBD 2019 database, we extracted the age-related number of cases and age-standardized rates (ASRs) or incidence rates during 2010–2019 globally among 5 socio-demographic index (SDI) regions, 21 geographical regions, and 204 countries and territories. The rates expressed as age-standardised are based on the GBD reference population (GBD 2017 Mortality Collaborators, 2018). In the GBD, the range of data point estimates is not expressed using 95% confidence intervals (CIs), but instead using 95% uncertainty intervals (UIs). Every estimate was calculated 1,000 times, and then the 95% UI was determined by the 25th and 97fifth value of the 1,000 values after ordering them from smallest to largest (Bu et al., 2022). We also extracted the SDI of each country and region. SDI is a compound measure of income, average years of schooling, and the fertility in each location and year in the GBD database that is used to measure socio-demographic development (Pan et al., 2020b). It is the geometric mean of the 0 to 1 index of total fertility rate under 25 years of age, average education level of the population aged 15 and over, and lagging income *per capita* (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). The location with an SDI of 0 will have a theoretical minimum level of development related to health, while the location with an SDI of 1 will have a theoretical maximum level of development. For GBD 2019, the values of SDI were multiplied by 100 on a scale of 0–100 (GBD 2019 Diseases and Injuries Collaborators, 2020). It is divided into five levels: high, middle-high, middle, low-middle, and low.

Statistical analysis

Estimated annual percentage changes (EAPCs) of incidence rates were used to evaluate the incidence trends during 2010–2019. EAPC is a summarizing and widely used measure that assesses ASR trends over a specified time period (Hankey et al., 2000; Sun et al., 2022). Natural logarithm of regression line fitting rates were used; that is, $y = a + \beta x + e$, where $y = \ln$ (ASR) and x is the calendar year. EAPC was calculated as $100\times[\exp(\beta)-1]$, and its 95% CI was also obtained from the linear regression model. If EAPCs and the lower limit of the 95% CI are both > 0, then ASR is considered to have an increasing trend. In contrast, if both EAPC estimation and the upper limit of the 95% CI are < 0, ASR has a downward trend. For other values ASR is considered stable. We also assessed the relationships among ASR of MDR-TB and XDR-TB, MDR and XDR rates, and SDI using locally weighted regression and Pearson's correlation coefficient. The MDR and XDR rates are the ratios of new MDR-TB and XDR-TB cases to new TB cases, respectively. The $p < 0.05$ was considered significant. R software (version 3.4.3) was used for the statistical analysis.

TABLE 1 The cases and ASR for incidence of MDR-TB and XDR-TB in 2019, their temporal incident trends from 2010 to 2019, and MDR and XDR rate of TB.

Characteristics	MDR-TB				XDR-TB			
	Incident cases	ASR per 100,000	EAPC	MDR rate	Incident cases	ASR per 100,000	EAPC	XDR rate
	No. × 10^3 (95% UI)	No. (95% UI)	No. (95% CI)	%	No. × 10^3 (95% UI)	No. (95% UI)	No. (95% CI)	%
Global	450.6 (247.83–785.37)	5.63 (3.12–9.73)	−1.36 (−2.19–−0.52)	5.30	25.06 (17.09–36.47)	0.31 (0.21–0.45)	0.69 (−0.15–1.54)	0.29
Socio-demographic index								
Low	83.78 (48.55–144.44)	9.53 (5.27–16.86)	0.07 (−0.19–0.34)	4.15	1.36 (0.64–2.69)	0.16 (0.07–0.33)	4.44 (4.27–4.61)	0.07
Low-middle	173.14 (67.91–377.69)	10.32 (4.01–22.66)	−0.26 (−0.53–0.02)	5.47	5.24 (2.44–10.26)	0.31 (0.15–0.62)	3.8 (3.72–3.89)	0.17
Middle	111.4 (55.2–207.28)	4.43 (2.22–8.16)	−2.18 (−3.51–−0.82)	4.58	6.16 (3.6–10.33)	0.24 (0.15–0.41)	1.57 (0.43–2.73)	0.25
Middle-high	79.55 (47.63–125.98)	4.83 (2.89–7.73)	−4.72 (−5.93–−3.5)	10.50	12.01 (8–17.15)	0.72 (0.48–1.02)	−0.69 (−1.64–0.27)	1.58
High	2.64 (1.6–4.56)	0.22 (0.14–0.39)	−2.83 (−3.55–−2.11)	2.13	0.29 (0.19–0.48)	0.02 (0.02–0.04)	1.34 (0.84–1.85)	0.24
Region								
Asia Pacific–high income	0.58 (0.14–1.84)	0.2 (0.05–0.64)	−3.62 (−4.13–−3.12)	1.22	0.07 (0.02–0.23)	0.03 (0.01–0.08)	1.26 (0.88–1.64)	0.15
Central Asia	10.68 (7.03–14.94)	11.42 (7.55–16.05)	−5.86 (−6.23–−5.49)	20.51	2.34 (1.54–3.27)	2.5 (1.65–3.52)	−0.56 (−0.74–−0.38)	4.49
East Asia	31.26 (7.07–95.81)	1.81 (0.41–5.52)	−6.8 (−9.18–−4.36)	4.10	2.85 (0.64–8.74)	0.16 (0.04–0.5)	−2.24 (−4.49–0.05)	0.37
South Asia	257.75 (72.44–595.41)	14.87 (4.18–33.94)	−0.39 (−0.84–0.05)	6.76	6.32 (1.78–14.59)	0.36 (0.1–0.83)	4.29 (4.04–4.54)	0.17
Southeast Asia	25.34 (14.88–41.38)	3.78 (2.23–6.16)	-1.25 (-2.23–0.27)	2.28	2.31 (1.36–3.77)	0.35 (0.2–0.56)	3.73 (2.91–4.56)	0.21
Australasia	0.05 (0.02–0.1)	0.17 (0.07–0.34)	4.25 (2.69–5.82)	2.75	0.01 (0–0.01)	0.02 (0.01–0.04)	9.44 (7.53–11.39)	0.35
Caribbean	0.09 (0.03–0.23)	0.18 (0.06–0.48)	4.71 (3.03–6.42)	0.56	0.01 (0–0.02)	0.01 (0.01–0.04)	9.92 (7.86–12.03)	0.04
Central Europe	0.41 (0.22–0.72)	0.29 (0.16–0.52)	−4.41 (−5.27–−3.55)	2.03	0.09 (0.05–0.16)	0.06 (0.03–0.11)	0.73 (-0.43–1.9)	0.44
Eastern Europe	44.87 (28.33–65.58)	18.87 (11.81–27.74)	−4.8 (−5.78–−3.81)	27.18	9.83 (6.21–14.37)	4.13 (2.59–6.08)	0.55 (−0.23–1.34)	5.96
Western Europe	0.68 (0.46–1)	0.16 (0.11–0.23)	−2.19 (−2.28–−2.1)	2.26	0.09 (0.06–0.13)	0.02 (0.01–0.03)	2.83 (2.62–3.05)	0.28
Andean Latin America	2.71 (1.5–4.57)	4.26 (2.36–7.14)	−4.09 (−6.16–−1.97)	6.46	0.21 (0.12–0.36)	0.34 (0.19–0.56)	0.56 (−1.34–2.49)	0.51
Central Latin America	1.35 (0.57–2.68)	0.54 (0.23–1.06)	0.76 (0.37–1.15)	2.97	0.11 (0.05–0.21)	0.04 (0.02–0.08)	5.75 (5.41–6.09)	0.23
Southern Latin America	0.11 (0.03–0.35)	0.16 (0.04–0.51)	−1.68 (−2.04–−1.33)	1.34	0.01 (0–0.04)	0.02 (0.01–0.06)	3.33 (3.05–3.62)	0.17
Tropical Latin America	2.05 (0.44–5.58)	0.86 (0.18–2.34)	3.22 (2.78–3.66)	3.07	0.16 (0.03–0.44)	0.07 (0.01–0.18)	8.36 (7.77–8.96)	0.24
North Africa and Middle East	4.45 (2.69–7.56)	0.76 (0.46–1.27)	−2.88 (−3.24–−2.51)	2.90	0.16 (0.09–0.27)	0.03 (0.02–0.04)	1.84 (1.69–2)	0.10

(Continued on following page)

TABLE 1 (*Continued*) The cases and ASR for incidence of MDR-TB and XDR-TB in 2019, their temporal incident trends from 2010 to 2019, and MDR and XDR rate of TB.

Characteristics	MDR-TB				XDR-TB			
	Incident cases	ASR per 100,000	EAPC	MDR rate	Incident cases	ASR per 100,000	EAPC	XDR rate
	No. × 10^3 (95% UI)	No. (95% UI)	No. (95% CI)	%	No. × 10^3 (95% UI)	No. (95% UI)	No. (95% CI)	%
North America–high income	0.13 (0.06–0.27)	0.03 (0.01–0.07)	−3.3 (−4.37–−2.22)	1.36	0.02 (0.01–0.03)	0 (0–0.01)	1.71 (0.79–2.63)	0.17
Oceania	0.42 (0.16–0.97)	3.53 (1.32–7.97)	11.09 (5.12–17.4)	3.43	0.04 (0.01–0.09)	0.32 (0.12–0.73)	16.14 (9.49–23.19)	0.31
Central Sub-Saharan Africa	7.84 (2.09–22.46)	7.38 (1.96–21.23)	1.16 (0.72–1.6)	2.42	0.05 (0.01–0.14)	0.05 (0.01–0.14)	5.8 (5.1–6.5)	0.02
Eastern Sub-Saharan Africa	29.93 (18.85–50.47)	9.17 (5.76–15.59)	1.9 (1.6–2.2)	3.29	0.19 (0.12–0.33)	0.06 (0.04–0.1)	6.59 (6.05–7.13)	0.02
Southern Sub-Saharan Africa	9.69 (4.84–18.68)	11.54 (5.82–22.19)	−0.83 (−2.35–0.72)	3.35	0.06 (0.03–0.12)	0.07 (0.04–0.14)	3.77 (2.41–5.15)	0.02
Western Sub-Saharan Africa	20.2 (9.45–40.6)	5.95 (2.77–12.22)	−2.7 (−3.28–−2.12)	3.29	0.13 (0.06–0.26)	0.04 (0.02–0.08)	1.89 (1.49–2.31)	0.02

Abbreviations: MDR, multidrug-resistant; XDR, extensively drug-resistant; TB, tuberculosis; ASR, age-standardized rate; CI, confidence interval; EAPC, estimated annual percentage change; UI, uncertainty interval.

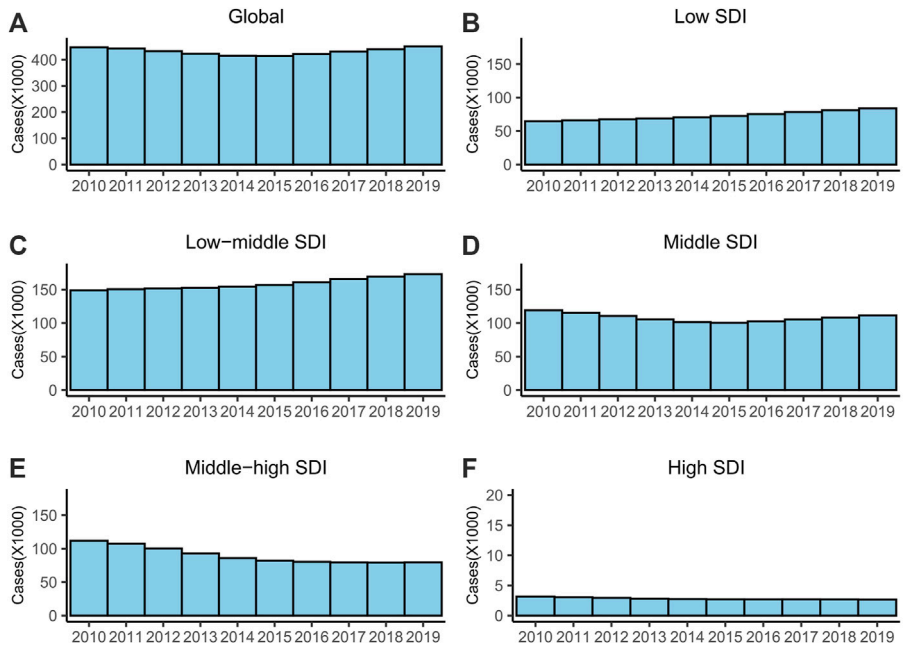

FIGURE 1
The cases of MDR-TB from 2010 to 2019. **(A)** Global, **(B)** low SDI regions, **(C)** low-middle SDI regions, **(D)** middle SDI regions, **(E)** middle-high SDI regions and **(F)** high SDI regions. Abbreviations: MDR, multidrug-resistant; TB, tuberculosis; SDI, socio-demographic index.

Results

Multidrug-resistant tuberculosis

Globally in 2019, the ASR of MDR-TB was 5.63 (95% UI = 3.12–9.73) per 100,000 among 450,600 cases (95% UI = 247,830–785,370), and the MDR incidence rate was 5.30% (Table 1). The distribution of cases during 2010–2019 was almost U-shaped (Figure 1A). The ASR decreased on average by 1.36% (EAPC = −1.36, 95% CI = −2.19 to −0.52) per year during 2010–2019 (Table 1).

For SDI regions, the ASR exhibited a stable trend in the low and low-middle SDI regions and decreased in the other three SDI regions

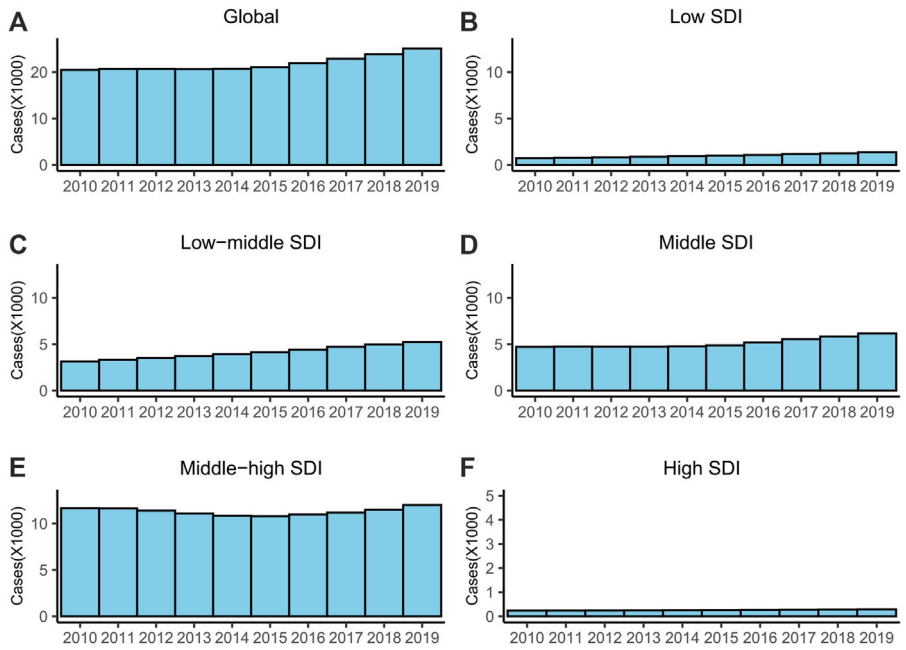

FIGURE 2
The cases of XDR-TB from 2010 to 2019. **(A)** Global, **(B)** low SDI regions, **(C)** low-middle SDI regions, **(D)** middle SDI regions, **(E)** middle-high SDI regions and **(F)** high SDI regions. Abbreviations: XDR, extensively drug-resistant; TB, tuberculosis; SDI, socio-demographic index.

(Table 1). The high SDI regions had the fewest cases, and the lowest ASR and MDR rates (Table 1; Figure 1). The number of MDR-TB cases increased monotonically in the low- and low-middle SDI regions (Figure 1).

The ASR of MDR-TB in 12 of the 21 geographical regions exhibited decreasing trends during 2010–2019, with the largest decrease observed in East Asia (EAPC = −6.8, 95% CI = −9.18 to −4.36), followed by Central Asia and Eastern Europe (Table 1). However, there were still two regions with stable ASR, and even seven with increased ASR (Table 1). Oceania had the largest increase (EAPC = 11.09, 95% CI = 5.12–17.4). Central Asia and Eastern Europe had the highest MDR rates, at 20.51% and 27.18%, respectively (Table 1).

The incidence trend of MDR-TB varied among the 204 countries and territories, decreasing in 116 of them, remaining stable in 35, and increasing in 53 (Supplementary Table S1). Countries with high MDR rates were mostly in Eastern Europe and Central Asia, which was consistent with the analysis at the regional level. For example, the ten regions with the highest MDR rates (in decreasing order) were the Republic of Moldova (MDR rate = 37.87%), Belarus (36.91%), Ukraine (29.52%), Russian Federation (26.14%), Kyrgyzstan (25.46%), Uzbekistan (23.92%), Kazakhstan (20.60%), Azerbaijan (20.35%), Georgia (18.12%), and Estonia (17.58%) (Supplementary Table S1).

Extensively drug-resistant tuberculosis

In 2019, there were 25,060 (95% UI = 17,090–36,470) new XDR-TB cases globally, which had increased by 22.5% compared with 2010, and the ASR was 0.31 (95% UI = 0.21–0.45) per 100,000 (Table 1; Figure 2A). The XDR rate was 0.29%. The ASR was stable during 2010–2019 (EAPC = 0.69, 95% CI = −0.15–1.54) (Table 1).

For SDI regions, the ASR was only stable in the middle-high SDI regions (Table 1). The ASRs and numbers of cases increased in the other four SDI regions (Table 1; Figure 2). The middle-high SDI had the most XDR-TB cases, and the highest ASR and XDR rates (Table 1; Figure 2). The high SDI region had the fewest XDR-TB cases and lowest ASR rate (Table 1; Figure 2).

The ASRs increased in 16 of the 21 geographical regions, was stable in 4, and decreased only in Central Asia. The increase was largest in Oceania (EAPC = 16.14, 95% CI = 9.49–23.19), followed by the Caribbean (EAPC = 9.92, 95% CI = 7.86–12.03) and Australasia (EAPC = 9.44, 95% CI = 7.53–11.39) (Table 1). Although the ASR decreased in Central Asia, its XDR rate was the second highest (XDR rate = 4.49%), and that of Eastern Europe was the highest (XDR rate = 5.96%).

The trend of ASR varied among the 204 countries and territories. The ASRs of most countries and territories (144 of 204) increased, while those of 24 were stable and it decreased in 36 (Supplementary Table S1). There was a close correspondence between countries with high MDR rates and high XDR rates; for example, the ten countries with the highest XDR rates also had the ten highest MDR rates (Supplementary Table S1).

Age distributions of MDR-TB and XDR-TB incidence rates, and MDR and XDR rates

The age distributions of the MDR and XDR incidence rates were similar, with both having two peaks. The MDR-TB incidence rate peaked in those aged 35–44 and 55–64 years. The XDR-TB

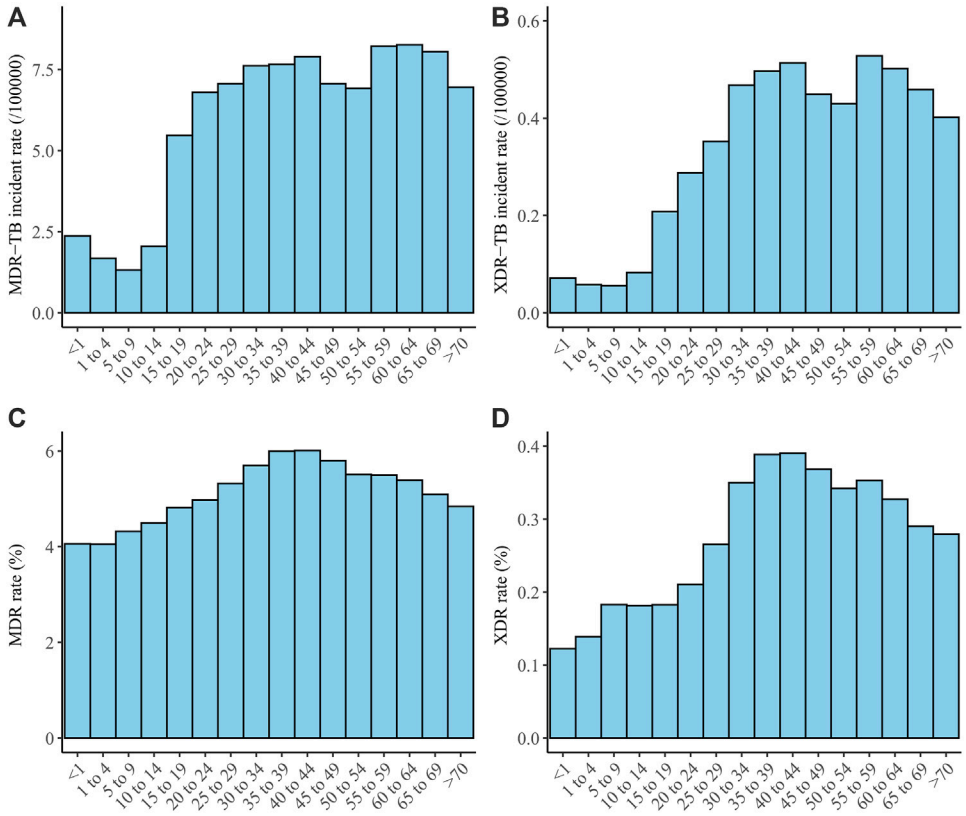

FIGURE 3
Age distribution of MDR-TB incidence rate **(A)**, XDR-TB incidence rate **(B)**, MDR rate **(C)**, and XDR rate **(D)**. Abbreviations: MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant.

incidence rates were similar, also peaking in those aged 35–44 and 55–64 years (Figures 3A, B). The MDR and XDR rates both peaked in those aged 35–44 years (Figures 3C, D).

Relationships among the ASRs of MDR-TB and XDR-TB, MDR and XDR rates, and SDI

We analyzed the relationships among the ASRs of MDR-TB and XDR-TB, MDR and XDR rates, and SDI based on national-level data. A significant negative correlation was found between the ASR of MDR-TB and SDI ($p < 0.001$, $\rho = -0.43$) (Figure 4A). No significant relationship was found between the ASR of XDR-TB ($p = 0.54$, $\rho = 0.04$) or the MDR incidence rate ($p = 0.86$, $\rho = 0.01$) and SDI (Figures 4B, C). A significant positive correlation was found overall between the XDR rate and SDI ($p = 0.03$, $\rho = 0.15$) (Figure 4D). However, as shown in Figure 4D, there was a negative relationship between them when the SDI exceeded about 0.75.

Discussion

MDR-TB and XDR-TB are serious problems that represent great threats and challenges to human and public health (Akkerman et al., 2019; Borisov et al., 2019; Shang et al., 2022). According to the End TB Strategy, TB incidence and mortality should have declined by at least 20% and 35%, respectively, between 2015 and 2020. However, the performance of the strategy has been suboptimal, with only 11% and 9.2% declines in TB incidence and mortality, respectively, by 2021 (Jeremiah et al., 2022). MDR-TB and XDR-TB played important roles in this poor performance (Seung et al., 2015; Jeremiah et al., 2022). In the present study, we analyzed the global incidence trends of MDR-TB and XDR-TB during 1990–2019 to help improve the current status of TB based on the GBD 2019 database.

The analyzed GBD database contains data from 1990 to 2019. We were more concerned about the current trend than the previous trend, and so this study focused on the data from the last 10-year period covered in the GBD. Previous data may affect the actual recent trends. For example, if the EAPC during 1990–2009 was significantly negative and that during 2010–2019 was significantly positive, it is possible that the EAPC during 1990–2019 would be significantly negative. Although this study found that the ASR of MDR-TB worldwide is declining, the current annual reduction in global TB incidence is 2%, which is too slow to achieve an end to the epidemic in the foreseeable future. According to the End TB Strategy (Uplekar et al., 2015; World Health Organization, 2019),

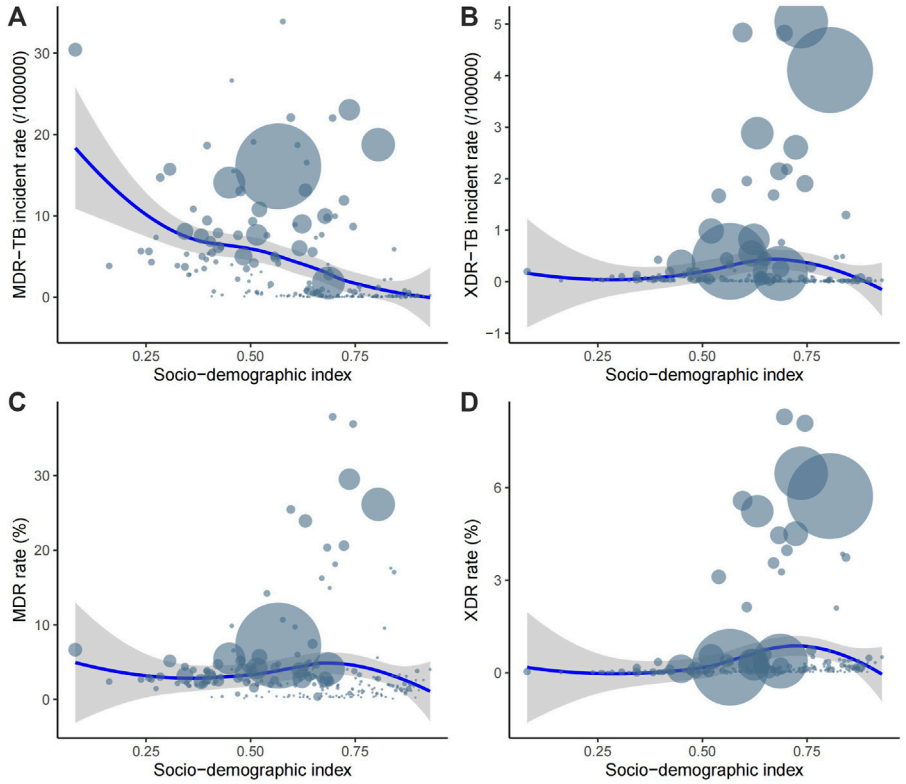

FIGURE 4
The correlation between ASR of MDR-TB **(A)**, ASR of XDR-TB **(B)**, MDR rate **(C)**, and XDR rate **(D)** and SDI. Each circle represents a country or territory. The size of the circle represents the number of cases. Abbreviations: ASR, age-standardized rate; MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant; SDI, socio-demographic index.

the annual decline in global TB incidence rates must increase to 10% annually by 2025. However, the EAPC of MDR-TB was −1.36, meaning that the ASR of MDR-TB decreased by 1.36% per year, which is far less than 10% or even 2%. This study found that the high ASR of MDR-TB was mostly attributable to Eastern Europe, South Asia, Southern Sub-Saharan Africa, Central Asia, Eastern Sub-Saharan Africa, and Central Sub-Saharan Africa. There are several possible reasons for the higher ASR of MDR-TB in these regions. The economic level is low and the accessibility to public health services is poor in these regions, and it includes many developing countries, which may have problems such as poverty, malnutrition, and poor living conditions (Lange et al., 2018). Our results also indicated that the ASR of MDR-TB had a significant negative correlation with SDI. SDI is a composite measure of income *per capita*, total fertility rate (age <25 years), and average education level (for those aged ≥15 years), and is used as a measure of sociodemographic development (GBD 2019 Risk Factors Collaborators, 2020; GBD 2019 Diabetes in the Americas Collaborators, 2022). As is well known, the incidence rate of TB is related to the socioeconomic and development levels (Nordholm et al., 2022; Soares et al., 2022). This affects the incidence rate of TB in various aspects. For example, public health systems are imperfect and the prevention and control of infectious diseases is weak in regions with low SDI. Both in terms of resource allocation and professional talent training, there are problems such as insufficient quantity, low quality, and unreasonable structure (Liu et al., 2019), which lead to an increase in the incidence rate of TB that can cause an increase in the incidence rate of MDR-TB. According to our analysis, the impact of social development level on the incidence rate of MDR-TB may be mostly attributed to its impact on the incidence rate of TB, rather than directly on that of MDR. We did not observe a significant correlation between MDR rate and SDI in this study. Eastern Europe and Central Asia had the highest MDR rates, which was consistent with previous reports (Dirlikov et al., 2015; Lange et al., 2018). It is promising that these regions had larger downward trends for the ASR of their MDR-TB compared with most regions. According to our results, XDR-TB should be considered because its ASR had no downward trend and actually increased in most regions. The trend was only declining in Central Asia. Regions with high MDR rate tend to have a high XDR rate, which was consistent with the principle of drug resistance in biology. There are two types of drug resistance in *Mycobacterium tuberculosis*: genetic and phenotypic resistance. Genetic drug resistance is caused by mutations in chromosomal genes in bacterial growth, while phenotypic resistance or drug tolerance is caused by epigenetic changes in gene expression and protein modification that induce drug

tolerance in non-growing bacterial persisters (Zhang and Yew, 2015). These two types are mostly caused by drug use. A high MDR rate may result in a high XDR rate by increasing the use of second-line drugs. In the present study, XDR-TB and MDR-TB had different relationships with SDI; that is, the XDR rate had a significant positive correlation with SDI, but the ASR of XDR-TB was not significantly correlated with SDI. Although the relationship between XDR rate and SDI was significant, it was not strong, with a ρ value of only 0.15. The ρ value represents the strength of the correlation in Pearson's coefficient (Pearson, 1920; Rodgers and Nicewander, 1988). This may mean that the XDR rate was more affected by other factors. We also analyzed the age distribution of MDR-TB and XDR-TB. The results indicated that there were two peaks for the incidence rates of MDR-TB and XDR-TB, in those aged 35–44 and 55–64 years. Nevertheless, there were also peaks for MDR and XDR rates, in those aged 35–44 years. The peaks for MDR and XDR rates were consistent with the first peaks of the incidence rates of MDR-TB and XDR-TB, which was logical since a high drug resistance leads to a high incidence rate in drug-resistant TB. A reasonable explanation for the absence of second peaks for MDR and XDR rates is that the mortality rate of TB is high among the elderly (Dhamnetiya et al., 2021), resulting in a small proportion of elderly patients having received previous treatment for TB. Drug-resistant TB mostly occurs in patients previously treated for TB (World Health Organization, 2021a). At the national level, India, China, and the Russian Federation are the countries with the three largest numbers of MDR-TB and XDR-TB cases, which account for most new cases in the world. This result for MDR-TB was consistent with a WHO report (World Health Organization, 2021b). WHO do not report the global incidence of XDR-TB, which is rarely reported. The incidence trends of MDR-TB and XDR-TB in China were declining. The incidence trend of MDR-TB in the Russian Federation was declining, while that of XDR was stable. India should receive more attention, because it has the most MDR-TB cases with a stable incidence trend and the second-highest rate of XDR-TB cases with an increasing incidence trend. Improving the incidence trends of MDR-TB and XDR-TB in India is important to improve control of the global incidence rates of MDR-TB and XDR-TB.

This study had several limitations, most notably being that the participants were from the GBD database and calculations were made using a model based on existing data in each country; that is, where data were not available, the results depended on predictive validity of the model for out-of-sample data. In addition, the MDR or XDR rate was the ratio of new MDR- or XDR-TB cases to new TB cases. Cases were point estimates, and their 95% UIs were determined through 1,000 calculations. This approach made it impossible to estimate the UIs or CIs of MDR and XDR rates.

The present study has performed the most comprehensive analysis of the global trends of MDR-TB and XDR-TB during 2010–2019. Although the incidence of MDR-TB was declining, the rate of decline was too slow; moreover, the incidence trend of XDR-TB was not declining. The incidence trends of MDR-TB and XDR-TB varied markedly among different regions and countries. High-risk age groups, regions and countries with high burdens, and low-SDI regions require careful consideration, and effective tools need to be developed to curb MDR-TB and XDR-TB.

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

This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Xi'an Children's Hospital.

Author contributions

Study design and data extraction: QB and HC; Statistical analysis: QB; Manuscript draft: QB, RQ, LF, XP, HZ, and HC; Charts and tables: QB and LF. All authors agreed to submit the final version of this manuscript.

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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.2023.1156249/full#supplementary-material

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Sales trends of psychotropic drugs in the COVID-19 pandemic: A national database study in Brazil

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Background: The social restrictions among coronavirus disease 2019 (COVID-19) pandemic have posed a thoughtful risk to mental health and have implications in the use of drugs, including antidepressants, anxiolytics and other psychotropics.

Objective: This study analyzed the sales data of the psychotropics prescribed in Brazil, in order to verify the change in consumption trends of these drugs during the COVID-19 pandemic.

Methods: This interrupted time-series analyzed psychotropic sales data, between January 2014 and July 2021, using the National System of Controlled Products Management from The Brazilian Health Regulatory Agency. The monthly mean DDDs per 1,000 inhabitants per day of psychotropic drugs was evaluated by analysis of variance (ANOVA) followed by Dunnett Multiple Comparisons Test. The changes in monthly trends in the use of the psychotropic studied were evaluated by Joinpoint regression.

Results: During the period studied, clonazepam, alprazolam, zolpidem and escitalopram were the most sold psychotropic drugs in Brazil. According to Joinpoint regression, an upward trend was observed in sales during the pandemic of pregabalin, escitalopram, lithium, desvenlafaxine, citalopram, buproprion and amitriptyline. An increase in psychotropic consumption was noted throughout the pandemic period, with the maximum consumption (2.61 DDDs) occurring in April 2021, with a downward trend in consumption that accompanied the drop in the number of deaths.

Conclusions: The increase in sales, mainly of antidepressants during the COVID-19 pandemic, draws attention to issues related to the mental health of the Brazilian population and on the need for greater monitoring in the dispensing of these drugs.

KEYWORDS

psychotropics, antidepressants, COVID-19 pandemic, psycoactive substances, COVI-19 pandemic

Introduction

On 11 March 2020, the World Health Organization declared COVID-19, caused by the new Coronavirus, as a new global pandemic (Vindegaard and Benros, 2020). The new virus settles in the respiratory system, leading to cases of viral pneumonia, which is the main factor of morbidity related to the disease. Since the beginning of the pandemic, uncertainties regarding

transmissibility, pathogenicity and lethality have taken hold of the scientific community and populations around the world, leading to feelings of apprehension, insecurity and fear (Castillo-Sánchez et al., 2022). World health agencies, in order to contain the pandemic, have established health protocols for the entire population, such as the use of alcoholic gel, masks, social isolation, *etc.* (Atalan, 2020) (Brodeur et al., 2021).

Modern civilization had never gone through a similar situation, when a part of it found itself "trapped" in their homes, avoiding contagion and infection or experiencing the early mourning of their family members. This naturally caused and continues to cause significant impacts on the mental health of everyone, whether infected or not (Brooks et al., 2020; Dubey et al., 2020; Ali et al., 2021; Castillo-Sánchez et al., 2022). On 25 February 2020, the first case of COVID-19 was confirmed in Brazil and, since then, there have been 24 million infected (January 2022 data), adding up to more than 600,000 deaths (Ministry, 2022).

The high mortality rates at the beginning of the pandemic, social isolation, associated with fear and insecurity due to lack of treatments; and/or the efficacy and availability of vaccines, led a large part of the population, including health professionals and young people (Wathelet et al., 2020; Meherali et al., 2021), to resort to chemical substances such as alcohol, illicit drugs and even psychotropic drugs in order to face this difficult situation (Garcia and Sanchez, 2020; Testino and Pellicano, 2020; Bennett et al., 2021; Levaillant et al., 2021; Madoz-Gúrpide et al., 2021; Søvold et al., 2021; Castillo-Sánchez et al., 2022; Estrela et al., 2022). Some studies have shown that the impact on the mental health of populations was important, with exacerbated conditions of depression, anxiety, panic, including suicidal ideation, especially among young people and health professionals (Gloster et al., 2020; de Vroege and van den Broek, 2021; Varga et al., 2021; Acharya et al., 2022; Appleby et al., 2022; Bozzola et al., 2022; Prudenzi et al., 2022).

In the United States, cases of depression and anxiety diagnosed among adults jumped from 36% to 41% between August 2020 and February 2021, reflecting the effects of the pandemic on this population (Vahratian et al., 2021). Likewise, visits to psychiatric offices also increased in the same period due to the pandemic (Holland et al., 2021). In Brazil, some studies have verified the prevalence and factors associated with depression or anxiety in health professionals or medical students and public-school teachers, during the COVID-19 pandemic. However, nationwide analyses of the sales profile of psychotropic drugs are still lacking in the literature.

In order to verify the impact of the COVID-19 pandemic on the mental health of the Brazilian population, this study used the national database on the dispensation of psychotropic drugs as an important resource for public health, since it can reflect the pattern of clinical and subclinical consumption of these drugs. Next, this study analyzed the sales data of psychotropic drugs prescribed in Brazil, in order to verify the consumption trend of these drugs during the COVID-19 pandemic.

Materials and methods

Study design

An interrupted time series was used to analyze the consumption trends of antidepressants and anxiolytics and other psychotropic medications (outcome of interest) during the COVID-19 pandemic (exposure of interest).

Setting and study

Pharmacies and drugstores in Brazil have been required to register the number of all psychotropic medications sold monthly, since 2007, in the National System of Controlled Products Management database (known by the acronym SNGPC) from The Brazilian Health Regulatory Agency (ANVISA) (Varga et al., 2021). Monthly sales volume data were collected between January 2014 and July 2021.

Data sources, measurement and variables

Data were publicly available on ANVISA website. The following variables were extracted: name of the active ingredient, trade name and respective presentations. The classification Anatomical Therapeutic Chemical (ATC) was used. Based on the commercial packaging of each psychotropic drug sold and the concentration of the active ingredient in each (e.g., pack of 10 pills of 20 mg each or pack of 30 pills of 10 mg each), the number of defined daily doses (DDDs)/1,000 inhabitants/day for each drug was calculated, as recommended by the World Health Organization (Acharya et al., 2022).

Statistical analysis

Psychotropic drugs were described in average units of commercial presentations sold between 2014 and 2019 and during the pandemic (January 2020 and July 2021).

The monthly mean DDDs per 1,000 inhabitants per day of psychotropic drugs was evaluated by analysis of variance (ANOVA) followed by Dunnett Multiple Comparisons Test (Instat GraphPad Software version 3.05). The changes in monthly trends in the use of the psychotropic studied were evaluated by Joinpoint regression (Joinpoint Regression Program, version 4.9.0.0. Statistical Research and Applications Branch, National Cancer Institute). Pearson's correlation coefficient verified the correlation between psychotropic consumption (expressed in DDDs/1,000 inhabitants/day) and the number of deaths in the same period. The level of statistical significance adopted was $p < 0.05$.

Results

Table 1 described the 22 most sold psychotropic drugs in Brazil, between January 2014 and July 2021. The data shows the average amount of commercial presentations sold between January 2014 and December 2019 and during the pandemic (January 2020 and July 2021).

Between January 2014 and July 2021, clonazepam, zolpidem, alprazolam and escitalopram were the most sold psychotropics in Brazil. When comparing the pandemic years with previous years (2014–2019), there were statistically significant increases ($p < 0.01$)

TABLE 1 Characterization and sales volume in Brazil of the studied psychotropics (January 2014 to July 2021).

Drugs	ATC code	DDD (mg)	Commercial presentations available in Brazil	Monthly commercial units sold (from 2014 January to December 2019)	Monthly commercial units sold in pandemic (January 2020 to July 2021)	Percentage of change during the pandemic (%)	*p*-value dunnett multiple comparisons test
Desvenlafaxine	N06AX23	50	95	128,257	376,340	193.43	<0.01
Pregabalin	N03AX16	300	101	247,499	566,553	128.91	<0.01
Quetiapine	N05AH04	400	147	387,505	768,629	98.35	<0.01
Zolpidem	N05CF02	10	67	622,704	1,180,424	89.56	<0.01
Escitalopram	N06AB10	10	167	600,022	1,105,859	84.30	<0.01
Lithium	N05AN01	889	20	114,617	198,031	72.78	<0.01
Sertraline	N06AB06	50	169	586,847	958,056	63.25	<0.01
Duloxetine	N06AX21	60	59	253,654	412,608	62.67	<0.01
Venlafaxine	N06AX16	100	129	313,622	498,415	58.92	<0.01
Trazodone	N06AX05	300	25	159,417	249,129	56.28	<0.01
Risperidone	N05AX08	5	143	313,277	471,593	50.54	<0.01
Amitriptyline	N06AA09	75	61	478,177	692,545	44.83	<0.01
Alprazolam	N05BA12	1	161	778,222	1,081,954	39.03	<0.01
Bupropion	N06AX12	300	66	172,191	236,244	37.20	<0.01
Paroxetine	N06AB05	20	105	327,938	446,277	36.09	<0.01
Fluoxetine	N06AB03	20	161	477,337	611,667	28.14	<0.01
Topiramate	N03AX11	300	102	167,985	214,237	27.53	<0.01
Clonazepam	N03AE01	8	98	1,591,101	1,772,727	11.42	NS
Citalopram	N06AB04	20	72	340,848	368,637	8.15	NS
Diazepam	N05BA01	10	75	254,338	240,858	−5.30	NS
Bromazepam	N05BA08	10	56	451,684	413,851	−8.38	NS
Lorazepam	N05BA06	2.5	42	219,716	185,807	−15.43	<0.01

ATC: anatomical therapeutic chemical; NS, non-significant ($p > 0.05$).

in almost all studied psychotropics (Table 1). The exceptions were Citalopram and benzodiazepines that did not show alterations. Lorazepam decreased by 15% during the studied period.

The data presented in Table 2 showed the consumption in DDD/1,000 inhabitants/day between 2014 and 2019 and during the pandemic, based on the historical series and on the level of significance related to the trend. There was an upward trend in sales of pregabalin, escitalopram, lithium, desvenlafaxine, citalopram, bupropion and amitriptyline.

Figure 1 shows the average consumption in DDD/1,000 inhabitants/day of psychotropic drugs (bars) and the evolution in the number of COVID-19 cases in the country (line). It was observed that at the beginning of the pandemic (March 2020) and throughout its period, there was an increase in sales of psychotropic drugs. There was an increase from 1.75 DDDs/1,000 inhabitants/day in February 2020 to 2.07 DDDs/1,000 inhabitants/day in the following month. The same was observed when the number of deaths reaches its peak in the country (March 2021); in the following month (April 2021), the consumption of these drugs jumps from 2.26 DDDs/1,000 inhabitants/day to the maximum sale (2.61 DDDs/1,000 inhabitants/day). This drop in the consumption of psychotropic drugs accompanied the drop in the number of deaths caused by COVID-19.

There was a strong correlation between the consumption of psychotropic drugs and cases of COVID-19 for most of psychotropics studied. For zolpidem there is very strong correlation (correlation coefficient: 0.91) (Figure 2).

Discussion

During the pandemic period, there was an upward trend in sales of psychotropic drugs in Brazil, mainly; desvenlafaxine, pregabalin, quetiapine, zolpidem, escitalopram and lithium; compared to the period between January 2014 and December 2019, in which there

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TABLE 2 Consumption in DDDs between 2014 and 2019 and during the pandemic (January 2020 to July 2021).

Monthly average DDD/ 1,000 inhabitants/day	2014	2015	2016	2017	2018	2019	Pandemic (2020 January to July 2021)	Time series (*p*-value)	Trend (increase, decrease or no change)
Desvenlafaxine	0.39	0.47	0.55	0.68	1.23	1.9	2.72	<0.01	↑
Pregabalin	0.15	0.21	0.27	0.34	0.43	0.55	0.75	<0.01	↑
Lithium	0.21	0.24	0.28	0.31	0.32	0.42	0.51	<0.01	↑
Bupropion	0.48	0.55	0.58	0.64	0.73	0.85	0.96	<0.01	↑
Amitriptyline	0.51	0.57	0.66	0.95	0.89	0.79	1.06	<0.01	↑
Escitalopram	2.06	2.63	3.26	3.92	4.68	5.8	7,47	<0.05	↑
Citalopram	1.49	1.59	1.66	1.69	1.7	2.11	3.27	<0.05	↑
Clonazepam	1.23	1.32	1.42	1.55	1.56	1.59	1.67	<0.05	↓
Trazodone	0.16	0.18	0.21	0.25	0.29	0.34	0.39	<0.05	↓
Venlafaxine	0.86	1.01	1.18	1.37	1.54	1.82	2.09	<0.05	↓
Alprazolam	2.7	2.98	3.26	3.47	3.9	4.4	5.04	NS	↔
Zolpidem	0.95	1.24	1.58	2	2.58	3.34	4.35	NS	↔
Quetiapine	0.11	0.14	0.17	0.21	0.26	0.32	0.42	NS	↔
Risperidone	0.32	0.39	0.45	0.52	0.58	0.73	0.97	NS	↔
Duloxetine	0.44	0.63	0.81	1.02	1.24	1.48	1.75	NS	↔
Sertraline	1.98	2.3	2.64	2.97	3.3	4.08	4.93	NS	↔
Paroxetine	1.17	1.26	1.37	1.45	1.57	1.71	1.91	NS	↔
Fluoxetine	1.77	1.95	2.2	2.53	2.59	2.75	2.99	NS	↔
Topiramate	0.2	0.23	0.25	0.27	0.28	0.3	0.33	NS	↔
Diazepam	0.89	0.94	1.03	1.17	1.18	1.08	1.02	NS	↔
Bromazepam	0.96	0.95	0.94	0.9	0.88	0.86	0.83	NS	↔
Lorazepam	0.7	0.69	0.68	0.66	0.63	0.57	0.56	NS	↔

NS, non-significant ($p > 0.05$).

were more sales of clonazepam, zolpidem, alprazolam and escitalopram. Between the period January 2014 to July 2021, the historical series showed an upward trend in sales of pregabalin, escitalopram, lithium, desvenlafaxine, citalopram, bupropion and amitriptyline.

The peak of the death toll in the country was in March 2021, when psychotropic consumption was at 2.26 DDDs/ 1,000 inhabitants/day. In the following month, consumption of these drugs jumped to 2.61 DDDs/1,000 inhabitants/day.

During the pandemic, a strong correlation was observed between the number of cases of deaths from COVID-19 in Brazil and the consumption of psychotropic drugs, especially zolpidem. Zolpidem is a hypnotic drug, non-benzodiazepine imidazopyridine with affinity to the α1 subunit of the GABA A receptor.

Another study conducted in the Brazilian capital (Escalante Saavedra et al., 2022) evaluated the impact of psychotropic consumption before and during the pandemic (2018–2020). The results showed Zolpidem consumption increasing from 6.2 Defined Daily Dose per 1,000 inhabitants-day (DHD) to 8.5 due to the COVID-19 Pandemic. Our data are very similar, showing an increase in Zolpidem consumption of around 89.5% (Table 1) in the studied period (2014–2021).

Milani et al. (2021), reported results similar to those found in the present study, showing an increase in the consumption of Z-hypnotics (zolpidem, zaleplon, and eszopiclone) among men and women in the United States and persisting in increased levels in the two waves of COVID-19 (Milani et al., 2021).

In the same sense, Levaillant et al. (2021), found even more alarming data in France, with a weekly increase of 2.5% in new users of hypnotics among young people (12–18 years old), during the pandemic period (Levaillant et al., 2021). In Portugal, a similar scenario was also observed during the pandemic, with a significant increase in the prescriptions of anxiolytics, hypnotics and sedatives, especially in the age group over 65 years (Estrela et al., 2022).

In France, researchers evaluated sleep habits in more than 1,000 patients and the pandemic's interference in their habits. The authors reported that before the pandemic, only 12% of these patients were using hypnotic drugs. During the pandemic, due to the difficulties imposed on everyone, that number jumped to 41% (Beck et al., 2021). In Brazil, higher education students in the health area reported similar

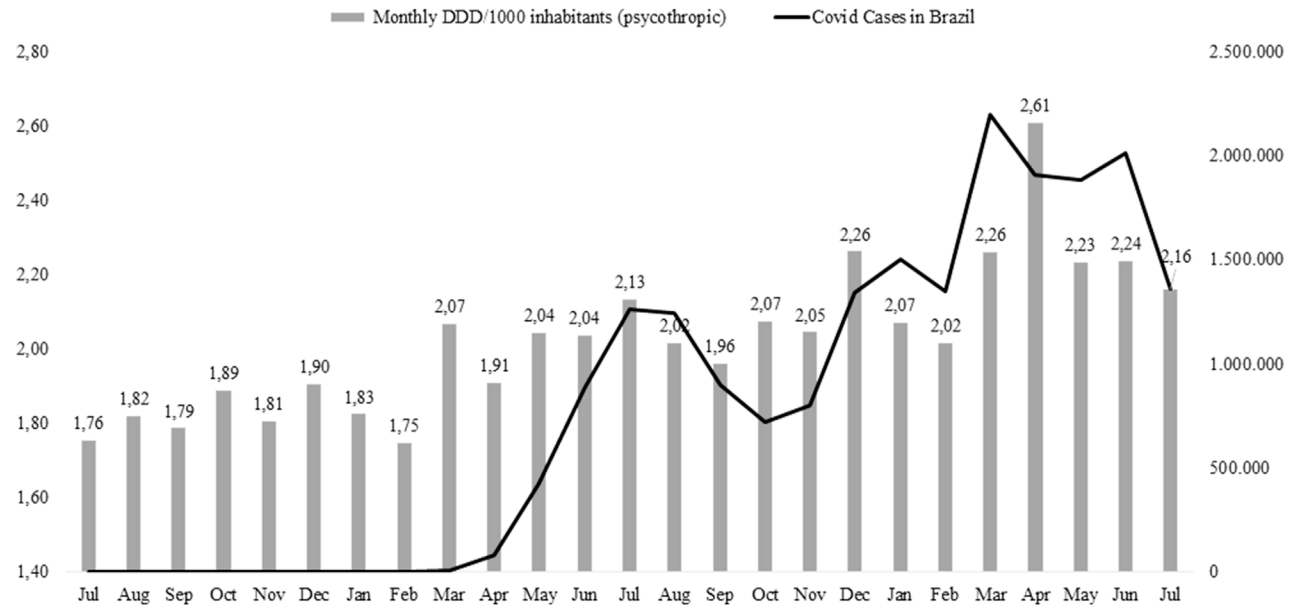

FIGURE 1
Monthly average (in DDDs) of psychotropic consumption in Brazil and number COVID-19 cases in Brazil (July 2019 to July 2021).

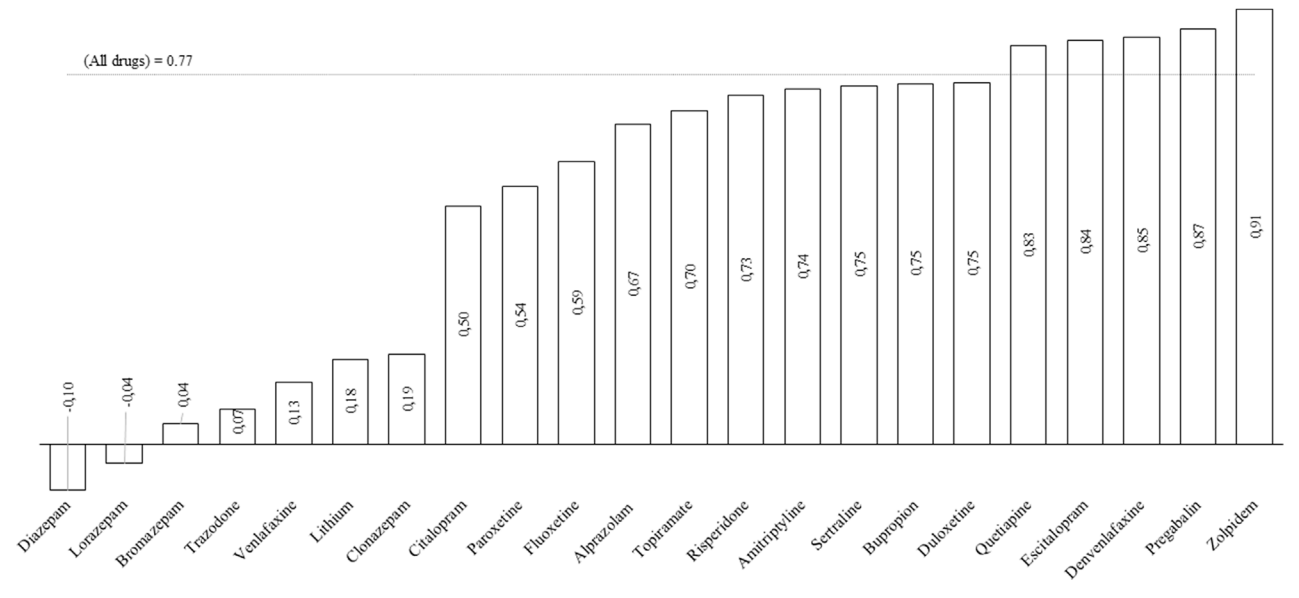

FIGURE 2
Pearson's Correlation Coefficient of psychotropic and COVID-19 cases in Brazil during the pandemic (2020 January to 2021 July).

behaviors, with an increase of around 11% in the consumption of anxiolytics during the pandemic (Mata et al., 2021). Italy has also shown a sharp increase in the consumption of psychotropic drugs during the pandemic (Farina et al., 2021).

The reasons for the increase in psychotropic consumption seem very clear to us. In the United States, cases of depression increased about 3 times in the pandemic when compared to previous periods

Certainly, the effects of the pandemic will not be restricted to the infectivity and pathogenicity of the virus, but will also leave important psychological consequences that, initially, have been treated with the use of psychotropic medications.

The reasons for the increase in psychotropic consumption seem very clear to us. In the United States, cases of depression increased about 3 times in the pandemic when compared to previous periods

(Ettman et al., 2020). Recent studies in several countries around the world are unanimous in showing a significant increase in the consumption of psychotropic drugs during the period of the COVID-19 pandemic. Studies from Canada (Ying et al., 2023), France (Benistand et al., 2022; Sanchez et al., 2022), Portugal (Estrela et al., 2022), Scandinavia (Tiger et al., 2023), United States (Amill-Rosario et al., 2022), Danish (Bliddal et al., 2023) showed that the effects of the pandemic were not restricted to the infectivity and pathogenicity of the virus at the level of the respiratory system, but also left important psychological sequelae with increased used of psychotropic medications.

The increase in sales verified in Brazil in the present study, in all classes of psychotropic drugs, shows, in addition to the controlled clinical use of these drugs (through medical records), the sub-clinical use of drugs with high potential for abuse and reinforces the need for a closer look aware of the consumption of these drugs and the consequences of abuse and dependence associated with them.

Conclusions

The increase in sales, mainly of antidepressants during the COVID-19 pandemic, draws attention to issues related to the mental health of the Brazilian population and makes us reflect on the need for greater monitoring in the dispensing of these drugs. Improving the national registration system for sales of psychotropic drugs could contribute with relevant information for the elaboration of public policies focused on mental health, seeking better guidance for personalized care and better doctor-patient decision making.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://dados.anvisa.gov.br/dados/SNGPC/Industrializados/

Author contributions

FD, CB, LL, SB-F and MS contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Conflict of interest

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

Publisher's note

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Association of thiamine administration and prognosis in critically ill patients with heart failure

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Background: Thiamine deficiency is common in patients with heart failure, and thiamine supplement can benefit these patients. However, the association between thiamine administration and prognosis among critically ill patients with heart failure remains unclear. Thus, this study aims to prove the survival benefit of thiamine use in critically ill patients with heart failure.

Methods: A retrospective cohort analysis was performed on the basis of the Medical Information Mart of Intensive Care-IV database. Critically ill patients with heart failure were divided into the thiamine and non-thiamine groups depending on whether they had received thiamine therapy or not during hospitalization. The association between thiamine supplement and in-hospital mortality was assessed by using the Kaplan–Meier (KM) method and Cox proportional hazard models. A 1: 1 nearest propensity-score matching (PSM) and propensity score-based inverse probability of treatment weighting (IPW) were also performed to ensure the robustness of the findings.

Results: A total of 7,021 patients were included in this study, with 685 and 6,336 in the thiamine and non-thiamine groups, respectively. The kaplan–meier survival curves indicated that the thiamine group had a lower in-hospital mortality than the none-thiamine group. After adjusting for various confounders, the Cox regression models showed significant beneficial effects of thiamine administration on in-hospital mortality among critically ill patients with heart failure with a hazard ratio of 0.78 (95% confidence interval: 0.67–0.89) in the fully adjusted model. propensity-score matching and probability of treatment weighting analyses also achieved consistent results.

Conclusion: Thiamine supplement is associated with a decreased risk of in-hospital mortality in critically ill patients with heart failure who are admitted to the ICU. Further multicenter and well-designed randomized controlled trials with large sample sizes are necessary to validate this finding.

KEYWORDS

thiamine, heart failure, in-hospital mortality, intensive care unit, MIMIC-IV database

Introduction

Heart failure is a syndrome caused by heart dysfunction, and it is the end stage of all heart diseases. Recently, the Global Burden of Disease 2019 study indicates that approximately 56 million people worldwide live with heart failure, making it a major threat to human health and social development (Wei et al., 2022). In the United States, approximately 10%–51% of patients hospitalized with heart failure require ICU treatment, and in-hospital mortality for patients with heart failure who are admitted to the ICU is 10.6%, which is higher than that for all patients with heart failure (4.0%) (Safavi et al., 2013; Peng et al., 2022). Although a variety of classical drug therapy for heart failure has been widely used, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone receptor antagonists, the mortality rate remains high. Therefore, new therapeutic interventions are urgently necessary to improve patient outcomes.

An imbalance in energy production and expenditure is associated with heart failure (Murashige et al., 2020). Micronutrient deficiency is common in patients with heart failure and it may cause poor clinical outcomes in these patients because micronutrient deficiency could reduce energy production in the myocardium (Lennie et al., 2018). Thiamine, a water-soluble vitamin, consists of a methylene bridge between a pyrimidine ring and a thiazole ring, and it is essential for the functioning of multicellular organisms. Thiamine has three forms, namely, thiamine monophosphate, thiamine pyrophosphate (TPP), and thiamine triphosphate (Kerns and Gutierrez, 2017). TPP is the main form of thiamine utilization in the human body. Under the action of thiamine pyrophosphokinase, thiamine entering cells is converted into TPP, which becomes a coenzyme of α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, transketolase, and branched α-ketoate dehydrogenase complex, which is involved in cell energy metabolism (Abdou and Hazell, 2015; Polegato et al., 2019). Thiamine deficiency can decrease the production of nicotinamide adenine dinucleotide phosphate and adenosine triphosphate, which reduced the activity of transketolase and weakened the transketolase action of the pentose phosphate pathway, thereby affecting organs sensitive to hypoxia, such as the brain and heart, resulting in impaired utilization of glucose (Calderón-Ospina and Nava-Mesa, 2020). In addition, thiamine deficiency can lead to neurotransmitter changes, oxidative stress response, lactic acidosis, inflammation, apoptosis, and blood–brain barrier dysfunction (Smith et al., 2021).

These important effects of thiamine indicate the importance of thiamine supplementation in critically ill patients. For example, thiamine combined with hydrocortisone and ascorbic acid to form HAT therapy in patients with sepsis is associated with improved organ dysfunction, reduced sequential organ failure assessment scores, increased lactate clearance, and decreased mortality (Marik et al., 2017; Litwak et al., 2019). Moreover, the application of thiamine can significantly reduce the mortality of patients with ventilator-associated pneumonia and acute kidney injury in the ICU settings (Li et al., 2022; Zhang et al., 2022). Thiamine deficiency, resulting in the accumulation of pyruvate and its conversion to lactic acid, causes a decrease in peripheral resistance, thereby increasing venous return to the heart (preload). This increased preload combined with myocardial dysfunction has been proposed as the etiological basis of congestive heart failure in thiamine deficiency (Ahmed et al., 2015). Some studies have shown that thiamine supplementation can improve cardiac function in patients with heart failure, but little consistent evidence has been found on whether thiamine use can improve survival outcomes in these patients (Schoenenberger et al., 2012; Smithline et al., 2019). Compared with general hospitalized patients with heart failure, critically ill patients with heart failure likely develop thiamine deficiency because of malnutrition, increased metabolic status, and diuretic use. Therefore, considerable attention should be paid to thiamine supplementation in critically ill patients with heart failure. This study aimed to evaluate the association between thiamine administration and in-hospital mortality in critically ill patients with heart failure based on the Medical Information Mart for Intensive Care (MIMIC)-IV database, which will provide a reference for guiding rational drug use to improve prognoses.

Materials and methods

Data source

Data of this study were extracted from the MIMIC-IV database (https://mimic-iv.mit.edu/). The MIMIC-IV, an update to the MIMIC-III, is a large, single-center, and freely available medical information database maintained by Beth Israel Deaconess Medical Center. This database contains more than 250,000 emergency department admissions and more than 60,000 ICU stays from 2008 to 2019. The patient information in this database was anonymous; thus, informed consent need not to be obtained. The authors have completed the corresponding training courses and obtained the certificates (No: 10012145) to gain access to the database.

Participants

Critically ill patients diagnosed with heart failure according to the International Classification of Disease 9 and 10 codes were initially screened. The inclusion criteria were as follows: 1) age ≥18 years old and 2) first admission to ICU. Patients were excluded in accordance with the exclusion criteria: 1) Stay in ICU for less than 2 days, 2) more than 15% of personal data missing, and 3) had diseases that weren't suitable for thiamine therapy, such as stone diseases.

Data extraction

The structured Query Language with PostgreSQL (version 9.6) was applied to extract data on the first day of admission from MIMIC-IV (Yang et al., 2020; Wu et al., 2021). The following variables were selected: 1) Demographic characteristics, including age, gender, ethnicity, and body mass index; 2) comorbidities, including myocardial infarct, hypertension, diabetes, liver disease, chronic renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, malignant cancer, and sepsis; 3) scoring systems, including the Charlson comorbidity index, Glasgow Coma Scale,

Sequential Organ Failure Assessment, and Acute Physiology Score III; 4) vital signs, including heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, temperature, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), oxygen saturation (SpO_2), and urine output; 5) laboratory tests, including hematocrit, hemoglobin, platelets, white blood cell, anion gap, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, sodium, potassium, hydrogen ion concentration (pH), lactate, prothrombin time, and N-terminal pro-brain natriuretic peptide (NT-proBNP); and 6) clinical therapy, including ACEIs, ARBs, implantable cardioverter defibrillator, beta-blockers, diuretics, renal replacement therapy, mechanical ventilation, and vasopressor. The primary outcome of this study was in-hospital mortality, which is defined as all-cause mortality during hospitalization. In order to minimize the bias caused by missing data, variables with over 30% missing data were removed from the analysis dataset, and others were duplicated using multiple imputation (Cummings, 2013). As a popular approach for addressing the presence of missing data, multiple imputation is a two-stage approach where missing values are imputed a number of times using a statistical model based on the available data and then inference is combined across the completed datasets.

Statistical analysis

Based on whether thiamine was used or not, patients were divided into two groups, namely, the non-thiamine group and thiamine group. Continuous variables were presented as medians with interquartile ranges (IQRs), and categorical variables were expressed as the number of cases and percentages (%). The between-group difference was compared by using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. The Kaplan-Meier (KM) method was applied to draw survival curves for in-hospital mortality and a log-rank test was conducted to determine the difference between the two groups. Cox proportional hazard models with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the effect of thiamine use on prognosis by adjusting various confounders, including demographic features, comorbidities, scoring systems, vital signs, laboratory tests, and clinical therapy (Liu et al., 2022). Potential multicollinearity among variables was tested using the variance inflation factor (VIF), with a VIF ≥5, indicating the presence of multicollinearity. A 1:1 nearest propensity-score matching (PSM) and propensity-score-based inverse probability of treatment weighting (IPW) were performed to ensure the robustness of the findings (Austin and Stuart, 2017). Subgroup analyses were performed to assess the effect of thiamine use on in-hospital mortality, including demographic features and comorbidities. Two-sided p values less than 0.05 were considered statistically significant. All statistical analyses were conducted using R (version 4.2.1).

Results

Baseline feature

As shown in Figure 1, data of 13,532 critically ill patients with heart failure were initially extracted from the MIMIC-IV database. After exclusion according to the exclusion criteria, a total of 7,021 patients were finally included in this study, consisting of 685 (9.8%) patients who received thiamine therapy during their stay in the ICUs. The median age of the original population was 76 years (IQR: 65–84) among whom 3,768 (53.7%) were male and 5,019 (71.5%) were white people.

Differences in baseline characteristics between the thiamine and non-thiamine groups are listed in Table 1. Most of the patients in the thiamine group were men, and they tended to be younger. In addition, they had a higher incidence of liver disease and sepsis but a lower rate of diabetes, chronic renal disease, and peripheral vascular disease. They also had higher values of lactate and NT-proBNP and lower values of platelets, bicarbonate, BUN, calcium, creatinine, and sodium compared with those in the non-thiamine group. Moreover, the patients in the thiamine group likely received diuretics and RRT, whereas those in the non-thiamine group were more likely to be treated with ACEIs and vasopressor.

After PSM, a total of 681 patients who received thiamine therapy were matched to 681 cases who didn't, and no difference in baseline characteristics was found between the two groups (Supplementary Table S1). A scatter plot based on the propensity score showed the matched and the unmatched cases in the two groups, indicating a good quality of the matched samples (Supplementary Figure S1A). Moreover, the histogram used to show the distribution of propensity score also suggested that the basic shapes of the two groups are highly consistent after matching, which further validated the matching effect (Supplementary Figure S1B).

Survival analysis

A total of 100 (14.6%) and 1,166 (18.4%) patients died during hospitalization in the thiamine and none-thiamine groups, respectively. As shown in Figure 2A, the thiamine group had a lower in-hospital mortality than the non-thiamine group in the original population ($p = 0.005$). After PSM ($p < 0.001$; Figure 2B) and IPW ($p = 0.005$; Figure 2C), the results of KM survival curves were consistent with that of the original population.

Considering that all VIFs were less than 5, no multicollinearity was determined among variables (Supplementary Table S3). We further analyzed the relationship between thiamine supplement and prognosis through Cox proportional hazard models and the results are listed in Table 2. A crude model of univariate Cox regression analysis revealed that thiamine use was significantly associated with a 26% reduction in the risk of in-hospital mortality in the original population with a HR of 0.74 (95% CI: 0.64–0.84, $p < 0.001$). After adjusting for a series of confounders, multivariate analyses indicated a significant beneficial effect of thiamine administration on in-hospital mortality among critically ill patients with heart failure with a HR of 0.78 (95% CI: 0.67–0.89, $p = 0.004$) in the fully adjusted model. After PSM and IPW, the crude models demonstrated that thiamine use was related to a decreased mortality risk with HRs (95% CIs) of 0.61 (95% CI: 0.48–0.79, $p < 0.001$) and 0.79 (95% CI: 0.68–0.90, $p = 0.004$), respectively. The PSM and IPW models also showed similar results with HRs of 0.68 (95% CI: 0.56–0.89, $p < 0.001$) and 0.84 (95% CI: 0.73–0.96, $p = 0.035$) in the fully adjusted models, respectively.

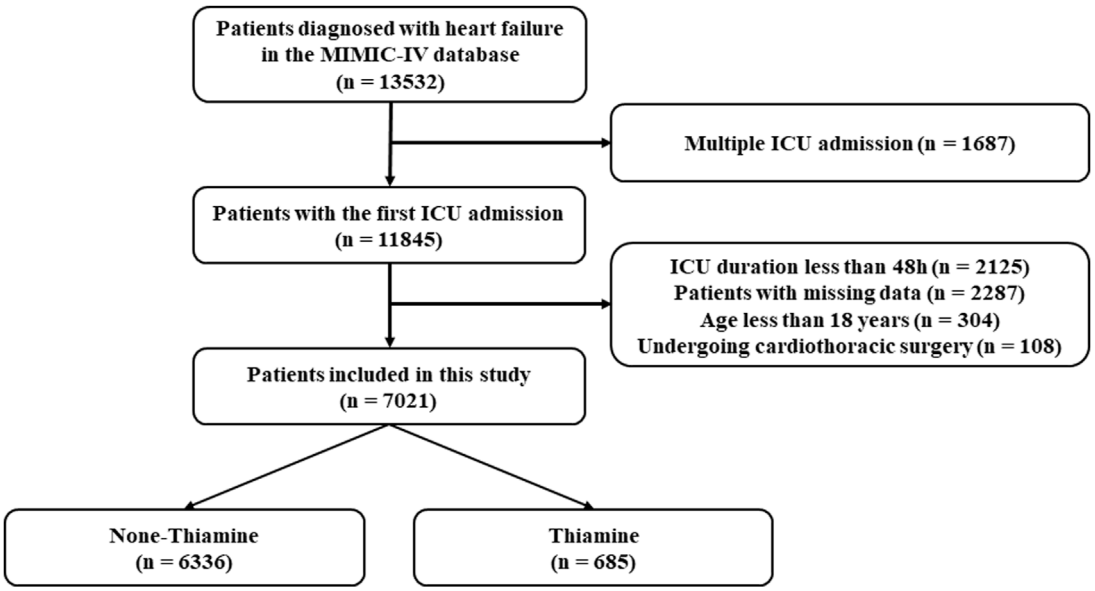

FIGURE 1
Inclusion and exclusion flowchart of the study.

Subgroup analysis

The results of subgroup analyses are listed in Figure 3. A significant association between thiamine use and in-hospital mortality was observed in all subgroups except for patients with liver disease, cerebrovascular disease, or malignant cancer. In addition, no significant interaction was observed between the thiamine and none-thiamine groups in all strata.

Discussion

Hospital admissions and mortality caused by heart failure are high. The treatment of patients with critical heart failure is expensive, and although several resources have been devoted to the development of drugs for the treatment of critical heart failure worldwide, the prognosis is still not ideal. Clinical recommendations primarily focus on limiting fluid and salt, as well as energy and protein intake, whereas recommendations for the supplementation of micronutrients, such as mineral and vitamin, are limited (van der Meer et al., 2019). Nutritional supplementation is economical and safe and, if proven effective, can significantly reduce the burden of heart failure. Thiamine supplementation can improve the state of heart failure caused by severe thiamine deficiency, but whether thiamine supplementation is effective in critically ill patients with heart failure remains unknown (Costa et al., 2022). Therefore, this study aimed to explore the correlation between thiamine use and prognosis in patients with HF. After controlling for potential confounding factors using Cox regression models, we found that thiamine supplementation in critically ill patients with heart failure could significantly decrease the risk of in-hospital mortality. The results of dual robustness tests for PSM and IPW also supported this finding.

Critically ill patients who were admitted to the ICUs are often in a state of fasting or undereating because of their critical condition, leading to inadequate thiamine intake. In particular, patients with obesity who routinely take multivitamin supplements aren't immune to thiamine deficiency (Manzanares and Hardy, 2011). In this study, critically ill patients with heart failure who were admitted to the ICUs were all over 55 years old, and overweight. Most of them had multiple complications, indicating that they had a high risk of thiamine deficiency. However, only less than 10% of these patients had received thiamine supplement, which was significantly lower than those in patients with sepsis and ventilator-associated pneumonia (Hu et al., 2022; Zhang et al., 2022). This apparent difference may be related to the variability of care providers. Considering that heart failure is a fatal disease, healthcare professionals tend to focus more on heart failure treatment. Moreover, although some guidelines and consensus suggest thiamine supplementation in patients with heart failure, recommendations regarding specific reference intake and ingestion methods vary, and clinical trials have not yielded consistent results. This may explain the lower-than-expected thiamine supplementation rate in patients with heart failure.

The human body cannot synthesize thiamine itself, and it has limited stocks; thus, it must rely on external sources for replenishment. Thiamine, as a key coenzyme in glycolysis, plays a key regulatory role in mitochondrial ATP synthesis and provides energy for cells; thus, the lack of thiamine could affect mitochondrial function (Page et al., 2011). Impaired mitochondrial function can cause cellular dysfunction, leading to serious complications of heart failure, neuropathy, gastrointestinal dysfunction, and lactic acidosis (Zhou and Tian, 2018; Eftekharpour and Fernyhough, 2022). Therefore, thiamine supplementation helps restore mitochondrial function and perfusion of damaged tissues, thereby reducing

TABLE 1 Baseline features of the original population.

Variable	Total (n = 7,021)	Non-thiamine (n = 6,336)	Thiamine (n = 685)	*p*-Value
Age, years	76 (65, 84)	76 (66, 85)	68 (59, 78)	<0.001
Gender, n (%)				<0.001
Male	3,768 (53.7)	3,335 (52.6)	430 (63.2)	
Female	3,253 (46.3)	3,001 (47.4)	252 (36.8)	
BMI, kg/m^2	27.9 (24.1, 32.9)	27.8 (24.1, 32.9)	27.8 (24.4, 32.9)	0.894
Ethnicity, n (%)				<0.001
White people	5,019 (71.5)	4,574 (72.2)	445 (65.0)	
Black people	812 (11.6)	734 (11.6)	78 (11.4)	
Others	1,190 (16.9)	102 (16.2)	162 (23.6)	
Comorbidities, n (%)				
Myocardial infarct	2,103 (30.0)	1922 (30.3)	181 (26.4)	0.038
Hypertension	5,090 (72.5)	4,590 (72.4)	500 (73.0)	0.760
Diabetes	3,017 (43.0)	2,780 (42.9)	237 (34.6)	<0.001
Liver disease	744 (10.6)	570 (9.0)	174 (25.4)	<0.001
Chronic renal disease	2,944 (41.9)	2,720 (42.9)	224 (32.7)	<0.001
Peripheral vascular disease	1,253 (17.8)	1,155 (18.2)	98 (14.3)	0.013
Cerebrovascular disease	937 (13.3)	847 (13.4)	90 (13.2)	0.914
Chronic pulmonary disease	3,078 (43.8)	2,787 (44.0)	291 (42.5)	0.475
Malignant cancer	738 (10.5)	659 (10.4)	79 (11.5)	0.394
Sepsis	4,565 (65.0)	4,052 (64.0)	513 (74.0)	<0.001
Clinical scores				
Charlson comorbidity index	7 (6, 9)	8 (6, 9)	7 (5, 9)	<0.001
GCS	14 (10, 15)	14 (11, 15)	13 (9, 14)	<0.001
SOFA	5 (3, 8)	5 (3, 8)	6 (4, 9)	<0.001
APSIII	51 (40, 67)	51 (40, 67)	56 (43, 77)	<0.001
Vital sign				
Heart rate, beats/min	83 (73, 95)	83 (73, 94)	86 (75, 99)	<0.001
Respiratory rate, beats/min	19 (17, 22)	19 (17, 22)	20 (17, 20)	0.645
SBP, mmHg	112 (103, 125)	112 (103, 125)	111 (103, 124)	0.107
DBP, mmHg	58 (52, 65)	58 (52, 65)	60 (54, 68)	<0.001
Temperature, ˚C	36.7 (36.4, 37.0)	36.7 (36.4, 37.0)	36.8 (36.5, 37.1)	0.024
PaO_2, mmHg	131.5 (86.5, 226.0)	131.5 (86.5, 226.0)	131.5 (87.5, 233.0)	0.989
$PaCO_2$, mmHg	41.5 (36.5, 48.5)	41.5 (36.5, 48.5)	41.0 (35.5, 47.0)	0.297
SpO_2, %	97 (96, 98)	97 (95, 98)	97 (96, 99)	0.038
Urine output, ml	1,470 (852, 2,345)	1,480 (855, 2,345)	1,405 (820, 2,348)	0.301
Laboratory test				
Hematocrit, %	31.5 (27.9, 35.9)	31.4 (27.0, 35.9)	31.7 (27.8, 36.2)	0.599
Hemoglobin, g/dL	10.3 (9.1, 11.8)	10.3 (9.1, 11.8)	10.4 (9.1, 12.0)	0.204
Platelets, $10^9/L$	200.5 (147.5, 266.5)	202.0 (148.5, 267.0)	190.0 (131.8, 256.0)	0.009
WBC, $10^9/L$	10.7 (7.9, 14.5)	10.7 (7.9, 14.5)	10.9 (7.5, 14.6)	0.195
Anion gap, mEq/L	14.5 (12.5, 17.0)	14.5 (12.5, 17.0)	15.0 (13.0, 17.5)	0.053
Bicarbonate, mmol/L	24.0 (21.5, 27.0)	24.5 (21.5, 27.5)	23.0 (20.0, 26.5)	<0.001
BUN, mg/dL	29.0 (19.5, 47.0)	29.5 (19.5, 47.0)	26.5 (17.0, 45.5)	0.006
Calcium, mmol/L	8.4 (7.9, 8.9)	8.4 (8.0, 8.9)	8.3 (7.8, 8.8)	<0.001
Chloride, mmol/L	103 (99.0, 107.0)	103.0 (99.0, 107.0)	103.5 (99.0, 108.0)	0.191
Creatinine, mg/dL	1.3 (1.0, 2.2)	1.4 (1.0, 2.2)	1.3 (0.9, 2.2)	0.022
Glucose, mg/dL	132.0 (110.0, 168.0)	132.5 (110.0, 168.0)	129.5 (106.5, 169.3)	0.180
Sodium, mmol/L	138.5 (135.5, 141.0)	138.5 (135.5, 141.0)	138.0 (135.5, 141.0)	0.035
Potassium, mmol/L	4.3 (3.9, 4.7)	4.3 (3.9, 4.7)	4.3 (3.9, 4.7)	0.818
pH	7.38 (7.33, 7.43)	7.38 (7.34, 7.43)	7.38 (7.32, 7.43)	0.434
Lactate, mmol/L	1.6 (1.1, 2.3)	1.6 (1.2, 2.3)	1.8 (1.3, 2.5)	<0.001
PT, seconds	14.9 (13.0, 19.1)	14.9 (13.0, 19.1)	15.1 (13.2, 18.7)	0.112
NT-proBNP, pg/mL	6,903 (2,825, 15,550)	6,169 (2,583, 14,007)	7,450 (3,075, 16,441)	0.004
Clinical Therapy, n (%)				

(Continued on following page)

TABLE 1 (*Continued*) Baseline features of the original population.

Variable	Total (n = 7,021)	Non-thiamine (n = 6,336)	Thiamine (n = 685)	*p*-Value
ACEIs	2,199 (31.3)	2021 (31.9)	178 (26.0)	0.002
ARBs	416 (5.9)	385 (6.1)	31 (4.5)	0.102
ICD	138 (2.0)	122 (1.9)	16 (2.3)	0.462
Beta-blockers	2,531 (36.1)	2,281 (36.0)	250 (36.5)	0.797
Diuretics	5,378 (76.6)	4,824 (76.1)	554 (80.9)	0.005
Vasopressor	6,704 (95.5)	6,065 (95.7)	639 (93.3)	0.005
RRT	718 (10.2)	621 (9.8)	97 (14.2)	<0.001
Mechanical ventilation	3,639 (51.8)	3,290 (51.9)	349 (50.9)	0.627
ICU length of stay, day	3.9 (2.1, 9.0)	3.4 (1.9, 7.9)	5.2 (2.5, 10.3)	<0.001
Hospital length of stay, day	10.5 (5.9, 17.2)	9.8 (5.5, 16.5)	12.1 (6.4, 18.7)	<0.001

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; APS, acute physiology score; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; GCS, glasgow coma scale; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; NT-proBNP, N-terminal pro-brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; pH, hydrogen ion concentration; PT, prothrombin time; RRT, renal replacement therapy; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; SpO2, oxygen saturation; WBC, white blood cell.

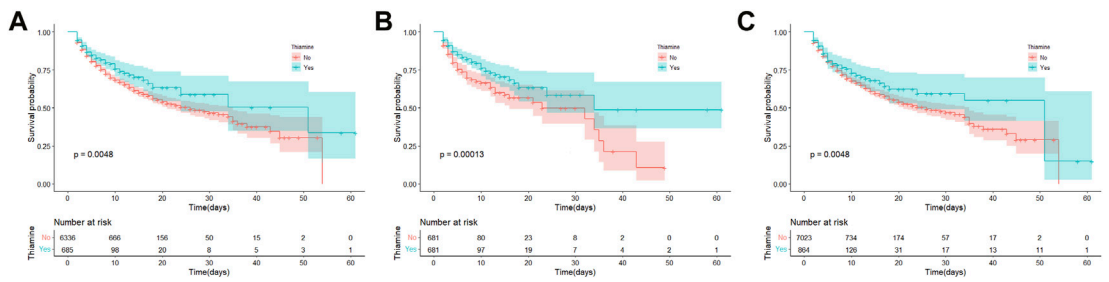

FIGURE 2
Kaplan-Meier survival curves between the thiamine and none-thiamine groups. **(A)** The original population; **(B)** After propensity score matching adjustment; and **(C)** After propensity score-based inverse probability of treatment weighting adjustment.

TABLE 2 Results of Cox proportional hazard models.

Models	Original population		PSM population		IPW population	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Crude model	0.74 (0.64–0.84)	<0.001	0.61 (0.48–0.79)	<0.001	0.79 (0.68–0.90)	0.004
Model 1	0.74 (0.64–0.84)	<0.001	0.61 (0.48–0.79)	<0.001	0.79 (0.69–0.90)	0.004
Model 2	0.76 (0.65–0.87)	<0.001	0.64 (0.50–0.83)	<0.001	0.80 (0.69–0.92)	0.011
Model 3	0.75 (0.64–0.87)	<0.001	0.65 (0.51–0.84)	<0.001	0.82 (0.70–0.94)	0.020
Model 4	0.76 (0.65–0.88)	0.001	0.64 (0.51–0.84)	<0.001	0.82 (0.70–0.94)	0.021
Model 5	0.77 (0.66–0.89)	0.002	0.67 (0.55–0.88)	<0.001	0.84 (0.72–0.96)	0.030
Model 6	0.78 (0.67–0.89)	0.004	0.68 (0.56–0.89)	<0.001	0.84 (0.73–0.96)	0.035

HR, hazard ratio; CI, confidence interval; PSM, propensity-score matching; IPW, inverse probability weighting.
[a]Model 1 was adjusted for demographic features, including age, gender, ethnicity, and BMI.
[b]Model 2 was additionally adjusted for comorbidities, including myocardial infarct, hypertension, diabetes, liver disease, chronic renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, malignant cancer, and sepsis.
[c]Model 3 was additionally adjusted for clinical scores, including Charlson comorbidity index, GCS, SOFA, and APSIII.
[d]Model 4 was additionally adjusted for vital signs, including heart rate, respiratory rate, SBP, DBP, temperature, PO_2, PCO_2, SpO_2, and urine output.
[e]Model 5 was additionally adjusted for laboratory tests, including hematocrit, hemoglobin, platelets, white blood cell, anion gap, bicarbonate, BUN, calcium, chloride, creatinine, glucose, sodium, potassium; PH, lactate; PT, and NT-proBNP.
[f]Model 6 was additionally adjusted for clinical therapy, including ACEI, ARB, ICD, beta-blocker, diuretics, renal replacement therapy, mechanical ventilation, and vasopressor.

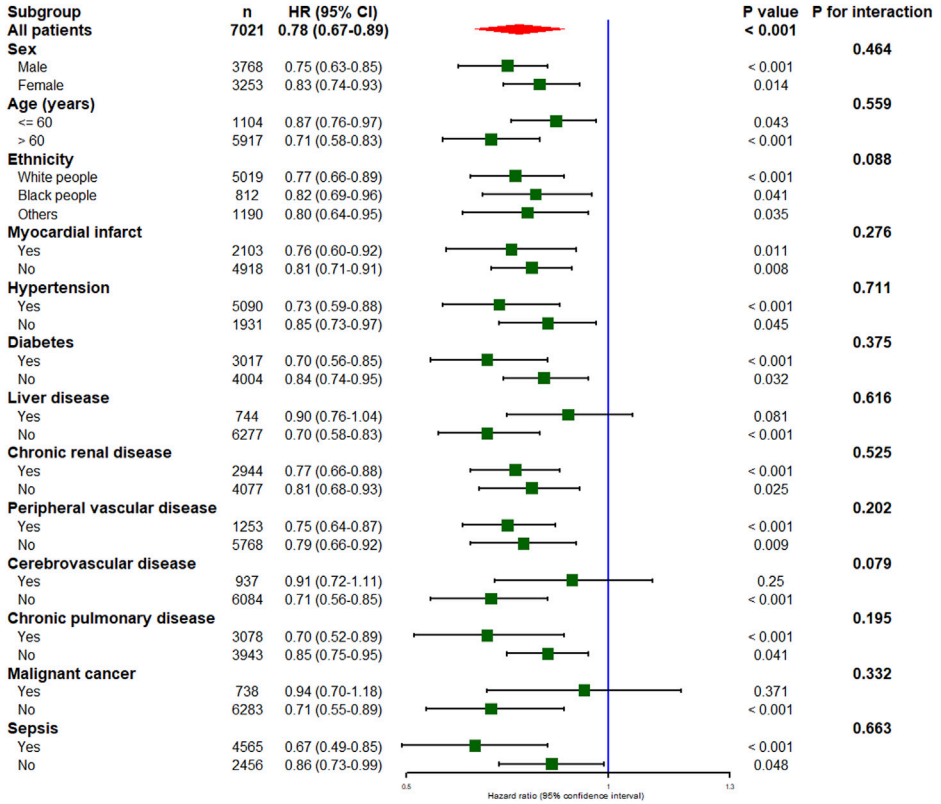

FIGURE 3
Subgroup analysis of the association between thiamine use and in-hospital mortality in critically ill patients with heart failure. HR, hazard ratio; CI, confidence interval.

the likelihood of organ dysfunction and improving patient prognosis. Apart from its vital role in energy metabolism, thiamine is also an antioxidant. In critically ill patients, changes in cell structure and the imbalance of oxidative and antioxidant systems lead to high levels of oxidative stress products such as reactive oxygen species, because of inflammatory response and tissue hypoxia (Zanza et al., 2019). Thiamine supplementation can reduce oxidative stress by inhibiting lipid peroxidation and oleic acid oxidation, thereby positively affecting oxidative stress level (Collie et al., 2017). Thiamine also has an antioxidant effect on neutrophil cells and a protective effect on macrophages against oxidative stress-induced NF-kB activation, and it plays an important role in the activity of p53 suppressor protein by inhibiting the intracellular activity of P43, thereby exerting an anti-inflammatory effect (Mitchell et al., 2020).

In this study, a close association was found between thiamine administration and a decreased risk of in-hospital mortality in critically ill patients with heart failure, regardless of adjustments on various confounders. After multiple robust verifications and subgroup analyses, the results all confirmed the important significance of thiamine supplementation in improving the prognosis among these patients. Moreover, based on the comparison of baseline characteristics between the thiamine and non-thiamine groups, thiamine supplement can reduce the use of ventilators, ACEI, and vasopressors in critically ill patients with heart failure, indicating that it is a safe and effective treatment.

This study has some advantages. First, electronic medical records from the MIMIC-IV database were used, which have a high focus on patients admitted to ICUs with a large sample size, thereby providing strong evidence for our conclusions. Second, we obtained the same result after adjusting the baseline level by using PSM and IPW and establishing a series Cox regression models to adjust various confounding factors, which further confirmed the reliability of the results (Zhong et al., 2022). However, this study also has some limitations. First, this study had a single-center retrospective observational design; thus, selection bias was inevitable (Yue et al., 2022). Second, we cannot identify thiamine deficiency because of the lack of baseline thiamine levels in MIMIC-IV. Therefore, we cannot infer whether all patients with heart failure benefit, or only individuals with thiamine deficiency. Third, we only grouped patients based on whether they received in-hospital thiamine supplementation or not, and we didn't consider dosage and duration of administration, which may limit the application of our findings. Fourth, the adjustments in our study may not be sufficient to address all confounding variables, and some confounding factors may remain unexplained, such as the variability of care providers. Despite a significant difference in mortality, the present results should be interpreted with caution. Finally, considering that the MIMIC-IV database rarely records lactate levels in patients, we cannot determine whether thiamine improved patient outcomes by reducing lactate concentrations.

Conclusion

Thiamine supplementation is beneficial to the prognosis of critically ill patients with heart failure who were admitted in ICUs. Given its low cost and relatively few side effects, thiamine supplementation may be useful in these patients. However, the results are not conclusive, and they should be validated by further clinical trials with large sample sizes.

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

JaW, LC, and XH conceived of and designed the work. SY, YZ, and JuW acquired and check the data. XH, EY, and JH performed statistical and computational analyses. JaW, EY, and DN assisted the analysis and explain of statistical methods. RY, JaW, LC, and DN provided professional clinical analyses. RY, SY, and YZ drafted the work. All authors read and approved the final manuscript.

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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.2023.1162797/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Baseline difference between the thiamine and non-thiamine groups before and after propensity score matching.

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Drug-induced tooth discoloration: An analysis of the US food and drug administration adverse event reporting system

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Background: Certain drugs can cause intrinsic or extrinsic tooth discoloration, which is not only a clinical issue but also an esthetic problem. However, limited investigations have focused on drug-induced tooth discoloration. The present work aimed to determine the drugs causing tooth discoloration and to estimate their risks of causing tooth discoloration.

Methods: An observational, retrospective, and pharmacovigilance analysis was conducted, in which we extracted adverse event (AE) reports involving tooth discoloration by using the data of the US Food and Drug Administration's Adverse Event Reporting System (FAERS) from the first quarter (Q1) of 2004 to the third quarter (Q3) of 2021. Disproportionality analyses were performed to examine risk signals for tooth discoloration and determine the drugs inducing tooth discoloration.

Results: Based on predefined inclusion criteria, 1188 AE reports involving 302 suspected drugs were identified. After data mining, 25 drugs generated positive risk signals for tooth discoloration, of which 10 were anti-infectives for systemic use. The top reported drug was tetracycline (n = 106), followed by salmeterol and fluticasone (n = 68), amoxicillin (n = 60), chlorhexidine (n = 54), and nicotine (n = 52). Cetylpyridinium (PRR = 472.2, ROR = 502.5), tetracycline (PRR = 220.4, ROR = 277), stannous fluoride (PRR = 254.3, ROR = 262.8), hydrogen peroxide (PRR = 240.0, ROR = 247.6), and chlorhexidine (PRR = 107.0, ROR = 108.4) showed stronger associations with tooth discoloration than the remaining drugs. Of 625 AE reports involving 25 drugs with positive risk signals, tooth discoloration was mostly reported in patients aged 45–64 (n = 110) and ≤18 (n = 95), and 29.4% (192/652) of the reports recorded serious outcomes.

Conclusion: This study revealed that certain drugs are significantly associated with tooth discoloration. Caution should be exercised when using these drugs, especially during pregnancy and early childhood.

KEYWORDS

drugs, tooth discoloration, FAERS, disproportionality analyses, data mining

Introduction

With the continuous improvement of living standards, increasing attention is paid to oral health and the esthetic demand of keeping teeth white and shiny is gradually rising. The color of a tooth is affected by its inherent color and stains (Joiner and Luo, 2017). The inherent color of the tooth is primarily determined by dentine color and is affected by intrinsic and extrinsic factors (Watts and Addy, 2001).

Depending on the location of the stains, tooth discoloration can be classified into two types: intrinsic and extrinsic. Intrinsic tooth discoloration is usually caused by abnormal tooth development or stains deposited in the enamel of dentine during development, which is hard to remove. Extrinsic tooth discoloration usually occurs on the surface of the tooth, which may be removed by scaling and polishing. There are various factors inducing tooth discoloration, comprising intrinsic factors (e.g., some drugs and metabolic diseases) and extrinsic factors (e.g., wine, coffee, tobacco, and mouth rinses) (Kahler, 2022). Certain drugs can cause tooth discoloration after administration, among which tetracycline is the most characterized (Sánchez et al., 2004). However, drug-induced tooth discoloration is generally difficult to recognize and unfamiliar to clinicians. Therefore, it is necessary to identify drugs causing tooth discoloration as well as the appropriate population and timing of taking these medications. Unfortunately, no study has focused on comprehensively identifying the drugs associated with tooth discoloration, especially from the perspective of a representative population-based AE database.

The Food and Drug Administration Adverse Event Reporting System (FAERS) constitutes a publicly available and spontaneous reporting database containing AE reports, medication error reports, and product quality complaints resulting in AEs. The FAERS supports the FDA's post-marketing safety surveillance program for drugs and therapeutic biologics (Hu et al., 2020). Herein, we retrieved AE reports involving tooth discoloration from the FAERS database. Disproportionality analyses were then performed to examine risk signals for tooth discoloration and to determine drugs causing tooth discoloration.

Materials and methods

Data source

This retrospective pharmacovigilance analysis was carried out with data in the FAERS database. In the current study, AE reports were extracted by using OpenVigil 2.1, an open web-based pharmacovigilance data extraction, cleaning, mining, and analysis tool used to examine the FAERS (Böhm et al., 2012).

Identification of AE reports and drugs

The informatic structure of the FAERS system follows the international safety reporting guidance of the International Conference on Harmonisation (ICH). AEs are coded based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA's hierarchical structure includes system organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lowest level term (LLT). Among them, PTs are single medical concepts, not a grouping (Mozzicato, 2009).

Herein, the MedDRA PT: "tooth discoloration" was employed to identify the relevant cases. Possible duplicate and multiple records were then examined and excluded. For each reported suspected drug, all possible drug names were taken into account, and the same active substance was combined by generic name. Anatomical therapeutic chemical (ATC) codes were assigned to each drug, in order to group all tooth discoloration cases for each active substance. The flow diagram of data mining is presented in Figure 1.

Statistical analysis

Disproportionality analyses were performed in this study. Two statistical metrics, proportional reporting ratio (PRR) and reporting odds ratio (ROR), were employed to characterize the association between the drug of interest and tooth discoloration.

Each analysis of the potential association between drug exposure and AE utilized a two-by-two contingency table (Table 1), through which disproportional AEs and drug combinations could be identified. The PRR is a disproportionate degree of adverse event reporting for a particular drug compared to the reports of the same adverse event for all other drugs in the database. Based on criteria presented by Evans and collaborators (Evans et al., 2001), a positive signal was commonly considered for PRR≥2, chi-square value ≥ 4, and ≥3 cases. The value of PRR is positively correlated to the strength of the association. The ROR is the ratio of the reporting rate of a particular event to the totality of other events for a particular drug to that of the remaining drugs included in the database. Signals were detected with the lower bound of the 95% two-sided confidence interval (CI) for the ROR above 1 (van Puijenbroek et al., 2002). The higher the value, the more pronounced the disproportionate performance.

To decrease the false-positive rate of risk signals, the threshold of detection criteria was improved in this study. For PRR, a positive signal was defined by PRR≥3, chi-square value ≥ 5, and ≥5 cases. For ROR, positive signals were identified with the low boundary of 95% CI > 2 and at least 5 cases submitted (Chen et al., 2022).

Results

Through OpenVigil 2.1, 9,217,181 AE reports were extracted between 2004 Q1 and 2021 Q3. Based on predefined inclusion criteria, 1188 AE reports involving 302 suspected drugs were identified. Table 2 describes the characteristics of AE reports regarding tooth discoloration. With respect to gender, most patients (59.3%) were males. The patients aged 45–64, ≤18, and 19–44 accounted for 17.0%, 11.9%, and 10.2%, respectively. Most reports (76.5%) were submitted from the United States.

Disproportionality analyses based on two algorithms were performed, and the results are presented in Table 3. After data mining, 25 drugs had positive risk signals for tooth discoloration. The most commonly reported drug associated with tooth discoloration was tetracycline (n = 106), followed by salmeterol and fluticasone (n = 68), amoxicillin (n = 60), chlorhexidine (n = 54), and nicotine (n = 52). Of all the 25 drugs examined, cetylpyridinium (PRR = 472.2, ROR = 502.5), tetracycline (PRR = 220.4, ROR = 277),

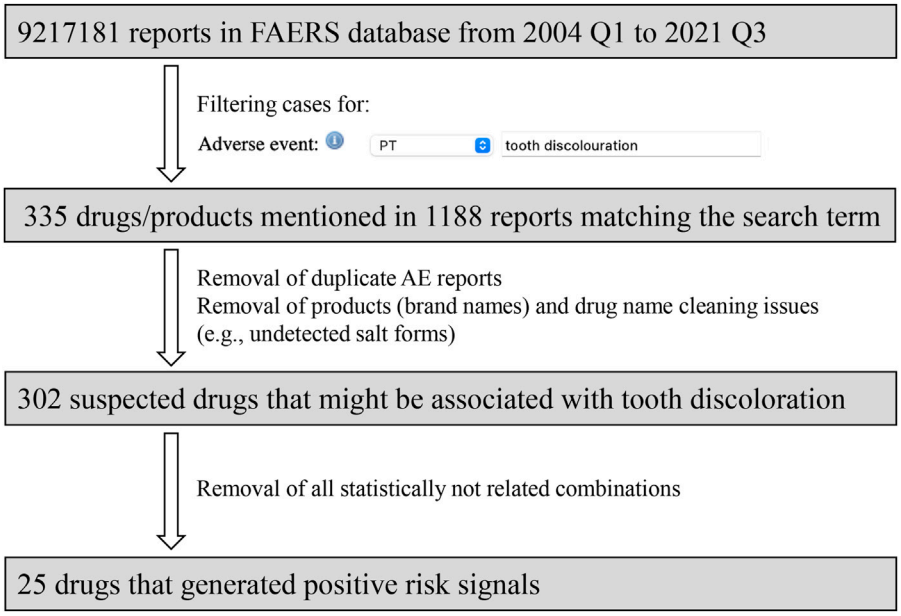

FIGURE 1
Flow diagram of drug identification in the FAERS.

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

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

Proportional reporting ratio (PRR): PRR = $\frac{a/(a+b)}{c/(c+d)}$, 95%CI = $e^{\ln(PRR)\pm1.96\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}}$
Reporting odds ratio (ROR): ROR = $\frac{a/c}{b/d}$, 95%CI = $e^{\ln(ROR)\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$

stannous fluoride (PRR = 254.3, ROR = 262.8), hydrogen peroxide (PRR = 240.0, ROR = 247.6), and chlorhexidine (PRR = 107.0, ROR = 108.4) showed stronger associations with tooth discoloration than the remaining drugs.

The characteristics of 652 AE reports involving 25 drugs with positive risk signals were presented in Table 4. We stratified dosage, patient age, and outcomes based on these 25 drugs. Most of them could be prescribed in appropriate dosage ranges except two cases of asenapine exceeding the recommended dosage. 49.8% (325/652) of the AE reports did not record patient age. Of the remaining 327 AE reports, tooth discoloration was mostly reported in patients aged 45–64 (n = 110) and ≤18 (n = 95). Since the labels of tetracyclines indicated that tooth development involved the second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years, we also paid attention to drug administration in patients aged under eight. In antimicrobial-related cases, some patients were younger than 8 years, such as amoxicillin (n = 28), tetracycline (n = 6), doxycycline (n = 3), azithromycin (n = 3), linezolid (n = 2), clarithromycin (n = 2), and cefprozil (n = 2). Also, there were nine and two cases involving patients aged under eight for budesonide and salmeterol and fluticasone, respectively. 29.3% (191/652) of the cases reported serious outcomes, which were documented as other (n = 161), hospitalization-initial or prolonged (n = 38), disability (n = 30), required intervention to prevent permanent impairment (n = 6), damage (n = 6), death (n = 4), life-threatening (n = 2), and congenital anomaly (n = 2). Of note, one AE report might record more than one serious outcome.

The distribution of the 25 drugs based on ATC code is exhibited in Figure 2, in which the column height represents the number of corresponding AE reports. The involved ATC classes included anti-infectives for systemic use (n = 10), alimentary tract and metabolism n = 4), musculo-skeletal system (n = 3), respiratory system (n = 2), dermatologicals (n = 2), nervous system (n = 2), cardiovascular system (n = 1), and various (n = 1).

Discussion

This represents the first report to comprehensively review drugs associated with tooth discoloration. Based on FAERS, 1188 AE

TABLE 2 The characteristics of AE reports pertaining to tooth discoloration.

Characteristics	N (%)
Patient gender	
Male	705 (59.3%)
Female	334 (28.1%)
Unknown or missing	149 (12.5%)
Patient age group (years)	
≤18	141 (11.9%)
19–44	121 (10.2%)
45–64	202 (17.0%)
65–74	68 (5.7%)
≥75	65 (5.5%)
Unknown or missing	591 (49.7%)
Reporting country	
United States	909 (76.5%)
United Kingdom	66 (5.6%)
Canada	15 (1.3%)
German	15 (1.3%)
Others	91 (7.7%)
Unknown or missing	92 (7.7%)
Reporting Region	
America	930 (78.3%)
Europe	136 (11.5%)
Asia	20 (1.7%)
Oceania	9 (0.8%)
Africa	1 (0.1%)
Unknown or missing	92 (7.7%)

reports were submitted in the study period. Totally 25 drugs were statistically associated with tooth discoloration, involving eight ATC classes. These drugs could be divided into two categories according to administration route, including 8 drugs for topical use and 17 for systemic use.

Drugs for topical use

Stomatological preparations

Stannous fluoride and sodium fluoride are fluorides, a class of compounds containing fluoride. Although fluoride-containing products promote tooth resistance to caries, long-term use of fluoride has adverse effects on the tooth. During enamel formation and maturation, tooth discoloration might be caused by high total daily intake of fluoride ions. Dental fluorosis constitutes a less severe form of chronic toxicity due to chronic intake of high fluoride amounts during tooth development and eruption (Abanto Alvarez et al., 2009). It features enamel hypomineralization, with white flecks mainly detected on cusp tips and facial surfaces of permanent teeth. In moderate-to-severe forms, extended brown stains and cavities are present on most permanent teeth. Dental fluorosis correlates with condition dose, and the higher the exposure level during tooth development, the severer the disorder. A four-year randomized controlled trial demonstrated markedly elevated tooth discoloration incidence in the intervention group compared with control patients not using any fluoride product (Frese et al., 2019).

Chlorhexidine as a broad-spectrum antiseptic has a well-documented dental plaque-inhibiting effect. Its mechanism of action is that chlorhexidine (positive charge) interacts with the microbial cell wall (negative charge), destabilizing the microorganism's osmotic equilibrium. Mouthwashes containing chlorhexidine are mainly indicated for utilization as adjuncts to mechanical cleaning, whereas long-term application induces several local adverse effects, prominently including the generation of brown stains on teeth and oral tissues (James et al., 2017). It is admitted stains mostly result from the precipitation of anionic dietary chromogens, including tea, coffee, and wine constituents, onto the adsorbed chlorhexidine cations, so the mechanism by which chlorhexidine causes extrinsic tooth staining seems to be highly related to its mechanism of action (Watts and Addy, 2001).

Hydrogen peroxide is a strong oxidizing agent, which has been widely used in dentistry to bleach teeth for more than 70 years. Hydrogen peroxide generates the perhydroxyl free radical HO_2^-, which has high reactivity and substantial oxidative potential, oxidizing tooth discoloration. Hydrogen peroxide can cause damage to the enamel of the teeth if used incorrectly. High hydrogen peroxide amounts can damage the integrity of the enamel surface, and teeth may show higher susceptibility to extrinsic discoloration following bleaching because of elevated surface roughness (Tredwin et al., 2006).

Drugs for obstructive airway diseases

Inhalation therapy is the mainstay of drug therapy for obstructive airway diseases. In this study, therapeutic drugs including salmeterol and fluticasone and budesonide generated positive risk signals for tooth discoloration. However, 10 patients with tooth discoloration were under 8 years old, which should be paid more attention to. Though few studies focused on inhalation-induced tooth discoloration, the latter might be attributed to tooth erosion via alteration of the mouth's chemical environment (Thomas et al., 2010). Erosion, abrasion, and attrition result in a gradual impairment of enamel and dentine, and manifest as tooth wear. As enamel thinning occurs, the tooth becomes darker with dentine color becoming more obvious (Watts and Addy, 2001). Inhalants expose patients to the risk of tooth erosion by decreasing the protective effects of saliva on external or intrinsic acids (Thomas et al., 2010). Saliva is a major factor neutralizing daily dietary acids in the oral cavity. Studies showed a reduced salivary flow rate in asthmatics administered beta-2 adrenoceptor agonists in comparison with non-asthmatic subjects. Reduced saliva flow or quality can affect proteins and chemical composition in the salivary pellicle, which plays a role in protecting teeth from erosive wear (Goswami et al., 2021). Decreased intraoral pH after the use of inhalers may also be associated with tooth erosion. O'Sullivan and colleagues reported anti-asthmatics, especially powdered products (beclomethasone diproprionate, fluticasone, salmeterol, and terbutaline sulfate powders), could induce a pH below the value of 5.5 that is required to dissolve hydroxyapatite (O'Sullivan and Curzon, 1998). A decrease in salivary pH after using an inhaler several times a day, particularly lactose-based inhalers, possibly causes tooth dissolution. Gastroesophageal reflux disease may be another risk factor for tooth erosion. Long-acting beta-agonists relax

TABLE 3 Drugs associated with tooth discoloration based on the FAERS.

Drugs	N	χ^2	PRR (95% CI)	ROR (95% CI)
Tetracycline	106	25,472.3	268.3 (220.4–326.6)	277.0 (226.3–339.2)
Salmeterol and fluticasone	68	191.0	4.8 (3.8–6.2)	4.8 (3.8–6.2)
Amoxicillin	60	478.6	10.5 (8.1–13.6)	10.5 (8.1–13.6)
Chlorhexidine	54	5310.3	107.0 (81.5–140.3)	108.4 (82.3–142.6)
Nicotine	52	364.7	9.4 (7.1–12.4)	9.4 (7.1–12.4)
Asenapine	34	1275.1	41.8 (29.7–58.7)	42.0 (29.8–59.1)
Minocycline	31	998.6	36.2 (25.3–51.6)	36.3 (25.4–51.9)
Linezolid	26	462.2	20.9 (14.2–30.8)	20.9 (14.2–30.9)
Budesonide	25	39.4	3.4 (2.3–5.1)	3.4 (2.3–5.1)
Doxycycline	23	148.2	8.8 (5.8–13.3)	8.8 (5.8–13.3)
Zoledronic acid	23	49.4	4.1 (2.7–6.2)	4.1 (2.7–6.2)
Alendronic acid	19	29.3	3.4 (2.2–5.3)	3.4 (2.2–5.3)
Sucroferric oxyhydroxide	18	831.3	51.6 (32.5–82.1)	52.0 (32.6–82.9)
Azithromycin	17	83.7	7.1 (4.5–11.6)	7.2 (4.5–11.7)
Clarithromycin	15	59.3	6.2 (3.7–10.3)	6.2 (3.7–10.3)
Sodium fluoride	13	886.2	76.6 (44.5–132.0)	77.4 (44.7–134.0)
Hydrogen peroxide	10	2129.3	240.0 (130.0–443.0)	247.6 (131.6–465.8)
Colestyramine	9	153.6	21.3 (11.1–41.1)	21.4 (11.1–41.3)
Cetylpyridinium	9	3745.7	472.2 (250.0–891.8)	502.5 (255.5–988.3)
Ertapenem	9	255.2	34.1 (17.7–65.6)	34.3 (17.8–66.1)
Rifampicin	9	39.0	6.9 (3.6–13.2)	6.9 (3.6–13.2)
Stannous fluoride	6	1264.7	254.3 (115.5–559.8)	262.8 (116.3–594.1)
Triclosan	6	430.3	87.9 (39.6–195.3)	88.9 (39.7–199.3)
Cefprozil	5	299.8	76.5 (31.9–183.4)	77.3 (32.0–186.8)
Pamidronic acid	5	21.8	7.5 (3.1–18.0)	7.5 (3.1–18.0)

PRR, proportional reporting ratio; ROR, reporting odds ratio; CI, confidence interval.

smooth muscles and potentially facilitate acid reflux (McCallister et al., 2011).

Antiseptics and disinfectants

Cetylpyridinium chloride, a quaternary ammonium compound, efficiently enhances the antimicrobial effects of oral hygiene products. It is widely used in over-the-counter products such as mouthwashes and toothpastes (Mao et al., 2020). As a cationic detergent, its interactions with cell membranes can lead to the leakage of cell components, disrupt bacterial metabolism, inhibit cell growth, and induce cell death.

Triclosan has been used since the 1960s as a broad-spectrum antibacterial agent and is added to a variety of consumer products such as soaps, hand sanitizers, toothpastes, mouthwashes, and cosmetics (Weatherly and Gosse, 2017). Triclosan has been incorporated into toothpaste with sodium fluoride to enhance inhibitory effects on bacterial metabolism in dental plaques. In this study, all six reported cases related to triclosan concomitantly used sodium fluoride.

Drugs for systemic use

Anti-infectives

Since 1948, tetracyclines have been utilized to treat a variety of infections, especially *brucella* infections for which they are the antibiotics of choice. In 1956, tetracycline was firstly reported to cause discoloration of children's teeth (Schuster and Shwachman, 1956), and many subsequent reports have indicated that tetracycline also causes tooth enamel hypoplasia. Tetracycline irreversibly binds to calcified structures in teeth when utilized during the calcification phase of tooth development, forming a visible discoloration when the tetracycline layer of the tooth is oxidized by light. The discoloration extent depends on the type of

TABLE 4 The characteristics of AE reports involving drugs with positive risk signals of tooth discoloration.

Drugs	N	Dosage (N)	Patient age group (years)						Serious Outcome[a]
			≤18	19–44	45–64	65–74	≥75	Unknown	
Tetracycline	106	20 mg/day (2)	7	6	18	1	0	74	12
		1000 mg/day (1)							
		Unknown (103)							
Salmeterol and fluticasone	68	1 puff/day (3)	8	1	8	8	3	40	10
		2 puffs/day (25)							
		Unknown (40)							
Amoxicillin	60	8–28 mL/day (25)	36	5	1	4	1	13	25
		1750–4,000 mg/day (3)							
		1–3 DF/day (9)							
		Unknown (23)							
Chlorhexidine	54	Unknown (54)	0	1	4	2	2	45	3
Nicotine	52	2 mg/day (5)	0	9	14	9	4	16	7
		4 mg/day (8)							
		Unknown (39)							
Asenapine	34	5 mg/day (1)	0	6	6	1	0	21	1
		10 mg/day (8)							
		15 mg/day (1)							
		20 mg/day (7)							
		25 mg/day (1)							
		30 mg/day (1)							
		Unknown (15)							
Minocycline	31	4 mg/day subgingival (2)	4	2	17	0	0	8	15
		100 mg/day (1)							
		200 mg/day (5)							
		300 mg/day (3)							
		Unknown (20)							
Linezolid	26	90 mg/kg/day (1)	6	6	4	1	1	8	6
		100 mg/day (1)							
		600 mg/day (2)							
		1200 mg/day (13)							
		Unknown (9)							
Budesonide	25	0.5 mg/day (1)	12	1	2	2	1	7	7
		1 mg/day (1)							
		160 μg/day (1)							
		180 μg/day (1)							
		320 μg/day (1)							
		360 μg/day (1)							

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TABLE 4 (*Continued*) The characteristics of AE reports involving drugs with positive risk signals of tooth discoloration.

Drugs	N	Dosage (N)	Patient age group (years)						Serious Outcome[a]
			≤18	19–44	45–64	65–74	≥75	Unknown	
		400 μg/day (1)							
		640 μg/day (1)							
		Unknown (17)							
Doxycycline	23	40 mg/day (1)	4	1	6	1	2	9	9
		100 mg/day (2)							
		200 mg/day (2)							
		250 mg/day (1)							
		Unknown (17)							
Zoledronic acid	23	3 mg/day (1)	0	1	5	1	1	15	22
		4 mg/day (9)							
		5 mg/day (2)							
		Unknown (11)							
Alendronic acid	19	70 mg, qw (5)	1	2	7	1	4	4	18
		Unknown (14)							
Sucroferric oxyhydroxide	18	2250 mg/day (2)	0	1	3	0	0	14	0
		Unknown (16)							
Azithromycin	17	4 mL/day (1)	9	1	2	0	0	5	12
		120 mg/day (1)							
		200 mg/day (2)							
		Unknown (13)							
Clarithromycin	15	1000 mg/day (4)	4	2	2	1	3	3	8
		Unknown (11)							
Sodium fluoride	13	Unknown (13)	1	1	1	0	1	9	3
Hydrogen peroxide	10	Unknown (10)	0	2	4	0	0	4	10
Colestyramine	9	4 g/day (4)	0	0	0	0	2	7	0
		8 g/day (3)							
		9 g/day (1)							
		Unknown (1)							
Cetylpyridinium	9	20 mL/day (2)	0	5	1	2	0	1	5
		Unknown (7)							
Ertapenem	9	1g/day (3)	0	0	1	2	1	5	6
		Unknown (6)							
Rifampicin	9	150 mg/day (5)	0	1	4	1	1	2	5
		450 mg/day (1)							
		Unknown (3)							
Stannous fluoride	6	20 mL (2)	0	1	0	2	0	3	1
		Unknown (4)							

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TABLE 4 (*Continued*) The characteristics of AE reports involving drugs with positive risk signals of tooth discoloration.

Drugs	N	Dosage (N)	Patient age group (years)						Serious Outcome[a]
			≤18	19–44	45–64	65–74	≥75	Unknown	
Triclosan	6	Unknown (6)	0	0	0	0	0	6	0
Cefprozil	5	Unknown (5)	3	0	0	0	0	2	1
Pamidronic acid	5	90 mg, qmon (2)	0	1	0	0	0	4	5
		Unknown (3)							

DF, dosage form.
[a]Serious outcome includes death, hospitalization-initial or prolonged, life-threatening, disability, congenital anomalies, and/or other.

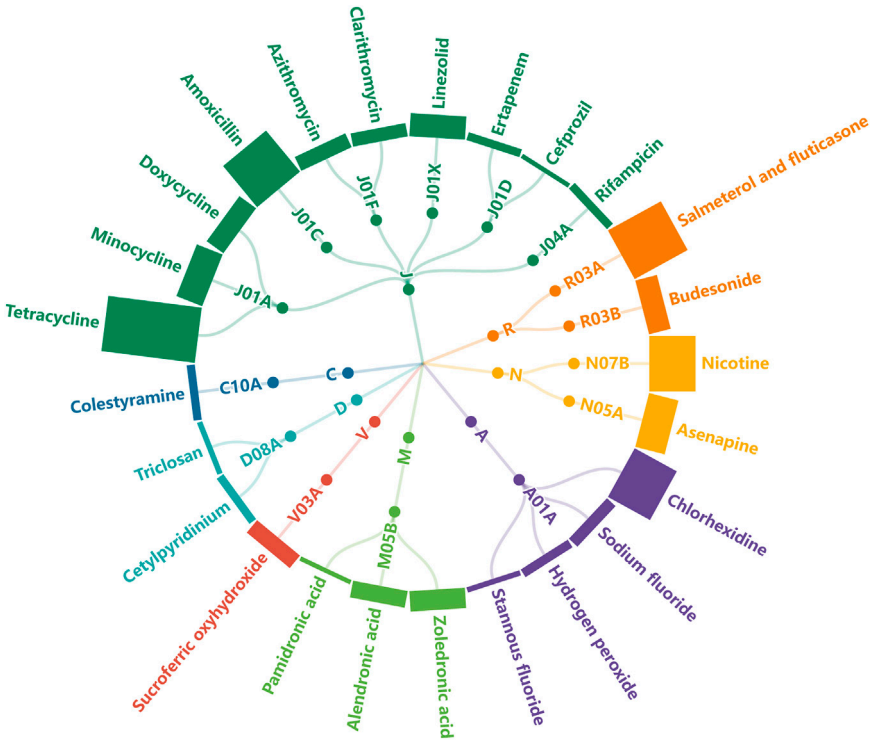

FIGURE 2
Radical tree of drugs grouped by ATC class. The height of each column represents the number of submitted AE reports (J: anti-infectives for systemic use, R: respiratory system, N: nervous system, A: alimentary tract and metabolism, M: musculo-skeletal system, V: various, D: dermatologicals, C: cardiovascular system).

tetracyclines, dosage, treatment time, and patient age at treatment. Deciduous teeth begin to calcify approximately at the end of pregnancy month four. The calcification of permanent teeth begins after birth and is completed at the age of seven-eight years. Therefore, administration of tetracyclines must be avoided in the second and third trimesters of gestation and pediatric patients below 8 years (Sánchez et al., 2004). In our study, six patients younger than 8 years old developed tooth discoloration after treating with tetracycline. Previous data showed that the incidence rates of tooth discoloration caused by different tetracyclines vary between 23% and 92% in children (Todd et al., 2015). Tooth discoloration was also found in adults after long-term use of tetracyclines (Chiappinelli and Walton, 1992).

Minocycline, a semisynthetic tetracycline antibiotic, is frequently applied to treat acne vulgaris and rosacea, and utilized as an adjunct treatment of periodontal disease. Minocycline causes tooth discoloration, with an incidence of 3%–6% in adults taking minocycline more than 100 mg/d for long-term use (Good and Hussey, 2003). Minocycline also causes abnormal pigmentation of skin, thyroid gland, nails, bones, sclera, and conjunctiva in adult individuals (Ran et al., 2021).

Doxycycline is a tetracycline derivative firstly marketed in 1967. Considering tooth staining, the FDA requires all tetracycline drugs must bear a warning label of not being suitable for children under 8 years unless no other effective antibiotic agents are available. Compared with other

tetracyclines, doxycycline has a lower affinity with calcium, and therefore, the risk of tooth staining is relatively lower. Six reports investigated tooth discoloration in ≥338 patients administered doxycycline below 8 years old (Stultz and Eiland, 2019). In the latter studies, tooth discoloration was similar between treated and control patients, indicating doxycycline is a safer alternative in case tetracyclines are required in patients under eight. The recommendation from the American Academy of Pediatrics points out that only doxycycline may be utilized for short treatments (<21 days) in all age groups (Stultz and Eiland, 2019). However, it should be noted there are still some case reports of doxycycline-induced discoloration of the permanent dentition (Ayaslioglu et al., 2005; Nelson and Parker, 2006). Herein, 23 AE reports of tooth discoloration involved doxycycline, of which three reports involved patients aged under eight.

Though not exerting a positive signal, tigecycline might be associated with tooth discoloration. Tigecycline could induce permanent discoloration of the teeth if administered by injection during tooth development (second half of pregnancy, infancy, and childhood before 8 years). A retrospective study evaluated the discoloration of permanent teeth in children below 8 years after tigecycline exposure. The study eventually included 12 patients, of whom two (16.7%) developed yellow discoloration of the tooth (Zhu et al., 2021).

Amoxicillin is one of the most widely used penicillins, designated by the WHO as a "core access antibiotic." Amoxicillin and amoxicillin/clavulanic acid are usually well tolerated. Amoxicillin/clavulanate appeared to increase the risk of gastrointestinal adverse events, Stevens-Johnson syndrome, purpura, and hepatitis compared with amoxicillin monotherapy (Salvo et al., 2007). In addition, a higher proportion of stomatological reactions were reported with amoxicillin/clavulanic acid. The AEs associated with oropharyngeal lesions (enanthema, gingivitis, stomatitis, tongue disorder, and tooth discoloration) occurred later compared with other AEs after drug administration. These stomatological reactions may be attributed to the alteration of the bacterial flora due to the elimination of sensitive micro-organisms, as a result of long-term treatment. Garcia-López and collaborators (Garcia-López et al., 2001) reported three pediatric tooth discoloration cases who took amoxicillin/clavulanic acid. The drug surveillance programs of Australia and the Netherlands also reported this AE, as well as a study using the data from the Spanish Regional Drug Surveillance Centre. Herein, we also found 28 patients aged below eight developed tooth discoloration after using amoxicillin.

Carbapenems are β-lactam antibacterial drugs with a very broad spectrum. To date, the most commonly applied carbapenems include meropenem, imipenem, and ertapenem. Ertapenem, a broad-spectrum agent with limited effects on non-fermentative Gram-negative bacilli, is most indicated for community-acquired infections (Keating and Perry, 2005). Tooth staining has been identified during post-approval use of ertapenem. Dry mouth is one of its gastrointestinal adverse reactions, which may result in tooth discoloration due to decreased saliva secretion.

Macrolides represent a diverse group of hydrophobic molecules comprising macrolide rings and variable side chains or groups that inhibit protein synthesis by targeting bacterial ribosomes. Commonly used macrolides in clinic include azithromycin, erythromycin, and clarithromycin. Gastrointestinal reactions represent the most common side effects of macrolides. During a 12-week course of treatment with clarithromycin and rifabutin, some pediatric patients had gastrointestinal complaints, fever, and tooth discoloration (Lindeboom, 2011). In the current study, tooth discoloration was also reported in three patients aged below eight after application of azithromycin, as well as two patients aged below eight treated with clarithromycin. Fortunately, tooth discoloration induced by macrolides was usually reversed by professional cleaning upon discontinuation of these drugs.

Linezolid is the first marketed antibiotic of the oxazolidinone class with demonstrated activity against a variety of Gram-positive bacteria. From a safety perspective, linezolid is generally safe and well-tolerated when used for short courses of treatment. Several mild-to-moderate adverse reactions have been reported, including myelosuppression, neuropathy (peripheral and optic), gastrointestinal effects, elevated liver enzymes, skin eruption, and lactic acidosis. Tooth discoloration as a rare side effect mostly occurred in children. Matson and Miller (Matson and Miller, 2003) described an 11-year-old female showing tooth discoloration in a 28-day oral treatment with linezolid (600 mg, bid). Ma (Ma, 2009) reported an eight-year-old female with brownish discoloration of teeth and tongue after orally taking 1 week of linezolid (30 mg/kg/day in three doses). Petropoulou and colleagues (Petropoulou et al., 2013) described three children with similar side effects during intravenous treatment with linezolid (30 mg/kg/day, q8h). Santos *et al.* (Santos et al., 2015) reported a nine-year-old female showing linear brownish enamel discoloration on both the upper and lower anterior teeth 4 weeks upon initiation of oral linezolid (30 mg/kg/day, q8h). Agrawal et al. (2018) reported dental hyperpigmentation in an adult who presented with discoloration of both the upper and lower teeth after treatment with linezolid (600 mg, bid) for 2 months. Zou et al. (2020) reported tooth discoloration induced by intravenous linezolid (10 mg/kg, q8h for 12 days) in children in Mainland China. Likewise, we also found two patients aged below eight with tooth discoloration after using linezolid. Tooth discoloration caused by linezolid is extrinsic and reversible, which can be removed by extensive dental cleaning (Kadam, 2008). For oral administration, tooth discoloration may be attributed to the direct exposure of teeth and tongue to linezolid. However, for intravenous administration, tooth discoloration may be associated with changes of the normal flora in the oral cavity (Santos et al., 2015). The incidence of tooth discoloration is higher in children than in adults, which may be attributed to the discrepancy in oral microbial communities between adults and children (Zou et al., 2020). Pediatric patients and their parents should be informed of this potential reversible side effect prior to linezolid treatment.

Rifampicin was firstly introduced in 1968 and remains a major anti-tuberculous drug (Abulfathi et al., 2019). It is well known that rifampicin can cause discoloration (yellow, orange, red, or brown) of

body fluids (urine, sweat, sputum, and tears), as well as tooth discoloration, which may be permanent.

Nervous system agents

As mentioned above, since saliva helps remove food particles and forms a biofilm on teeth, the reduction of salivary secretion may lead to extrinsic tooth staining. The salivary gland secretion primarily involves the parasympathetic nervous system, as well as the sympathetic nervous system. Medications blocking the nervous system can result in decreased salivation, which is indirectly associated with tooth discoloration (Tredwin et al., 2005). Our findings showed that the neurologic drug asenapine was associated with tooth discoloration, with an ROR of 41.983, which may be related to sublingual administration. Nicotine in tobacco, although colorless, turns yellow after oxidation and sticks to the teeth, causing tooth discoloration. Nicotine replacement treatment is broadly applied to effectively address tobacco dependence. All licensed forms (gum, transdermal patch, nasal spray, inhalator, and sublingual tablet/lozenge) can help elevate the chances of successful cessation in people who attempt to quit smoking. Of 52 nicotine-related cases, 12 were buccal route, 2 were inhaled, and 3 were oral. *In vitro* tests have shown that nicotine polacrilex gum utilized to treat smoking cessation may exert stain-reducing (i.e., whitening) effects on smokers' teeth. In a randomized controlled trial, a nicotine replacement gum removed stains and whitened teeth better than a nicotine replacement sub-lingual tablet during a six-week smoking cessation program. Smoking cessation interventions combined with stain removal or tooth whitening effects might further motivate to quit, and oral healthcare givers could provide patients with smoking cessation advices and support (Whelton et al., 2012).

Drugs affecting bone structure and mineralization

Bisphosphonates constitute a drug group preventing bone density reduction, which are commonly utilized for the treatment of osteoporosis and related disorders. Structurally, bisphosphonates are derivatives of inorganic pyrophosphate. Two groups of bisphosphonates are known, i.e., non-nitrogen-containing (e.g., etidronate, clodronate, and tiludronate, considered first-generation bisphosphonates) and nitrogenous (e.g., alendronate, pamidronate, and zoledronic acid, considered second- and third-generation bisphosphonates) molecules. Bisphosphonates have very high affinities for bone minerals because of their interaction with hydroxyapatite crystals, inhibiting osteoclast activity and thereby effectively suppressing bone resorption. Hydroxyapatite is the major mineral component of vertebrate bones and teeth. The enamel and dentin of human teeth are composed of 97% and 70% inorganic components, respectively. These inorganic phases are mainly composed of hydroxyapatite (Chen et al., 2021). The shape and size of hydroxyapatite crystallites in dentin are very similar to those in bone. Therefore, it is speculated that bisphosphonates may cause tooth discoloration by affecting hydroxyapatite. Additionally, due to the local effects of oral bisphosphonates on the esophagus and/or gastric mucosa, upper gastrointestinal adverse effects, e.g., reflux, esophagitis, and esophageal ulcer, are frequent causes of intolerance to oral bisphosphonates. Of note, reflux may affect tooth color by lowering the pH of the oral microenvironment and eroding hydroxyapatite in enamel and dentin.

Other therapeutic drugs

Drugs containing metallic compounds can lead to extrinsic staining of teeth. Addy et al. (1985) reported that certain metals (especially iron and tin) can cause tooth discoloration. For example, dark brown to black discoloration was observed in people taking iron supplements, and oral iron salts in liquid form could cause the teeth to appear greenish black (Teoh et al., 2019). Sucroferric oxyhydroxide represents a phosphate binder that effectively controls serum phosphorus amounts in chronic kidney disease cases on dialysis and is mainly supplied as chewable tablets for oral use in a brown color. Tooth discoloration was reported during its post-marketing use.

The FAERS database is a great tool with sufficient reports to identify rare adverse reactions that are difficult to detect in conventional epidemiologic studies. However, some inherent limitations still exist. A major limitation is the high risk of selection and reporting biases. The self-reported data in FAERS do not accurately estimate the actual volume of AEs to the drugs, since they are inherently limited by underreporting of cases. Therefore, the FAERS may not be utilized to estimate the true incidence of a given AE for the drug. Another limitation is the data quality issues in terms of duplicate reports and missing information (such as age, dosage, and treatment course), which affect further analyses of these data. It also should be noted that the positive risk signals obtained from the analysis can only demonstrate associations and not causality. In other words, whether the suspected drug mentioned in the report can lead to the AE of interest is uncertain. Further epidemiologic studies are still warranted to clarify such associations in the appropriate clinical setting.

Conclusion

This study assessed drug-related tooth discoloration by analyzing AEs reported in the FAERS database. We found 25 drugs were associated with tooth discoloration, among which anti-infectives, stomatological preparations, and drugs affecting bone structure and mineralization accounted for the majority. Together with previous investigations, our data provide further evidence that certain drugs may cause tooth discoloration. Caution should be exercised when using these drugs, particularly during pregnancy and early childhood. In addition, patients should be instructed to pay special attention to oral hygiene measures. Further investigation is still needed to confirm these findings and unveil the underpinning mechanism of tooth discoloration.

Data availability statement

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

Author contributions

JW and DZ participated in study design. JW and YL were responsible for data collection. JW and DZ contributed to data analysis. JW was involved in drafting the manuscript. PL and CG made appropriate revisions. All authors have read and approved the final manuscript.

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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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Ondansetron: recommended antiemetics for patients with acute pancreatitis? a population-based study

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Objective: Ondansetron administration is a common antemetic of acute pancreatitis therapy in the intensive care unit (ICU), but its actual association with patients' outcomes has not been confirmed. The study is aimed to determine whether the multiple outcomes of ICU patients with acute pancreatitis could benefit from ondansetron.

Methods: 1,030 acute pancreatitis patients diagnosed in 2008–2019 were extracted from the Medical Information Mart for Intensive Care (MIMIC)-IV database as our study cohort. The primary outcome we considered is the 90-day prognosis, and secondary outcomes included in-hospital survival and overall prognosis.

Results: In MIMIC-IV, 663 acute pancreatitis patients received ondansetron administration (OND group) during their hospitalization, while 367 patients did not (non-OND group). Patients in the OND group presented better in-hospital, 90-day, and overall survival curves than the non-OND group (log-rank test: in-hospital: $p < 0.001$, 90-day: $p = 0.002$, overall: $p = 0.009$). After including covariates, ondansetron was associated with better survival in patients with multiple outcomes (in-hospital: HR = 0.50, 90-day: HR = 0.63, overall: HR = 0.66), and the optimal dose inflection points were 7.8 mg, 4.9 mg, and 4.6 mg, respectively. The survival benefit of ondansetron was unique and stable in the multivariate analyses after consideration of metoclopramide, diphenhydramine, and prochlorperazine, which may also be used as antiemetics.

Conclusion: In ICU acute pancreatitis patients, ondansetron administration was associated with better 90-day outcomes, while results were similar in terms of in-hospital and overall outcomes, and the recommended minimum total dose might be suggested to be 4–8 mg.

KEYWORDS

ondansetron, acute pancreatitis, MIMIC-IV, multiple outcomes, recommended dose

Introduction

The onset of acute pancreatitis (AP) is insidious, and the symptoms are complex and changeable (Lankisch et al., 2015). Most mild patients are usually cured within a week, but 20% of patients will eventually develop into moderate or even severe acute pancreatitis, with a high fatality rate (Boxhoorn et al., 2020). The main symptom of AP is persistent, poorly localized epigastric pain, some radiating to the back, while most patients will also suffer from nausea and vomiting. Patients with acute pancreatitis tend to experience vomiting early, severely, and frequently. And the epigastric pain does not relieve after vomiting (Mergener and Baillie, 1998). Severe vomiting might even lead to fluid loss and eventual tissue hypoperfusion. The current therapeutic principle of acute pancreatitis is early goal-directed fluid resuscitation, analgesia, and nutritional support (Boxhoorn et al., 2020). At the same time, symptomatic treatment of patients with nausea and vomiting is an unavoidable problem for clinicians, which can not only reduce fluid loss in severe acute pancreatitis but also significantly advance the time for patients to start enteral nutrition (Tenner et al., 2013). Therefore, the use of antiemetics should be considered.

Ondansetron is a selective serotonin 5-hydroxytryptamine-3 receptor (5-HT_3 R) antagonist, well-established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy, anesthesia, and surgery (Wilde and Markham, 1996). It is also one of the most commonly used antiemetics in the ICU and emergency room (Athavale et al., 2020; Tao et al., 2021). Due to the close correlation between the 5-HT receptor and inflammation, many studies recently focused on the anti-inflammatory effect of ondansetron (Liu et al., 2011; Gong et al., 2019). One basic research has already confirmed that ondansetron could reduce pancreatic injury in the mice model of acute pancreatitis induced by cerulein (Tsukamoto et al., 2017). However, to date, no retrospective clinical study has analyzed the effects of ondansetron on multiple outcomes in ICU patients with acute pancreatitis to support this finding.

The good news is that the MIMIC-IV database, an extensive, open-access, long-term follow-up, and detailly-recorded patients information platform, allows us to analyze the multiple prognostic effects of ondansetron on ICU AP patients through real-world data and try to explore the optimal dose or medication time. In our preliminary study, we have already found that the proportion of ondansetron administration increased year by year from 2008 to 2019 for 4,060 initial admissions and 1,030 initial ICU admissions of patients with acute pancreatitis recorded in the MIMIC-IV database. As shown in Supplementary Figure S1, the proportion of ondansetron in ICU patients increased from 59.2% to 70.7% from 2008 to 2019. In general, it is essential to investigate the prognostic effects of ondansetron on ICU patients with acute pancreatitis and the possible more appropriate dose and timing.

Methods

Data source description

Our study cohort was extracted from the MIMIC database. The Medical Information Mart for Intensive Care (MIMIC) program is an extensive, single-center, and freely accessible clinical database hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (MIT) (Johnson et al., 2022). The newly released MIMIC-IV (v2.0), updated on 12 June 2022, contains well-documented information on laboratory tests, medical behavior, and vital signs of 315,460 patients enrolled in Beth Israel Deaconess Medical Center (BIDMC), Boston, from 2008 to 2019 (Johnson et al., 2022). The most significant improvement over the previous version was the availability of out-of-hospital mortality from state death records, which allowed us to explore the impact of the intervention on the long-term outcome of patients, which was not covered by previous similar studies.

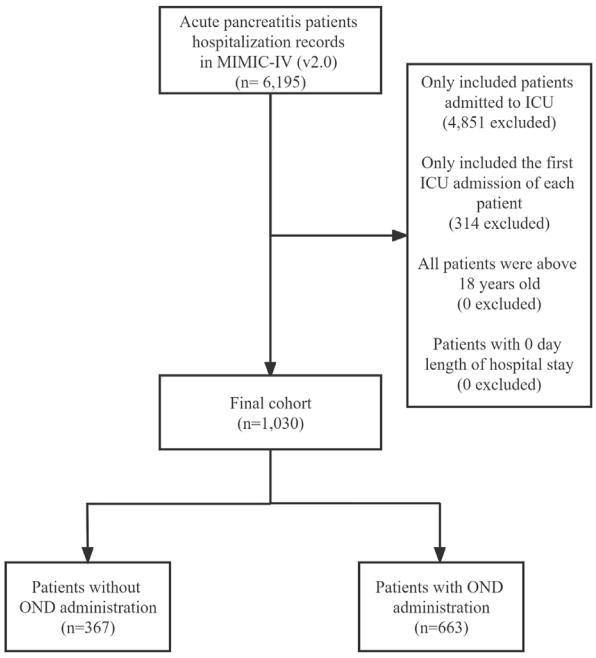

FIGURE 1
Study sample screening process of 1,030 acute pancreatitis patients from the MIMIC-IV database. ICU intensive care unit. OND ondansetron administration.

Study population

Patients whose diagnostic description included "acute pancreatitis" were enrolled in the study. A total of 6,195 hospitalization records of patients with acute pancreatitis were collected in the MIMIC-IV database. The patients who were not admitted to ICU were deleted, and only the first ICU records were kept. Finally, our study cohort determined 1,030 patients with acute pancreatitis during their first ICU admissions. The number of patients in each diagnosed title in the ICD (International Classification of Diseases) standard is shown in Supplementary Table S1. Patients were assigned to the "ondansetron administration group" (OND group) if all medication records for that hospitalization included at least one ondansetron administration record or to the "non-ondansetron administration group" (non-OND group) if they did not. The detailed screening process of the entire research cohort is shown in Figure 1.

Variable extraction and outcomes

The demographic characteristics of patients we considered included the age of the admission, gender, admission period, and first measured weight. And the intervention records we focused on included renal replacement therapy (RRT) and mechanical ventilation (MV) during the first 24 h of ICU admission. Records of comorbidities enrolled congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes, and malignancy. In addition, the patient's vital signs during the first 24 h in the ICU: mean heart rate, mean arterial pressure (MAP), mean respiratory rate, and mean body temperature were also considered. Laboratory tests were performed within the first 24 h, with values associated with the patient's worst clinical status, including hemoglobin, platelets, white blood cells (WBC), hematocrit (HCT), alanine aminotransferase (ALT), creatinine, albumin, and lactate levels. Furthermore, we also determined the time point at which patients were first treated with ondansetron and the total dose of ondansetron during hospitalization in milligrams for subsequent sensitivity analysis.

Patient outcomes we studied included in-hospital survival, 90-day prognosis, and overall prognosis. Follow-up began on the day of admission and ended on the date of censored or MIMIC-IV (v2.0) updated.

Statistical analysis

Continuous variables were described by medians with interquartile ranges (IQRs) and compared by *t*-test or Wilcoxon rank-sum test between groups. As for categorical variables, we used total numbers and percentages to present and compare the proportions by $\chi 2$ or Fisher exact tests. Moreover, standardized mean differences (SMD) were also used to represent the differences in variables between groups in both the original and matched cohorts. In terms of survival analysis, both in-hospital survival and overall prognosis could be extracted directly from the database, and the 90-day prognosis was calculated using total follow-up and overall status. After that, Kaplan-Meier (K-M) survival analyses were performed to generate curves of multiple outcomes and the log-rank tests to determine statistical differences between treatment groups. We further applied the multivariate Cox models to determine covariates' independent effect on patient outcomes, including the administration of ondansetron. This model also served as the common basis for subsequent more complex multivariate analyses. Variables incorporated in multivariate analyses covered all mentioned above except the admission period. The numbers and percentages of missing data for each variable are shown in Supplementary Table S2. At the same time, we used multiple imputations to mitigate the estimation bias caused by missing data and assuming that data were missing randomly.

Imbalanced covariates between the intervention and control groups could lead to inaccurate multivariate analysis results, so we used the inverse probability of treatment weighting (IPTW) method to match the inter-group differences. This method calculated each patient's weight to construct two virtual populations to balance constituent variables (Graffeo et al., 2019). In addition, we reconstructed a multivariate Cox model by treating ondansetron administration as a time-dependent covariate. The principle of this method is to treat the state of ondansetron patients before medication as the control group and to be included in the intervention group after medication to reduce the immortal bias of the traditional model effectively (Platt et al., 2019). Furthermore, we enrolled the restricted cubic spline (RCS) method to investigate the possible non-linear relationship between different drug doses or first medication timing and patient outcomes. Based on the multivariate Cox model, the method fits the non-linear relationship between continuous variables and patient outcomes by setting different knots, which could determine the vertex or inflection points according to the different shapes of the curve by the R package "rcssci," thus providing more effective clinical guidance (Lv et al., 2018).

All our patients' data from the database were extracted in SQL (Structured Query Language), and all statistical analyses were performed by Rstudio software (v4.2.2). Two-sided $p < 0.05$ was considered statistically significant.

Results

Patients baseline characteristics

In the ICU cohort we focused on for acute pancreatitis, a total of 663 patients received ondansetron during hospitalization (OND group), while the remaining 367 did not (non-OND group). Regarding demographic characteristics, patients in the OND group were younger (59 (46–72) vs. 62 (49–76); $p = 0.014$) and more female (55.5% vs. 62.1%; $p = 0.046$) than those in the non-OND group, and patients admitted between 2014 and 2019 appeared to be more likely to receive ondansetron (69.0% vs. 61.4%; $p = 0.014$). In terms of comorbidities and interventions, the OND group had a higher rate of malignancies (10.1% vs. 4.1%; $p = 0.001$) and lower rates of renal replacement therapy (4.8% vs. 9.3%; $p = 0.008$) and mechanical ventilation (28.2% vs. 45.5%; $p < 0.001$). As for laboratory tests, the OND group had a higher platelet level and lower creatinine. There was no statistical difference in other laboratory indicators. More detailed intergroup baselines are shown in Table 1.

Survival differences

Overall, the OND group had significantly better multiple outcomes than the non-OND group. First, the in-hospital mortality rate was 11.1% (74/663) in the OND group and 16.0% (59/367) in the non-OND group. Furthermore, the 90-day mortality rate was 15.6% (104/663) in the OND group and 23.1% (85/367) in the non-OND group. There was also a noticeable difference in overall survival between treatment groups at the end of follow-up (29.8% vs. 37.3%, $p = 0.009$). The K-M survival curves of treatment groups with different outcomes are shown in Figures 2A–C. Moreover, we performed IPTW matching between the two groups, and the inter-group

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

Covariates	MIMIC-IV (n = 1,030)				
	All patients	non-OND	OND	*p*-value	SMD
N	1,030	367	663		
Age	60 (47–73)	62 (49–76)	59 (46–72)	0.014	0.156
Male (%)	596/1,030 (57.9)	228/367 (62.1)	368/663 (55.5)	0.046	0.135
Weight (kg)	81.4 (69.4–98.7)	81.1 (68.5–98.8)	81.5 (70.0–98.7)	0.875	0.049
Admission period, n (%)				0.016	0.162
2008–2013	630/1,030 (61.2)	243/630 (38.6)	387/630 (61.4)		
2014–2019	400/1,030 (38.8)	124/400 (31.0)	276/400 (69.0)		
Interventions, n (%)					
RRT use (1st 24 h)	66/1,030 (6.4)	34/367 (9.3)	32/663 (4.8)	0.008	0.174
MV use (1st 24 h)	354/1,030 (34.4)	167/367 (45.5)	187/663 (28.2)	<0.001	0.365
Comorbidities, n (%)					
CHF	205/1,030 (19.9)	85/367 (23.2)	120/663 (18.1)	0.062	0.125
COPD	223/1,030 (21.7)	92/367 (25.1)	131/663 (19.8)	0.057	0.128
Diabetes	319/1,030 (31.0)	117/367 (31.9)	202/663 (30.5)	0.690	0.030
Malignancy	82/1,030 (8.0)	15/367 (4.1)	67/663 (10.1)	0.001	0.236
Vital signs					
Heart rate (bpm)	93 (80–107)	91 (78–104)	94 (81–108)	0.006	0.182
MAP (mmHg)	80.6 (72.4–91.1)	78.7 (70.8–87.7)	81.4 (73.4–91.7)	0.001	0.189
Respiratory rate (bpm)	20 (17–24)	20 (18–24)	20 (17–23)	0.254	0.059
Temperature (°C)	36.9 (36.7–37.3)	36.9 (36.6–37.3)	36.9 (36.7–37.3)	0.479	0.109
Laboratory tests					
Hemoglobin (g/dL)	10.4 (8.9–12.0)	10.5 (9.1–12.0)	10.3 (8.8–12.0)	0.682	0.003
Platelet ($\times 10^9$/L)	167.0 (112.0–237.8)	152.0 (108.5–218.0)	174.0 (118.0–248.0)	0.003	0.134
WBC ($\times 10^9$/L)	13.8 (9.8–19.6)	14.0 (9.8–20.4)	13.7 (9.8–19.0)	0.411	0.086
HCT (%)	31.5 (26.7–35.8)	31.7 (27.0–36.0)	31.4 (26.5–35.8)	0.707	0.007
ALT (IU/L)	57.0 (26.0–170.8)	61.0 (28.5–171.5)	55.0 (25.0–170.5)	0.235	0.051
Creatinine (mg/dL)	1.1 (0.8–2.1)	1.4 (0.9–2.5)	1.1 (0.7–1.8)	<0.001	0.245
Albumin (g/dL)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	0.857	0.016
Lactate level (mmol/L)	1.9 (1.3–3.3)	1.9 (1.3–3.7)	1.9 (1.4–3.2)	0.504	0.070

OND, ondansetron administration; *SMD*, standardized mean differences; *RRT*, renal replacement therapy; *MV*, mechanical ventilation; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *MAP* mean arterial pressure; *WBC*, white blood cell; *HCT*, hematocrit; *ALT*, alanine aminotransferase.

baseline characteristics after matching are shown in Supplementary Table S3, which shows the algorithm balanced the inter-group differences of all variables well. The K-M curves after matching are shown in Supplementary Figure S2. We found a noticeable difference in in-hospital survival between groups. Although the results suggested that the 90-day and overall survival of the OND group were still better than that of the non-OND group, the difference was not statistically significant.

Multivariate analysis

We further tested the independent effect of ondansetron on outcomes in ICU AP patients in different multivariate models, as Figure 3 shows. First, in the original multivariate Cox model, the administration of ondansetron was considered an independent prognostic factor, with consistent benefits for in-hospital (HR: 0.50, 95% CI: 0.34–0.74, $p = 0.001$), 90-day (HR: 0.63, 95% CI: 0.46–0.86, $p = 0.004$), and overall (HR: 0.66, 95% CI: 0.52–0.84, $p = 0.001$) prognoses in ICU AP patients after the influence of other variables was balanced. These results were later confirmed in an IPTW-matched cohort with well-balanced baseline diversities, where ondansetron continued to benefit patients with multiple outcomes significantly. We added ondansetron into the multivariate Cox model as a time-dependent covariable to further verify the results. The results suggested that ondansetron still provided noticeable benefits to patients in terms of overall survival and tended to benefit in-hospital and 90-day survival, although not statistically significant.

In order to improve the robustness of the study results, we deleted all patients with missing data and finally obtained a cohort with complete data. The baseline characteristics of this patient cohort are shown in Supplementary Table S4. We repeated the above analysis for this cohort, and the results were similar, as shown in Supplementary Figure S3. In

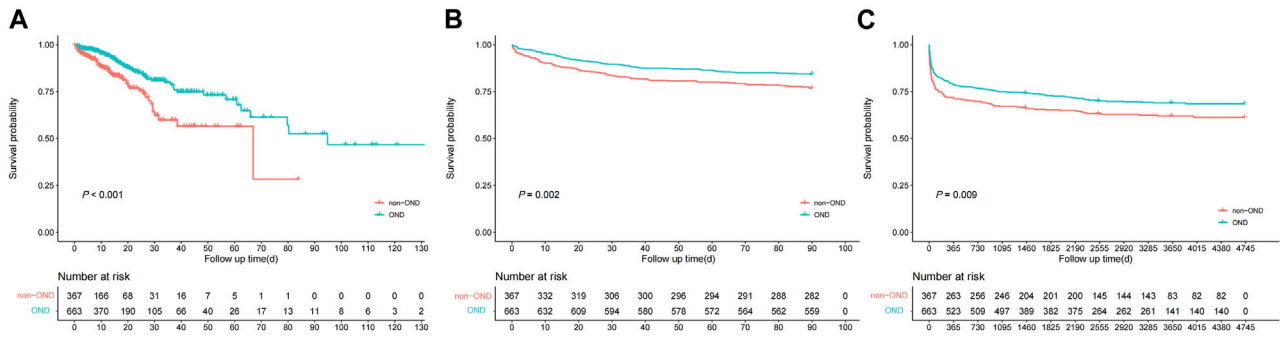

FIGURE 2
Kaplan-Meire survival curve analysis between treatment groups of multiple outcomes from the MIMIC-IV database. **(A)** in-hospital mortality **(B)** 90-day mortality **(C)** overall mortality.

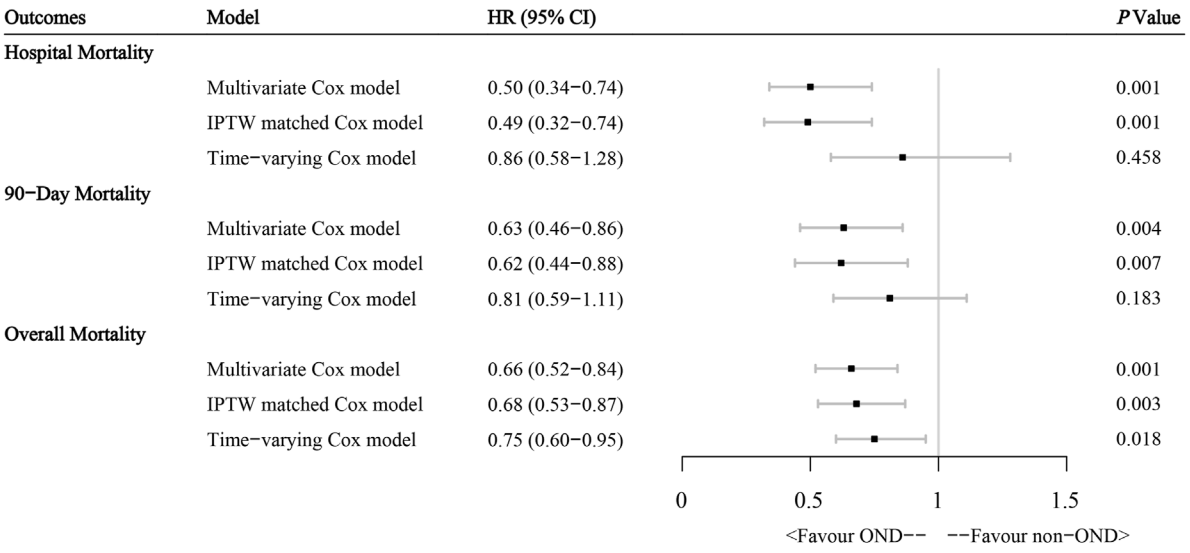

FIGURE 3
Effect of ondansetron administration on multiple outcomes in acute pancreatitis patients from the MIMIC-IV database through different multivariate Cox regression models. HR hazard ratio, IPTW inverse probability of treatment weighting.

addition, the administration of metoclopramide, diphenhydramine, and prochlorperazine was also identified from all study patients' medication records to exclude interference from the effects of other antiemetics. Our drug screening process was to include drugs with antiemetic primary pharmacological action in more than 50 prescriptions of all medications prescribed in the study cohort of 1030 ICU AP patients. Finally, the four drugs, including ondansetron, were eventually included in the study. After the collinearity problem of the model was eliminated, four commonly used antiemetics, including ondansetron, were enrolled in the multivariate Cox model, and the final results were shown in Supplementary Figure S4. After considering all drugs with an apparent clinical antiemetic effect, we found that ondansetron's multiple prognostic benefits for ICU AP patients remained stable and were significantly superior to other antiemetics.

Recommended application dose and time

To investigate the appropriate dose of ondansetron, we calculated the total dose for each patient during hospitalization in milligrams. We then replace the "1"used to refer to "intervention" in the traditional multivariate Cox model with the total ondansetron dose value, which is included in the restricted cubic spline analysis based on the multivariate Cox model. As Figure 4 shows, there are significant non-linear relationships between total doses of ondansetron and multiple outcomes in ICU patients with acute pancreatitis. The results suggested that the administration of 7.8 mg, 4.9 mg, and 4.6 mg ondansetron had the most significant survival benefit for in-hospital, 90-day, and overall outcomes, respectively, with the minimum dose. In addition, we also pay attention to whether the timing of administration is influential. As shown in Supplementary Figure S5, within the OND group, the time of initial

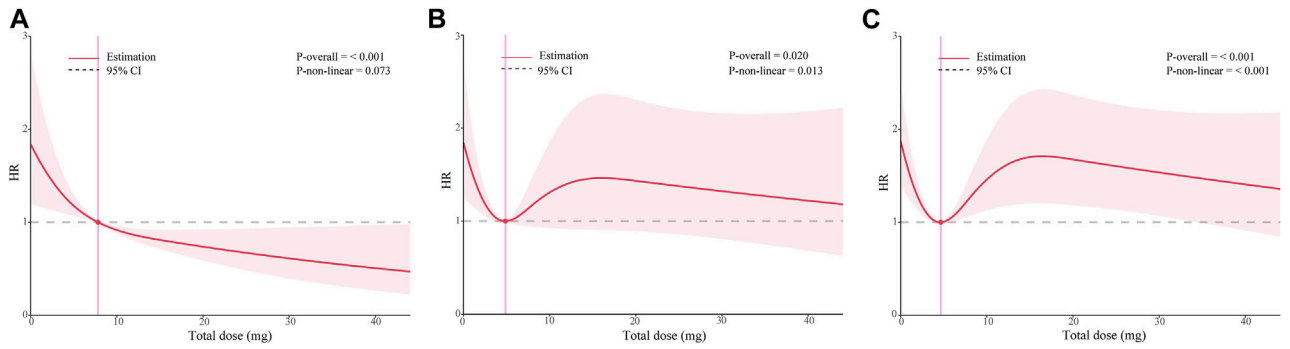

FIGURE 4
Dose-response curves of the relationship between ondansetron dose and multiple outcomes in patients with acute pancreatitis from the MIMIC-IV database. **(A)** in-hospital survival **(B)** 90-day prognosis **(C)** overall prognosis. HR hazard ratio.

ondansetron receipt and the interval between patient admission was not statistically associated with any of the three outcomes of interest.

Discussion

In general, through a retrospective cohort of 1,030 acute pancreatitis patients diagnosed from 2008 to 2019 in the MIMIC-IV database, our study indicated for the first time that ondansetron administration could benefit in-hospital, 90-day, and overall outcomes of ICU AP patients. And the optimal doses were 7.8 mg, 4.9 mg, and 4.6 mg, respectively. Moreover, the survival benefit of ondansetron was not associated with the start time of medication. This result was robust in subsequent IPTW-matched cohort and sensitivity analyses. Therefore, we could conclude that ondansetron might be a recommended antiemetic for ICU patients with acute pancreatitis.

Ondansetron, a highly selective 5-HT_3 receptor antagonist, was first used in the treatment of nausea and vomiting after chemoradiotherapy and anesthesia, which has also been widely used as an antiemetics in the emergency and ICUs at present (Wilde and Markham, 1996; Athavale et al., 2020). The mechanism of nausea and vomiting in acute pancreatitis is complex. At present, it is possible to infer that it starts from the stimulation of inflammation and toxins in the intestine, the secretion of the 5-HT_3 receptor by the enteric chromaffin cells, and then passes into the vomiting center through the vagus nerve. Finally, the efferent fibers of the vomiting center are mainly through the vagus nerve to produce subsequent nausea and vomiting reflex (Heckroth et al., 2021). In addition to antiemesis, some studies found that antagonists of 5-HT_3 R might also inhibit the incoming signals of the pancreatic vagus nerve and then reduce pancreatic secretion (Li et al., 2000; Mussa et al., 2008). Therefore, the application of ondansetron in ICU patients with acute pancreatitis has a plausible mechanism basis. As we suspected, acute pancreatitis patients in the MIMIC-IV database had a much higher proportion of ondansetron than the general ICU population (Fang et al., 2022), and the proportion showed an apparent upward trend from 2008 to 2019. However, retrospective clinical studies on the effect of ondansetron on the prognosis of ICU AP patients are still blank.

It is well known that the primary cause of death in patients with severe acute pancreatitis are systemic inflammation and severe organ failure (Boxhoorn et al., 2020). In recent years, many studies have focused on the anti-inflammatory effects of 5-HT_3 receptor antagonists, which we consider one of the potential mechanisms by that ondansetron could provide survival benefits to ICU AP patients (Liu et al., 2011; Gong et al., 2019). One research found that ondansetron could reduce liver injury in rats with a hemorrhagic shock through the p38 mitogen-activated protein kinase (MAPK) dependent pathway (Liu et al., 2011). In addition, granisetron has been found to inhibit the accumulation of phosphorylated p38(P-p38) effectively and the transactivation of nuclear factor κB(NF-κB) in macrophages, protecting mice from death due to sepsis (Gong et al., 2019). More importantly, one basic research has found that ondansetron could reduce pancreatic injury in the cerulein-induced acute pancreatitis model (Tsukamoto et al., 2017). The authors randomly divided 33 mice with cerulein-induced acute pancreatitis into the control and experimental groups. They gave the experimental group a subcutaneous injection of 3 mg/Kg ondansetron. The blood levels of amylase, lipase, and interleukin (IL) −6 were determined, and histopathological grading of pancreatic injury was also performed. Finally, this study found that the blood indexes above were significantly reduced in the ondansetron injection group, and the inflammatory damage of pancreatic tissue was also alleviated. In addition to the anti-inflammatory effects described above, the study also speculated that ondansetron might reduce the secretion of pancreatic enzymes by acting on pancreatic acinar cells, thereby reducing blood amylase and lipase levels in mice. The mechanism may be related to the previously mentioned inhibition of pancreatic vagus signaling by 5-HT3 R antagonists, or it may result from decreased secretion of enzyme granules associated with 5-HT-dependent cytoskeletal dynamics (Sonda et al., 2013).

In addition, early stop emesis could effectively advance enteral nutrition's start time (Tenner et al., 2013). A review of 11 RCTs showed that enteral nutrition initiated within 48 h of admission significantly reduced the risk of multiple organ failure, pancreatic complications, and death compared with

parenteral nutrition (Petrov et al., 2009). Aside from the potential risk of dehydration associated with severe vomiting, the benefits of early enteral nutrition are also evident. In summary, we analyzed that ondansetron may provide survival benefits for patients with acute pancreatitis from various perspectives. These hypotheses support our main findings at various levels: ondansetron administration is associated with improved in-hospital, 90-day, and overall outcomes in ICU patients with acute pancreatitis.

In the research on the recommended dose of ondansetron, we found a clear inflection point at which the minimum dose can achieve sufficient clinical benefit for in-hospital, 90-day, and overall prognosis,7.8 mg, 4.9 mg, and 4.6 mg, respectively, similar to previous studies (Roila and Del, 1995; Hendren et al., 2015; Fang et al., 2022). In a retrospective study of all ICU patients in the MIMIC-IV database, moderate (8–16 mg) and low (0–8 mg) doses were associated with significant prognostic benefits for patients, but not high doses (Fang et al., 2022). Previous studies have shown that high doses of ondansetron have a significant potential risk of prolonged QTc secondary arrhythmia, which may be more significant in ICU patients receiving multiple medications (Kuryshev et al., 2000; Sutherland et al., 2022). Our study is the first to more clearly present the dose-response curve between ondansetron and three outcomes in ICU AP patients, suggesting that receiving a single dose (4 mg) of ondansetron may have achieved a near-maximum 90-day survival benefit in ICU AP patients. Of course, this conclusion needs to be confirmed by higher-quality research.

Furthermore, no statistical difference was found between the time point of administration and the outcome of patients in the OND group (Supplementary Figure S5), but combined with the benefits of early enteral nutrition, early control of vomiting symptoms may still be necessary. In a multivariate analysis that also considered several other commonly used antiemetics, we found that the prognostic benefits of ondansetron were prominent and stable compared with metoclopramide, diphenhydramine, and prochlorperazine, which was consistent with the conclusions of several previous studies (Crucitt et al., 1996; Koseoglu et al., 1998; Morris et al., 1998). Diphenhydramine is a first-generation antihistamine that antagonizes the H1 receptors (Hendren et al., 2015), and metoclopramide is a dopamine D2 receptor blocker that also acts centrally as peripherally (Camilleri and Shin, 2012). In addition, prochlorperazine is a phenothiazine, a dopamine receptor antagonist, and because of more side effects, which was no longer the first-line antiemetic drug (Gan et al., 2007). We speculate that the reason may be that the anti-inflammatory effect of Ondansetron as a 5-HT3 R antagonist is more significant in AP patients, not only in its antiemetic effect.

Our study still has limitations. First of all, as a retrospective study, even though we have enhanced the stability of the research results through various methods, there may still be variable interference that we cannot consider, so high-quality prospective research is still urgently needed. Secondly, due to the limitation of data sources, we cannot know patients' real cause of death, so we can only use all-cause death as the outcome, which might be one-sided. In addition, because of the difficulty in obtaining the occurrence of side effects after administration, our dosage recommendations have limitations, and studies on ondansetron dosage need to be confirmed later. Nevertheless, this study is the most unambiguous indication yet of the effect of ondansetron on prognosis in patients with acute pancreatitis and can serve as an important basis for the principles of drug treatment in the ICU of acute pancreatitis.

Conclusion

In ICU acute pancreatitis patients, ondansetron administration was associated with better 90-day outcomes, while results were similar in terms of in-hospital and overall outcomes, and the recommended minimum total dose might be suggested to be 4–8 mg. We recommend ondansetron as the drug of choice for ICU acute pancreatitis with nausea and vomiting.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://physionet.org/content/mimiciv/2.0/.

Author contributions

Study concept and design: WQ and ZW; Acquisition, analysis, or interpretation of data: All authors; Drafting of the manuscript: GW, YM, and ZW; Critical revision of the manuscript: ZW and WQ; Statistical analysis: GW, YM, WW, JZ, YH, and YS; Obtained funding: ZW and WQ; Administrative, technical, material support: JZ, YH, and YS; Study supervision: WQ and ZW. 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.2023.1155391/full#supplementary-material

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A real-world disproportionality analysis of apalutamide: data mining of the FDA adverse event reporting system

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Background: Apalutamide is a new drug class, which is approved to treat prostate cancer (PCa). The aim of our study was to assess the safety profiles of apalutamide in real-world through data mining of the United States Food and Drug Administration Adverse Event Reporting System (FAERS).

Method: We included adverse event (AE) reports regarding apalutamide submitted to the FAERS from 2018 quarter 1 (2018Q1) to 2022 quarter 1 (2022Q1). Disproportionality analyses, including reporting odds ratio (ROR), were performed to identify the signals of AEs in patients receiving apalutamide. A signal was detected if the lower limit of the 95% confidence interval (CI) of ROR >1 and at least 3 AEs were reported.

Results: The FAERS database documented 4,156 reports regarding apalutamide from 1 January 2018, to 31 March 2022. A total of 100 significant disproportionality preferred terms (PTs) were retained. Frequently observed AEs in patients receiving apalutamide included rash, fatigue, diarrhea, hot flush, fall, weight decreased, hypertension. The most significant system organ class (SOC) was "skin and subcutaneous tissue disorders", which mainly consisted of dermatological adverse events (dAEs). The additional AEs observed with the significantly signal contain lichenoid keratosis, increased eosinophil count, bacterial pneumonia, pulmonary tuberculosis, hydronephrosis.

Conclusion: Our findings provide valuable evidence for apalutamide safety profile in the real-world, which could help clinicians and pharmacists to enhance their vigilance and improve the safety of apalutamide in clinical practice.

KEYWORDS

apalutamide, FDA adverse event reporting system, disproportionality analyses, adverse event, real-world

1 Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed cancers in men and has the fifth highest mortality globally (Sung et al., 2021). Approximately 15%–30% of PCa patients may experience prostate-specific antigen (PSA) recurrence with radical treatment (Zumsteg et al., 2015; Cornford et al., 2021). Majority of these patients will receive androgen

deprivation therapy (ADT) as initial treatment (Mohler and Antonarakis, 2019). However, long-term exposure to ADT eventually results in castration-resistant prostate cancer (CRPC), which contains metastatic (m) and nonmetastatic (nm) disease states (Karantanos et al., 2013; Mateo et al., 2019). The androgen receptor (AR) is overexpressed in such patients, which indicates that AR plays a central role in the pathogenesis of PCa. Studies have shown that direct inhibition of AR in addition to ADT may provide more complete blockade of androgen signaling than ADT alone (Clegg et al., 2012; Dai et al., 2017).

Apalutamide (Erleada®), an oral selective AR inhibitor, binds directly to the ligand-binding domain of AR. It impeded AR-mediated gene transcription and impaired nuclear localization and DNA binding in PC cells. Apalutamide has been approved for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC) in various countries (Al-Salama, 2019; Boukovala et al., 2020; Dror and Chi, 2020; Hoy, 2020). The recommended dose is 240 mg (four 60 mg tablets) administered orally once daily, and patients should also receive ADT. Meanwhile, the efficacy of apalutamide has been investigated recently. The large landmark randomized, double-blind, placebo-controlled clinical trials SPARTAN (NCT01946204) (Perez-Ruixo et al., 2020; Smith et al., 2021) and TITAN (NCT02489318) (Chi et al., 2019; Chi et al., 2021) confirmed that the addition of apalutamide to ADT prolongs metastasis-free survival and overall survival, maintained health-related quality of life, and the safety profile did not differ substantially from the placebo group. The most common AEs to apalutamide are fatigue, hypertension, rash, diarrhea, nausea, decreased weight, arthralgia, falls, hot flushes, decreased appetite, fracture, and peripheral edema.

Clinical trials are conducted under widely varying conditions, and AEs observed in the clinical trials of a drug may not reflect all AEs observed in practice. Thus, it is essential to evaluate the postmarketing safety profile of apalutamide in the real-world. The United States food and drug administration (FDA) adverse event reporting system (FAERS) is a well-known AE spontaneous reporting system (SRS), which can be employed to assess the potential association between drugs and AEs (Sakaeda et al., 2011; Michel et al., 2017). In this study, we aimed to explore the postmarketing safety profile of apalutamide based on AE reports from the FAERS database.

2 Materials and methods

2.1 Study design and data source

We extracted data from the FAERS database (http://www.fda.gov/) ranging from the first quarter of 2018 (2018Q1) to the first quarter of 2022 (2022Q1). The apalutamide was approved by the United States Food and Drug Administration (FDA) in February 2018, so the first quarter of 2018 was choosed as the start date. The generic and brand names (apalutamide, Erleada®) were used as keywords for data mining. Only reports documenting apalutamide as "primary suspect" or "secondary suspect" drug were included in our analysis. The AEs reports in FAERS database are coded with Preferred Terms (PTs) by the Medical Dictionary for Regulatory Activities (MedDRA). Tehierarchical structure of MedDRA allows grouping of PTs into relevant System Organ Class (SOC) which is the top level of MedDRA.

TABLE 1 Clinical characteristics of reports associated with apalutamide from the FAERs database.

Characteristics	Number(n)	Proportion (%)
Number of reports	4,156	
Sex		
Male	3,797	91.36
Unknown	359	8.64
Age(year)		
<45	1	0.02
45–64	176	4.23
65–74	640	15.40
≥ 75	1,353	32.56
Unknown	1,986	47.79
Serious outcomes		
Hospitalization-initial or prolonged (HO)	1,021	24.57
Disability (DS)	40	0.96
Life-threatening (LT)	102	2.45
Death (DE)	672	16.17
Other serious (OT)	1,100	26.47
Unknown	1,221	29.38
Reporting year		
2018	345	8.30
2019	891	21.44
2020	1,371	32.99
2021	1,049	25.24
2022Q1	500	12.03

Only the reports which contain all three elements (identifiable patients, suspected drugs, and AE reports) were included in the present study. The duplicative reports were removed according to FDA guidelines, when case_id and fda_dt were the same, duplicate records under the same case were removed while keeping the latest fda_dt. Otherwise, AEs related to "product issues", "medication and other product use errors", "adverse event", "death", "social circumstances", "prostatic neoplasms malignant", "neoplasms benign", "malignant benign", "therapeutic procedures", "product administration errors and issues", "off-label use", "drug ineffective", and "disease progression" were excluded for which were not drug-related AEs.

2.2 Statistical analysis

Descriptive analysis was used to show the clinical characteristics of all AE reports associated with apalutamide

TABLE 2 Signal strength of AEs of apalutamide at the system organ class (SOC) level in FAERS database.

SOC	N	ROR (95% CI)
Reproductive system and breast disorders	**28**	**3.12(2.15, 4.52)**
Vascular disorders	**296**	**2.87(2.55, 3.22)**
Skin and subcutaneous tissue disorders	**899**	**2.78(2.98, 3.19)**
Endocrine disorders	20	2.50 (1.61, 3.88)
Metabolism and nutrition disorders	197	2.26 (1.96, 2.61)
Investigations	518	1.81 (1.65, 1.98)
Cardiac disorders	192	1.68 (1.46, 1.94)
General disorders and administration site conditions	847	1.57 (1.47, 1.69)
Nervous system disorders	577	1.43 (1.31, 1.55)
Injury, poisoning and procedural complications	189	1.37 (1.18, 1.60)
Ear and labyrinth disorders	29	1.33 (0.92, 1.91)
Respiratory, thoracic and mediastinal disorders	213	1.17 (1.02, 1.34)
Blood and lymphatic system disorders	91	1.12 (0.91, 1.38)
Gastrointestinal disorders	502	1.08 (0.99, 1.18)
Musculoskeletal and connective tissue disorders	273	1.03 (0.91, 1.16)
Renal and urinary disorders	104	0.97 (0.80, 1.17)
Hepatobiliary disorders	27	0.97 (0.67, 1.42)
Infections and infestations	205	0.93 (0.81, 1.07)
Psychiatric disorders	188	0.84 (0.73, 0.98)
Eye disorders	24	0.76 (0.51, 1.13)
Immune system disorders	21	0.33 (0.21, 0.50)

The bold values are the most significant SOC.

from the FAERs database. Disproportionate analysis was performed to identify statistical associations between apalutamide and all AEs. The reporting odds ratio (ROR) were used to identify signals indicating a potentially increased risk of drug-associated AEs for apalutamide. A two-by-two contingency table was used to calculate ROR (Supplementary Table S1). A PT was considered positive singal if the lower limit of 95% CI was > 1, and the reported number was ≥ 3 (Sakaeda et al., 2013). The higher ROR inherently implies a stronger disproportion and strength signal, indicating that the specific drug is more likely to induce a specific AE than all other drugs (Zink et al., 2013).

3 Results

3.1 Population characteristics

The FAERs database received a total of 33461775 AE reports from 1 January 2018, to 31 March 2022, among which approximately 4,156 reports included 7,959 PTs for apalutamide. Patient characteristics and AE reports regarding apalutamide are presented in Table 1. Due to the specific indications, the patients were predominantly male (91.36%), while the sex of 8.64% of patients was unknown. Elderly patients (age > 65 years) contributed to the majority proportion of AE reports (47.96%), excluding unknown reports. Hospitalization-initial or prolonged (24.57%) was the most common serious outcome. AEs resulting in death were noted in 16.17% of reports, and the high proportion of deaths might be related to the disease progression of cancer. Most reports were submitted by physicians (23.56%) and consumers (32.36%). The United States (77.21%) represented the main source of reports, followed by Japan (10.08%). The number of reports increased yearly, except for the reports in the first quarter of 2022.

3.2 Disproportionality analysis

The signal strength of AEs of apalutamide at the system organ class (SOC) level in the FAERS database is shown in Table 2. The frequently observed AEs in patients receiving apalutamide were referred to 20 organ systems. The most significant SOCs were “skin and subcutaneous tissue disorders”, “vascular disorders”, and “reproductive system and breast disorders”. Otherwise, the signals for “general disorders and administration site conditions”, “nervous system disorders” and “investigations” were also frequent and important.

Totally 100 PTs were detected as positive signals for apalutamide, which are presented in Table 3. Among thess signals, rash (PT:10037844), fatigue (PT:10016256), diarrhea (PT:10012735), hot flush (PT:10060800), fall (PT:10016173), weight decreased (PT:10047895), hypertension (PT:10020772) were the most common AEs, which were consistented with the manufacturer’s labeling and clinical trials. Some PTs with high ROR signals were found, including cerebrovascular accidents (ROR = 66.80, PT:10008190), exfoliative generalized dermatitis (ROR = 26.82, PT:10012456), increased blood thyroid stimulating hormone (ROR = 16.09, PT:10005833), increased blood testosterone (ROR = 23.55, PT:10005815), duodenal perforation (ROR = 25.28, PT:10013832), and right ventricular dysfunction (ROR = 18.05, PT:10058597). The additional observed AEs which were uncovered in the manufacturer’s labeling were found, such as lichenoid keratosis (ROR = 15.66, PT: 10064000), increased eosinophil count (ROR = 6.30, PT: 10064000), bacterial pneumonia (ROR = 6.03, PT: 10060946), pulmonary tuberculosis (ROR = 8.05, PT: 10037440), and hydronephrosis (ROR = 8.76, PT: 10020524).

3.3 Time-to-onset analysis

Approximately 1,609 AE reports were extracted from the FAERs database, which reported the onset time. The mean onset time was 126 days, and the median onset time was 62 days (interquartile range [IQR] 21–167 days). Our data demonstrated that the onset time of most AEs was less than 30 days (n = 530, 32.94%). Interestingly, AEs might still have occurred after 1 year for apalutamide treatment, with a proportion of 13.42% (Figure 1).

TABLE 3 Signal strength of reports of apalutamide at the perferred terms (PTs) level in FAERs database.

	PT	N	ROR (95% CI)
Expect AEs	rash	444	8.25 (7.50, 9.07)
	fatigue	325	3.17 (2.84, 3.55)
	hot flush	**154**	**17.93(15.28, 21.04)**
	diarrhoea	151	1.79 (1.52, 2.10)
	fall	125	2.90 (2.43, 3.46)
	decreased appetite	122	4.04 (3.37, 4.83)
	weight decreased	108	2.77 (2.29, 3.35)
	dizziness	102	1.77 (1.46, 2.15)
	asthenia	95	2.06 (1.68, 2.52)
	oedema peripheral	93	2.14 (1.75, 2.63)
	arthralgia	87	1.64 (1.33, 2.03)
	hypertension	82	3.22 (2.59, 4.00)
	pruritus	73	1.67 (1.32, 2.10)
	acute coronary syndrome	54	3.44 (2.63, 4.50)
	interstitial lung disease	50	7.61 (5.76, 10.06)
	blood pressure increased	45	2.01 (1.50, 2.69)
	seizure	38	2.11 (1.53, 2.90)
	cerebrovascular accident	**35**	**66.80(47.80, 93.34)**
	balance disorder	32	2.82 (1.99, 3.99)
	hyperhidrosis	30	2.14 (1.49, 3.06)
	chest pain	30	2.35 (1.64, 3.37)
	dysgeusia	30	4.37 (3.05, 6.26)
	constipation	30	1.61 (1.12, 2.30)
	ischaemic stroke	29	2.96 (2.06, 4.27)
	cardiac failure	28	2.78 (1.92, 4.03)
	rash pruritic	27	4.56 (3.12, 6.65)
	dysphagia	27	2.51 (1.72, 3.66)
	rash erythematous	25	5.01 (3.38, 7.42)
	atrial fibrillation	25	2.07 (1.40, 3.07)
	toxic epidermal necrolysis	**24**	**14.46(9.68, 21.60)**
	blood thyroid stimulating hormone increased	**22**	**16.09(10.58, 24.47)**
	haematuria	22	3.12 (2.06, 4.75)
	dermatitis exfoliative generalised	**20**	**26.82(17.27,41.65)**
	drug eruption	**18**	**9.19(5.79, 14.60)**
	drug reaction with eosinophilia and systemic symptoms	17	4.55 (2.82, 7.32)
	taste disorder	16	6.04 (3.70, 9.87)
	urinary retention	16	4.05 (2.48, 6.62)
	rash maculo-papular	14	5.10 (3.02, 8.62)

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TABLE 3 (*Continued*) Signal strength of reports of apalutamide at the perferred terms (PTs) level in FAERs database.

	PT	N	ROR (95% CI)
	cardiac disorder	14	1.80 (1.07, 3.04)
	febrile neutropenia	14	1.70 (1.01, 2.87)
	cough	13	7.15 (4.15, 12.32)
	eczema	12	2.69 (1.53, 4.74)
	flatulence	12	1.80 (1.02, 3.18)
	hypokalaemia	12	2.07 (1.17, 3.64)
	hypothyroidism	12	3.04 (1.72, 5.35)
	Stevens-Johnson syndrome	11	5.66 (3.13, 10.24)
	hip fracture	11	2.86 (1.58, 5.16)
	dysuria	11	2.44 (1.35, 4.41)
	pollakisuria	11	2.18 (1.21, 3.94)
	ageusia	10	3.60 (1.93, 6.69)
	blood cholesterol increased	10	2.07 (1.11, 3.84)
	electrocardiogram qt prolonged	10	2.03 (1.09, 3.78)
	erythema multiforme	9	8.79 (4.57, 16.91)
	angina pectoris	7	2.17 (1.04, 4.56)
	gastric ulcer	6	2.42 (1.09, 5.40)
	hypertensive crisis	6	3.89 (1.75, 8.66)
	cardiac arrest	6	2.26 (1.01, 5.03)
	acute generalised exanthematous pustulosis	5	5.06 (2.10, 12.16)
	chest discomfort	**5**	**11.64(4.84,28.00)**
	generalised oedema	5	4.38 (1.82, 10.54)
	blood testosterone increased	**5**	**23.55(9.77, 56.73)**
	aortic dissection	**5**	**13.46(5.59, 32.40)**
	respiratory tract congestion	5	2.57 (1.07, 6.18)
	subdural haematoma	5	2.62 (1.09, 6.29)
	hyperthyroidism	5	2.48 (1.03, 5.95)
	subarachnoid haemorrhage	4	3.18 (1.19, 8.48)
	supraventricular tachycardia	4	3.97 (1.49, 10.58)
	ventricular extrasystoles	4	4.25 (1.59, 11.39)
	urine odour abnormal	4	5.13 (1.92, 13.67)
	dermatitis psoriasiform	**3**	**12.21(3.93, 37.93)**
	exfoliative rash	**3**	**11.54(3.72, 35.85)**
	pustular psoriasis	3	8.61 (2.77, 26.73)
	rash vesicular	3	5.12 (1.65, 15.89)
	duodenal perforation	**3**	**25.28(8.12, 78.67)**
	mucous stools	3	4.60 (1.48, 14.28)
	cytomegalovirus infection reactivation	3	8.33 (2.68, 25.87)
	heart valve incompetence	3	7.47 (2.41, 23.18)
	right ventricular dysfunction	**3**	**18.05(5.80, 56.10)**

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TABLE 3 (*Continued*) Signal strength of reports of apalutamide at the perferred terms (PTs) level in FAERs database.

	PT	N	ROR (95% CI)
	lumbar vertebral fracture	3	5.11 (1.65, 15.85)
	urinary bladder haemorrhage	**3**	**10.71(3.45, 33.26)**
	vanishing bile duct syndrome	**3**	**30.54(9.81, 95.11)**
Unexpected AEs	urinary tract infection	41	1.74 (1.28, 2.36)
	muscular weakness	23	1.68 (1.11, 2.53)
	Lethargy	16	2.68 (1.64, 4.38)
	Hallucination	15	1.69 (1.02, 2.81)
	Dementia	13	3.72 (2.16, 6.41)
	eosinophil count increased	8	6.30 (3.15, 12.62)
	Hydronephrosis	8	8.76 (4.38, 17.54)
	Agranulocytosis	8	3.83 (1.92, 7.67)
	pneumonia bacterial	7	6.03 (2.87, 12.67)
	abnormal dreams	7	3.00 (1.43, 6.30)
	restless legs syndrome	6	2.71 (1.22, 6.05)
	libido decreased	6	5.63 (2.53, 12.54)
	sensory disturbance	5	3.15 (1.31, 7.58)
	lichenoid keratosis	**4**	**15.66(5.87, 41.82)**
	muscle atrophy	4	3.01 (1.13, 8.02)
	pulmonary tuberculosis	4	8.05 (3.02, 21.48)
	Urosepsis	4	3.28 (1.23, 8.74)
	sjogren's syndrome	3	4.14 (1.33, 12.85)
	middle ear effusion	3	9.89 (3.19, 30.72)

Expect AEs: predictable events on the basis of apalutamide mechanism of action or anticipated from pre-marketing pivotal trials with a safety signal. Unexpected AEs: unexpected or previously unreported events, not mentioned in the drug label. The bold values are the PTs with high ROR.

4 Discussion

Apalutamide, a high-affinity AR inhibitor, binds directly to the ligand-binding domain of AR and inhibits nuclear localization and DNA binding within prostate cancer cells (Al-Salama, 2018; Rathkopf and Scher, 2018). Apalutamide is a well-tolerated drug for PCa patients and is associated with a favorable trend of improved overall survival. The recent guidelines were updated to recommend apalutamide in patients with nmCRPC and mCSPC with background ADT therapy (Mohler and Antonarakis, 2019; Cornford et al., 2021). Thus, there may be an increasing annual trend of prescriptions, as well as growing clinical experience with apalutamide. It is important to underline monitoring safety and postmarketing surveillance for apalutamide. The present study provides real-world data on the safety profile of apalutamide.

We systematically reviewed the literature to evaluate the safety profiles of apalutamide. Ten clinical trial studies for apalutamide in PCa were identified (Supplementary Table S2) (Rathkopf et al., 2013; Smith et al., 2016; Rathkopf et al., 2017; Chi et al., 2019; Tsuchiya et al., 2019; Perez-Ruixo et al., 2020; Chi et al., 2021; McKay et al., 2021; Saad et al., 2021; Smith et al., 2021). The addition of apalutamide to ADT resulted in a safety profile that showed no substantial difference from placebo plus ADT. The most frequently investigated AEs were skin rash, fatigue, fracture, hypertension, hot flush, diarrhea, seizures, arthralgia and so on. Our disproportionality analyses revealed that the most common and frequently reported PTs for apalutamide were rash, fatigue, hot flush, diarrhea, falls, decreased appetite, decreased weight, and dizziness. The results were mostly consistent with the manufacturer's labeling and clinical trials. We also identified that rash was more frequently reported, while falls, hypothyroidism, and seizures occurred in only a few patients.

Otherwise, our findings raise some different safety concerns. First, we detected some rare AEs with a high ROR, such as increased blood testosterone, duodenal perforation, and right ventricular dysfunction. Second, we found some unexpected PTs with high ROR, included lichenoid keratosis, increased eosinophil count, bacterial pneumonia, pulmonary

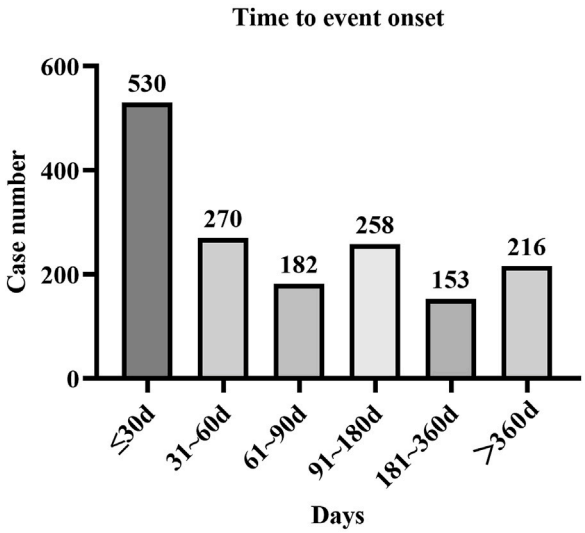

FIGURE 1
Time to onset of AEs in patients receiving apalutamide.

tuberculosis, hydronephrosis. Notably, clinicians and pharmacists should be aware of these rare, new and additional observed AEs. Furthermore, no signals were detected following disproportionality for several frequently reported AEs listed on the drug label, such as nausea, vomiting, fracture, hematuria. These discrepancies could be explained by the fact that AEs are fairly common for all drugs in the FAERS database. Signal scores can be suppressed by a large number of reports for an AE associated with multiple drugs. Disproportionality requires that an AE is reported more (or less) frequently for a specific drug. The absence of a signal does not imply the absence of relative AEs; it only indicates that there was no disproportion seen for these AEs.

Our disproportionality analyses identified that the most common and significant SOCs for apalutamide were "skin and subcutaneous tissue disorders". Interestingly, majority PTs belongs to "skin and subcutaneous tissue disorders" were dermatological adverse events (dAEs) (e.g., rash, pruritus, heperhidrosis). The SPARTAN and TITAN trials reported that the incidence of skin rash was 23.8% and 27.1%, respectively (Uemura et al., 2020). However, most skin rashes were grade 1–3 and rarely caused dose reduction or discontinuation. The highest frequency of dAEs commonly occurs 1–4 months post apalutamide initiation for PCa. Interestingly, the other AR inhibitor enzalutamide, darolutamine, showed a low rash incidence in clinical trials. This difference may be due to the chemical structure of apalutamide, which has a more reactive 2-cyanopyridine moiety and more readily activates the immune system by increasing lymph node cellularity and T cell and B cell counts (Drago et al., 2021; Pan et al., 2022). A published study showed that high apalutamide exposure was significantly associated with skin rash; thus, dose reductions may help prevent dAE recurrence (Perez-Ruixo et al., 2020). Most dAEs were effectively managed with moderate to high-potency topical steroids and oral antihistamines.

Pain and fatigue are common symptoms in metastatic PCa, while fatigue is also a common and substantial AE of ADT (Holm et al., 2018). Data mining from the FAERs database for apalutamide shows that fatigue is a frequently reported AE (ROR = 3.17). The *post hoc* analysis for the TITAN study showed that pain and fatigue were improved or not worsened in patients with mCSPC treated with apalutamide compared with placebo (Agarwal et al., 2021). The analysis demonstrated that patients benefitted through delayed disease progression, and they also maintained HRQoL with no additional pain or fatigue burden.

Due to the presence of incomplete reports in the FAER database, we could not identify the grade of the AE reports. Hence, the serious outcomes of AEs reports were explored in this study. About 44.15% AE reports suffered specific serious outcomes, including hospitalization-initial or prolonged (24.57%) and death (16.17%). The risk factors (such as weight, age, dose) for serious AEs was explored, however there was no sufficient clinical information to certify these. Hence, we remind clinicians and pharmacists that the prescriber's information should be followed for managing AE related dose interruptions and/or modifications. Besides, we found that in the death reports most were related to the cardiovascular and cerebrovascular disease (a grouped term that included various events), excepted the reports related to the disease progression of cancer. Patients with clinically significant cardiovascular and cerebrovascular disease who are prescribed apalutamide should be monitored for risk factors (Morgans et al., 2021).

The results of this study indicated that the median onset time was 62 days, and most AEs occurred within the first month ($n = 530$, 32.94%) after exposure to apalutamide. The majority of AEs were reported within half a year, but AEs might still have occurred after 1 year. Thus, a longer follow-up period is needed to observe the AEs of apalutamide in future clinical studies.

Several limitations of the present study need to be addressed. The FAERs database is a spontaneous reporting database, so the rates of occurrence of each AE for apalutamide could not be estimated. Besides, the existence of a report does not establish causation in the FAERS database, so the results in the present study merely showed the potential AEs that meant the clinicians and pharmacists to enhance their vigilance. Meanwhile, the estimates of exposure adjusted AEs was not possible owing to incomplete information extracted from the FAERs database. The ROR was used as the measure of disproportionality, which provided the highest number of signals, which only report information on a possible causal relationship between an adverse event and a drug. Further well-organized clinical trials were need to investigate the causal relationship. Lastly, we could not distinguish AE reports related to apalutamide and concomitant ADT therapy owing to incomplete information. Hence, the association between concomitant ADT therapy and some related AEs could not be examined. Despite these limitations, the FAERs is still very useful for post-marketing safety surveillance.

5 Conclusion

In conclusion, the present study scientifically and systematically quantified the safety profile of apalutamide by the FAERS database. The frequent AEs (e.g.,, rash, fatigue, diarrhea, hot flush, fall) and additional observed AEs (e.g., lichenoid keratosis, increased eosinophil count, bacterial pneumonia, pulmonary tuberculosis) need to be monitored. Moreover, we observed strong signals for dermatological adverse events associated with apalutamide. Overall AE profile detected in this study is consistent with the clinical trial experience reported in the past and the manufacturer's drug label for apalutamide. We hope that further studies and clinical practice will provide valuable evidence for the safety profile of apalutamide.

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

CJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZF drafted the manuscript, ZX and WZ were involved in the statistical analysis. MY managed the study design and reviewed 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.2023.1101861/full#supplementary-material

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Risk-factor analysis and predictive-model development of acute kidney injury in inpatients administered cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium: a single-center retrospective study

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Objective: Acute kidney injury (AKI) is a common adverse reaction observed with the clinical use of cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium. Based upon real-world data, we will herein determine the risk factors associated with AKI in inpatients after receipt of these antimicrobial drugs, and we will develop predictive models to assess the risk of AKI.

Methods: Data from all adult inpatients who used cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium at the First Affiliated Hospital of Shandong First Medical University between January 2018 and December 2020 were analyzed retrospectively. The data were collected through the inpatient electronic medical record (EMR) system and included general information, clinical diagnosis, and underlying diseases, and logistic regression was exploited to develop predictive models for the risk of AKI. The training of the model strictly adopted 10-fold cross-validation to validate its accuracy, and model performance was evaluated employing receiver operating characteristic (ROC) curves and the areas under the curve (AUCs).

Results: This retrospective study comprised a total of 8767 patients using cefoperazone-sulbactam sodium, of whom 1116 developed AKI after using the drug, for an incidence of 12.73%. A total of 2887 individuals used mezlocillin-sulbactam sodium, of whom 265 developed AKI after receiving the drug, for an incidence of 9.18%. In the cohort administered cefoperazone-sulbactam sodium, 20 predictive factors ($p < 0.05$) were applied in constructing our logistic predictive model, and the AUC of the predictive model was 0.83 (95% CI, 0.82–0.84). In the cohort comprising mezlocillin-sulbactam sodium use, nine predictive factors were determined

by multivariate analysis ($p < 0.05$), and the AUC of the predictive model was 0.74 (95% CI, 0.71–0.77).

Conclusion: The incidence of AKI induced by cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium in hospitalized patients may be related to the combined treatment of multiple nephrotoxic drugs and a past history of chronic kidney disease. The AKI-predictive model based on logistic regression showed favorable performance in predicting the AKI of adult in patients who received cefoperazone-sulbactam sodium or mezlocillin-sulbactam sodium.

KEYWORDS

cefoperazone-sulbactam sodium, mezlocillin-sulbactam sodium, acute kidney injury, pharmacoepidemiology, risk factors, logic regression model

1 Introduction

Acute kidney injury (AKI) is a common and complex kidney disease in clinical practice, is associated with poor patient prognosis (Belavgeni et al., 2020), and portends severe consequences (Palevsky, 2006), including increased mortality (Clermont et al., 2002; Thakar et al., 2005). AKI is very common among hospitalized patients, with an incidence in adult patients of 0.7%–77% (James et al., 2010; Han et al., 2013). In addition, it is reported that AKI results in a high mortality of between 14% and 60% in hospitalized adults (Uchino et al., 2005; Bihorac et al., 2013; Chang et al., 2015).

There are over 200 types of clinical medications that induce AKI as observed from investigations of drug-induced AKI (Osman et al., 2017). In addition, among various nephrotoxic drugs that cause AKI, the proportion consisting of antibiotic drugs ranks in the top few percent, of which β-lactam antibiotics accounted for 12.24% of the total. Cephalosporins account for 93.04% of all β-lactam drugs that cause AKI, and their metabolites tend to accumulate in cells as they are excreted by the kidney, resulting in nephrotoxicity. On the other hand, β-Lactam antibiotics or their metabolites can be used as haptens to combine with macromolecular substances *in vivo* to become antigens (Al-Harbi et al., 2003). As a result, the body will produce antibodies, undergo immune reactions, and damage the kidney. Moreover, some authors had confirmed through animal experiments that the nephrotoxicity of cefoperazone-sulbactam sodium was mainly manifested by a large amount of focal necrosis and calcification in the kidney proximal tubule epithelium, as well as the presence of protein and granular tubules in the collecting duct (Erfurth and Hoff, 2000). The second-most prevalent drug used is penicillin, which generally exerts no direct nephrotoxicity but generates acute interstitial nephritis and then acute kidney injury due to allergic reactions (Capelletti et al., 2020). However, there are relatively few studies that focus on risk-factor analysis of AKI in inpatients, particularly in Asian populations. In the present study, we focused on an unbiased estimate of the incidence of AKI in hospitalized patients who received cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition. In addition, we attempted to analyze the relevant risk factors and develop logistic regression models for AKI vis-à-vis these drugs on the basis of real-world data from our center.

2 Materials and methods

2.1 Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (approval no. YXLL-KY-2022-024), and we did not use personally identifiable information in the present study.

2.2 Data sources and searches

The current data were extracted from the electronic medical records of the First Affiliated Hospital of Shandong First Medical University. The collected patient information primarily included the social and demographic characteristics of patients, comorbidities, length of stay, hospitalization expenses, laboratory examination results, medical advice, and diagnosis. We included patients who were discharged from the hospital between 1 January 2018, and 31 December 2020, and who underwent treatment with cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium (details on the methodology concerning inclusion and exclusion criteria can be found in the Supplementary Material).

2.3 Case definition

Our AKI cases were defined in accordance with the 2012 KDIGO Clinical Practice Guidelines for AKI (Kellum et al., 2013), and the diagnostic criteria were shown in Supplementary Table S1. As continuous urine volume monitoring was difficult to perform during the hospitalization of patients in the present study, we based the screening of AKI patients chiefly on the relevant criteria with respect to serum creatinine (sCr) in the AKI diagnostic criteria published by KDIGO. In addition, to reduce missed diagnoses caused by an inability to detect creatinine or a delay in creatinine-detection time and to fully evaluate the correlation between AKI and the use of the target drug and increase the accuracy of the determination of drug-induced AKI for the target drug—we determined the actual AKI diagnosis process in this study based on the AKI clinical practice guidelines published by KDIGO.

According to KDIGO guidelines and combined with the use of target drugs, those patients who met one of the following conditions were determined as having AKI. 1) Patients during hospitalization

TABLE 1 Cefoperazone sulbactam sodium related AKI and patient characteristics.

Group	AKI (n = 1116)	Non-AKI (n = 7651)	Total (n = 8767)	χ^2/Z	p value
Sex					
Male	712 (63.80%)	4,794 (62.66%)	5,506 (62.80%)	0.54	0.461
Female	404 (36.20%)	2,857 (37.34%)	3,261 (37.20%)		
Age	67 (55,79)	65 (54,76)	66 (54,76)	18,767,274	<0.001
Age group					
Youth	139 (12.46%)	1,190 (15.55%)	1,329 (15.16%)	49.12	<0.001
Middle age	449 (40.23%)	3,673 (48.01%)	4,122 (47.02%)		
Old age	528 (47.31%)	2,788 (36.44%)	3,316 (37.82%)		
Smoking					
Yes	404 (36.20%)	2578 (33.70%)	2982 (34.01%)	2.72	0.098
No	712 (63.80%)	5073 (66.30%)	5785 (65.99%)		
Length of hospital stay*	16.95 (2.03, 187.11)	17.06 (2.02, 160.66)	17.04 (2.02, 357.1)	4,347,199.50	0.324
Hospital cost*	101,269.39 (8733.58, 1718345.17)	56,175.75 (142.60, 911656.83)	60,424.85 (142.6, 1718345.17)	2,652,208.50	<0.001

*Two sample Wilcoxon rank sum test was used.
AKI, acute kidney injury.

with β-lactam drugs were used as a starting point, with the most recent sCr value before the first use of the target drug during the patient's hospitalization and all measured sCr values before discharge used as target data. If the most recent value was determined within the continuous 48-h observation period where the creatinine samples were sorted from front-to-back according to the acceptance date, and the maximal change in the later test value was ≥26.5 compared with any previous test value in μ mol/L (≥0.3 mg/dl), the value was considered to meet the AKI judgment standard. 2) When hospitalization and β-lactam drug administration were used as a starting point, all the most recently measured sCr values before the first use of the target drug during the patient's hospitalization and before discharge were used as the target data. It is known or assumed that functional kidney damage occurs within 7 days. From the most recent value (if within the continuous observation period of 7 days), the creatinine samples were sorted from front-to-back according to the acceptance date, and if the ratio between the latest detection value and any forward detection value was ≥1.5, it was considered to meet the AKI judgment standard.

We excluded the patients diagnosed with AKI before admission and took into account the AKI caused by other risk factors during the hospitalization of patients before using the study drug. The inpatients with AKI after using β-lactam drugs were then also included.

2.4 Outcomes

In this study, we analyzed the incidence of AKI and potential risk factors in hospitalized patients who received cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium and developed predictive models for AKI risk for inpatients who underwent these drug treatments.

2.5 Statistical analyses

We conducted data analysis using R software (version 3.6.3) and implemented the use of big data platforms for healthcare at the First Affiliated Hospital of Shandong First Medical University. Our research variable was designated the independent variable, the AKI group was used as the dependent variable, and the Chi-squared test was applied for univariate analysis. Those variables with $p < 0.05$ in the univariate analysis were then included in multivariate logistic regression analysis. We expressed the analytical results as odds ratios (ORs) and 95% confidence intervals (95% CIs). All p values were bilateral, and a p value < 0.05 was considered statistically significant. Details regarding our statistical analyses are depicted in Supplementary Material.

2.6 Model development

In the present study, the logistic regression models were developed with routinely collected patient information. Logistic regression is the result of linear regression performed by bending the sigmod function. It predicts the probability of a result with only two values. Prediction is based on the use of one or more predictive variables (numerical and categorical). Logistic regression uses maximum likelihood estimation to obtain model coefficients that relate predictive factors to the target. After the initial function estimation, repeat the process until the logarithmic likelihood does not significantly change. Due to the ability to calculate the correlation coefficient between the prediction factor and the target, the model is easy to understand and discover relevant factors.

All predictions with respect to AKI are based on routinely collected patient information, and there were no missing values in the variables required by the AKI predictor. Since no external

TABLE 2 Mezlocillin sulbactam sodium related AKI and patient characteristics.

Group	AKI (*n* = 265)	Non-AKI (*n* = 2622)	Total (*n* = 2887)	χ^2/Z	*p* value
Sex					
Male	166 (62.64%)	1,760 (67.12%)	1,926 (66.71%)	2.18	0.140
Female	99 (37.36%)	862 (32.88%)	961 (33.29%)		
Age	67 (55,79)	65 (54,76)	66 (54,76)	18,767,274	<0.001
Age group					
Youth	35 (13.21%)	532 (20.29%)	567 (19.64%)	8.09	0.017
Middle age	144 (54.34%)	1,353 (51.60%)	1,497 (51.85%)		
Old age	86 (32.45%)	737 (28.11%)	823 (28.51%)		
Smoking					
Yes	88 (33.21%)	854 (32.57%)	942 (32.63%)	0.04	0.833
No	177 (66.79%)	1768 (67.43%)	1945 (67.37%)		
Length of hospital stay*	14.28 (2.13, 118.09)	14.13 (2.02, 141.68)	14.14 (2.02, 141.68)	327,805.50	0.129
Hospital cost*	67,261.22 (10159.43, 90349.49)	36,758.32 (3205.32, 838505.01)	38,466.87 (3205.32, 903495.49)	237,879	<0.001

*Two sample Wilcoxon rank sum test was used.
AKI, acute kidney injury.

validation dataset was obtained, we herein adopted a strict 10-fold cross-validation (CV) to test the validity of our model. We employed receiver operating characteristic (ROC) curves and areas under the ROC curves (AUCs) when evaluating the performance of the model to assess its predictive performance. It is conventionally recognized that patients who develop AKI represent only a minority of all hospitalized patients, and the data set used for the present study reflected a great imbalance between positive and negative cases. The presence of a positive/negative case imbalance thus generated the few categories upon which we focused and that were typically ignored by predictive models.

3 Results

3.1 Demographic characteristics of AKI

We included a total of 8,767 inpatients using cefoperazone-sulbactam sodium. Of these individuals, there were 1,116 cases who met the AKI criteria of the KDIGO 2012 guidelines, suggesting that the incidence of AKI in patients who received cefoperazone-sulbactam sodium was 12.73% (1116/8767). After exclusions, there were 2,887 patients included in the mezlocillin-sulbactam sodium cohort, and of these, 265 patients were diagnosed as AKI cases, with an incidence of 9.18% (265/2887).

The patient characteristics for the cefoperazone sulbactam sodium cohort are shown in Table 1. There were 712 men (63.80%) and 404 women (36.20%) in the AKI group, and 4,794 males (62.66%) and 2857 females (37.34%) in the non-AKI group (we noted no statistical differences between the sexes; p = 0.46). Our analysis of age showed that the highest incidence was in the elderly group (66 years or above, 15.92%) relative to the young (18–40 years old, 10.46%) and middle-aged groups (41–65 years old, 10.89%) ($p < 0.001$). Particular attention should be given to the kidney function of elderly patients who use this drug and who experienced favorable prevention. Of the patients included in our study, there was no significant difference in the length of the hospital stay between the two groups (16.95 days vs. 17.06 days, $p = 0.32$), but the hospitalization costs for the AKI group were significantly higher than those for the non-AKI group (101,269.39 yuan vs. 56,175.75 yuan; $p < 0.001$).

Of the AKI cohort administered mezlocillin-sulbactam sodium, 166 patients (62.64%) were men and 99 patients (37.36%) were women; these proportions did not differ in the group without AKI, with 1760 male patients (67.12%) and 862 female patients (32.88%) (Table 2). Similar to the situation for patients using cefoperazone-sulbactam sodium, the two groups of patients using mezlocillin-sulbactam sodium also exhibited significant differences in age, suggesting that older age was considered a risk factor for AKI. We also noted that compared with non-AKI patients, the hospitalization costs of patients with AKI were higher, and that the length of hospitalization was longer ($p < 0.001$; Table 2).

3.2 Comorbidities and concomitant therapies

Based on a review of diagnoses and complications found on the first page of inpatient medical records with respect to target drugs, most patients often had one or more underlying diagnoses or multiple disease complications during hospitalization. In the cefoperazone-sulbactam sodium cohort, patients with AKI tended to demonstrate multiple underlying diseases as shown in Table 3. Several basic diseases showed significant differences between the two groups, including hypertension (χ^2, 42.68; $p < 0.001$), diabetes (χ^2, 36.79; $p < 0.001$), cerebral apoplexy (χ^2, 118.13; $p < 0.001$), anemia

TABLE 3 Comorbidities and concomitant therapies of cefoperazone-sulbactam sodium-related AKI.

	AKI (*n* = 1116)	Non-AKI (*n* = 7651)	Total (*n* = 8767)	χ^2	*p* value
Comorbidities					
Hypertension	573 (51.34%)	3137 (41.00%)	3710 (42.32%)	42.68	<0.001
Diabetes	336 (30.11%)	1678 (21.93%)	2014 (22.97%)	36.79	<0.001
Cerebral apoplexy	499 (44.71%)	2192 (28.65%)	2691 (30.69%)	118.13	<0.001
Anemia	201 (18.01%)	724 (9.46%)	925 (10.55%)	75.40	<0.001
Coronary heart disease	424 (37.99%)	1974 (25.80%)	2398 (27.35%)	72.86	<0.001
Pneumonia	509 (45.61%)	1816 (23.74%)	2325 (26.52%)	239.13	<0.001
Shock	221 (19.80%)	242 (3.16%)	463 (5.28%)	539.10	2.975
Sepsis	41 (3.67%)	42 (0.55%)	83 (0.95%)	101.42	<0.001
Heart failure	182 (16.31%)	427 (5.58%)	609 (6.95%)	173.38	<0.001
Skin tissue infection	10 (0.90%)	58 (0.76%)	68 (0.77%)	0.24	0.624
Neoplastic disease	200 (17.92%)	1961 (25.63%)	2161 (24.65%)	31.17	<0.001
Gout	14 (1.25%)	50 (0.65%)	64 (0.73%)	4.85	0.027
Chronic renal insufficiency	72 (6.45%)	217 (2.84%)	289 (3.30%)	39.93	<0.001
Pancreatitis	35 (3.14%)	276 (3.61%)	311 (3.55%)	0.63	0.427
COPD	38 (3.41%)	186 (2.43%)	224 (2.56%)	3.71	0.054
Hypokalemia	75 (6.72%)	327 (4.27%)	402 (4.59%)	13.32	<0.001
Hyponatremia	60 (5.38%)	232 (3.03%)	292 (3.33%)	16.62	<0.001
Cirrhosis	54 (4.84%)	379 (4.95%)	433 (4.94%)	0.03	0.869
Hyperlipidemia	28 (2.51%)	141 (1.84%)	169 (1.93%)	2.29	0.131
Combination therapy					
NSAIDs	405 (36.29%)	2362 (30.87%)	2767 (31.56%)	13.23	<0.001
ARB	196 (17.56%)	1152 (15.06%)	1348 (15.38%)	4.70	0.031
ACEI	74 (6.63%)	414 (5.41%)	488 (5.57%)	2.76	0.096
PPI	961 (86.115)	1856 (24.26%)	2817 (32.13%)	59.24	<0.001
Aminoglycoside	162 (14.52%)	1414 (18.48%)	1576 (17.98%)	10.38	<0.001
Diuretics	1005 (90.05%)	3096 (40.47%)	4101 (46.78%)	391.02	<0.001

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ARB, angiotensin II receptor inhibitor drugs; ACEI, angiotensin-converting enzyme inhibitor; PPI, proton pump inhibitor.

(χ^2, 75.40; $p < 0.001$), coronary heart disease (χ^2, 72.86; $p < 0.001$), pneumonia (χ^2, 239.13; $p < 0.001$), sepsis (χ^2, 101.42; $p < 0.001$), heart failure (χ^2, 173.38; $p < 0.001$), neoplastic diseases (χ^2, 31.17; $p < 0.001$), chronic renal insufficiency (χ^2, 39.93; $p < 0.001$), hypokalemia (χ^2, 13.32; $p < 0.001$), and hyponatremia (χ^2, 16.62; $p < 0.001$). The application of several combined medications also produced significant difference between different groups, including nonsteroidal anti-inflammatory drugs (NSAID) (χ^2, 13.23; $p < 0.001$), angiotensin II receptor inhibitor (ARB) drugs (χ^2, 4.70; $p < 0.001$), proton pump inhibitors (PPIs) (χ^2, 59.24; $p < 0.001$), aminoglycosides (χ^2, 10.38; $p < 0.001$), and diuretics (χ^2, 391.02; $p < 0.001$).

In the total study population of the mezlocillin-sulbactam sodium cohort, a majority of patients showed one or more underlying diseases or multiple disease complications during hospitalization (as shown in Table 4). We thus noted that diabetes (χ^2, 4.65; $p < 0.031$), cerebral apoplexy (χ^2, 7.77; $p = 0.005$), anemia (χ^2, 5.35; $p < 0.020$), coronary heart disease (χ^2, 14.84; $p < 0.001$), pneumonia (χ^2, 24.88; $p < 0.001$), shock (χ^2, 91.14; $p < 0.001$), heart failure (χ^2, 15.12; $p < 0.001$), chronic renal insufficiency (χ^2, 4.31; $p = 0.031$), pancreatitis (χ^2, 3.54; $p = 0.049$), and hypokalemia (χ^2, 8.11; $p < 0.001$) constituted adverse factors that affected the occurrence of AKI in patients. Patients with such diseases were often more likely to have had AKI. Similarly, several combined medications also exhibited significant differences, including NSAIDs (χ^2, 5.31; $p < 0.021$), angiotensin-converting enzyme inhibitor (ACEI) drugs (χ^2, 7.11; $p = 0.007$), PPIs (χ^2,

TABLE 4 Comorbidities and concomitant therapies for mezlocillin-sulbactam sodium-related AKI.

	AKI (n = 265)	Non-AKI (n = 2622)	Total (n = 2887)	χ^2	p value
Comorbidities					
Hypertension	110 (41.50%)	1014 (38.67%)	1124 (38.93%)	0.81	0.367
Diabetes	62 (23.40%)	472 (18.00%)	534 (18.50%)	4.65	0.031
Cerebral apoplexy	72 (27.17%)	522 (19.91%)	594 (20.57%)	7.77	0.005
Anemia	26 (9.81%)	161 (6.14%)	187 (6.48%)	5.35	0.020
Coronary heart disease	72 (27.17%)	460 (17.54%)	532 (18.43%)	14.84	<0.001
Pneumonia	91 (34.34%)	550 (21.05%)	641 (22.20%)	24.88	<0.001
Shock	34 (12.83%)	56 (2.13%)	90 (3.12%)	91.14	<0.001
Heart failure	18 (6.80%)	67 (2.56%)	85 (2.94%)	15.12	<0.001
Neoplastic disease	65 (24.53%)	688 (26.24%)	753 (26.08%)	0.37	0.545
Chronic renal insufficiency	11 (4.15%)	56 (2.14%)	67 (2.32%)	4.31	0.037
Pancreatitis	5 (1.89%)	20 (0.76%)	25 (0.87%)	3.54	0.049
COPD	7 (2.64%)	74 (2.82%)	81 (2.81%)	0.03	0.865
Hypokalemia	15 (5.66%)	68 (2.59%)	83 (2.87%)	8.11	<0.001
Hyponatremia	8 (3.02%)	62 (2.35%)	70 (0.24%)	0.44	0.509
Cirrhosis	8 (3.02%)	66 (2.52%)	74 (2.56%)	0.24	0.622
Hyperlipidemia	1 (0.38%)	26 (0.99%)	27 (0.94%)	0.05	0.827
Combination therapy					
NSAIDs	72 (27.17%)	552 (21.05%)	624 (21.61%)	5.31	0.021
ARB	28 (10.57%)	293 (11.17%)	321 (11.11%)	0.09	0.764
ACEI	14 (5.28%)	65 (2.48%)	79 (2.74%)	7.11	0.007
PPI	72 (27.17%)	1426 (54.39%)	1498 (51.89%)	33.24	<0.001
Aminoglycoside	55 (20.75%)	1013 (38.63%)	1068 (36.99%)	33.01	<0.001
Diuretics	190 (71.70%)	1092 (41.65%)	1282 (44.41%)	88.04	<0.001

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ARB, angiotensin II receptor inhibitor drugs; ACEI, angiotensin-converting enzyme inhibitor; PPI, proton pump inhibitor.

33.24; $p < 0.001$), aminoglycosides (χ^2, 33.01; $p < 0.001$), and diuretics (χ^2, 88.04; $p < 0.001$).

3.3 Relationships between AKI risk and other laboratory indicators

There are several common indicators that reflect kidney function in clinical practice, including sCr, uric acid, and bilirubin. We collected effective clinical indicators from patients in the AKI and non-AKI groups to evaluate the relationship between changes in kidney function and target drug use. As shown in Supplementary Tables S2, S3, several indicators manifested significant difference between AKI and non-AKI groups after using cefoperazone-sulbactam sodium—including sCr, white blood cell count, red blood cell count, platelet count, β-2 microglobulin, total bilirubin, and uric acid. After using mezlocillin-sulbactam sodium, the majority of the kidney function indicators showed significant differences between the two groups, except for uric acid.

3.4 Multivariate logistic regression analysis

A multiple logistic regression analysis of risk factors was additionally performed based on the variables with significant differences between the AKI and non-AKI groups. As shown in Table 5, in the cefoperazone-sulbactam sodium cohort several risk factors showed significant association with AKI in hospitalized patients, including cerebral apoplexy (OR, 1.39; 95% CI, 1.16–1.66), pneumonia (OR, 1.60; 95% CI, 1.35–1.90), sepsis (OR, 2.29; 95% CI, 1.25–4.16), heart failure (OR, 1.52; 95% CI, 1.17–1.95), combined use of PPI (OR, 1.41; 95% CI, 1.13–1.76), and the combined use of diuretics (OR, 3.29; 95% CI, 2.56–4.28). In the mezlocillin-sulbactam sodium cohort, the risk

TABLE 5 Multivariate logistic regression analysis of AKI associated with cefoperazone and sulbactam sodium in inpatients.

Variable	β	Wald value	OR and 95% CI	*p* value
Age	0.14	2.07	1.15 (0.95–1.38)	0.151
Comorbidity				
Cerebral apoplexy	0.33	13.69	1.39 (1.16–1.66)	<0.001
Anemia	0.06	0.24	1.06 (0.83–1.33)	0.621
Coronary heart disease	0.02	0.04	1.02 (0.83–1.24)	0.837
Pneumonia	0.47	29.98	1.60 (1.35–1.90)	<0.001
Sepsis	0.83	7.47	2.29 (1.25–4.16)	0.006
Heart failure	0.42	10.37	1.52 (1.17–1.95)	0.001
Neoplastic disease	−0.07	0.43	0.93 (0.76–1.14)	0.512
Hyponatremia	0.16	0.64	1.17 (0.78–1.71)	0.425
Combination therapy				
NSAIDs	−0.16	2.83	0.85 (0.71–1.02)	0.092
ARB	−0.15	1.90	0.85 (0.68–1.06)	0.168
Aminoglycosides	−0.02	0.03	0.98 (0.79–1.21)	0.870
PPI	0.35	9.57	1.41 (1.13–1.76)	0.002
Diuretics	1.19	82.61	3.29 (2.56–4.28)	<0.001
Laboratory Values				
sCr	0.01	85.93	1.01 (1.00–1.01)	<0.001
White blood cell count	0.04	47.83	1.04 (1.02–1.05)	<0.001
Red blood cell count	−0.18	11.87	0.83 (0.75–0.92)	0.001
Platelet count	−0.01	19.27	0.98 (0.97–1.00)	<0.001
β-2 microglobulin	0.02	4.25	1.01 (1.00–1.03)	0.039
Total bilirubin	0.01	14.76	1.01 (1.00–1.04)	<0.001
Intervention				
CRRT	1.76	37.53	5.82 (3.35–10.38)	<0.001

NSAIDs, nonsteroidal anti-inflammatory drugs; ARB, angiotensin II receptor inhibitor drugs; PPI, proton pump inhibitor; sCr, serum creatinine; CRRT, continuous renal replacement therapy.

factors showing a significant association with AKI in hospitalized patients included age (OR, 0.45; 95% CI, 0.27–0.71), combined use of aminoglycosides (OR, 0.48; 95% CI, 0.33–0.68), combined use of diuretics (OR, 1.91; 95% CI, 1.33–2.74), and continuous renal replacement therapy (OR, 4.77; 95% CI, 1.14–25.26) (Table 6).

3.5 Model building

The ROC curve for our model with 10-fold CV is illustrated in Figures 1A for all patients treated with cefoperazone and sulbactam sodium. The curve provided a favorable AUC value of 0.83 (95% CI, 0.82–0.84), with a specificity and sensitivity of 76.1% and 74.7%, respectively. The ROC curve for the model with 10-fold CV is shown in Figures 1B for the mezlocillin-sulbactam sodium group, and it provided an AUC value of 0.74 (95% CI, 0.71–0.77), with a specificity and sensitivity of 74.2% and 71.7%, respectively.

4 Discussion

The incidence of AKI in hospitalized patients using cefoperazone-sulbactam sodium in the present study was 12.73%, while the rate in hospitalized patients using mezlocillin-sulbactam sodium was 9.18%. These results were higher than the 2.0% reported by the First Hospital of Peking University in 2015 (Yang et al., 2015), but equivalent to the 11.6% reported by Southern Medical University in 2013 (Fang et al., 2010). The high incidence rate of acute kidney injury caused by cefoperazone-sulbactam sodium may be related to its wide application and combination of drugs. This was consistent with the conclusions of previous studies. In our previous study, we demonstrated that the incidence of AKI associated with diuretics was significantly higher than with the aforementioned two drugs at 14.26% (2589/18,148) (Zhang et al., 2022), which may be related to the large number of diuretic drugs used at our hospital. Although the clinical information in the previously published and

TABLE 6 Multivariate logistic regression analysis of AKI associated with mezlocillin sulbactam sodium in inpatients.

Variable	β	Wald value	OR and 95% CI	*p* value
Age	−0.80	10.87	0.45 (0.27–0.71)	0.001
Comorbidity				
Coronary heart disease	−0.03	0.02	0.96 (0.64–1.43)	0.879
Pneumonia	0.14	0.59	1.14 (0.80–1.61)	0.442
Shock	0.02	0.04	1.02 (0.83–1.24)	0.837
Anemia	−0.05	0.02	0.95 (0.45–1.87)	0.899
Heart failure	−0.51	1.34	0.59 (0.23–1.36)	0.247
Chronic renal insufficiency	0.29	0.61	1.34 (0.61–2.72)	0.436
Hypokalemia	0.92	2.76	2.52 (0.76–7.00)	0.096
Pancreatitis	−0.03	0.02	0.96 (0.64–1.43)	0.879
Combination therapy				
NSAIDs	−0.04	0.04	0.96 (0.65–1.38)	0.835
ACEI	0.42	1.38	1.52 (0.72–2.98)	0.240
Aminoglycosides	−0.73	15.80	0.48 (0.33–0.68)	<0.001
PPI	0.21	1.41	1.23 (0.87–1.75)	0.235
Diuretics	0.65	12.51	1.91 (1.33–2.74)	<0.001
Intervention				
CRRT	1.56	4.15	4.77 (1.14–25.26)	0.042
Mechanical ventilation	0.67	8.55	1.95 (1.23–3.04)	0.003
Laboratory Values				
White blood cell count	0.03	4.63	1.02 (1.00–1.05)	0.031
Red blood cell count	0.05	0.29	1.05 (0.87–1.27)	0.587
β-2 microglobulin	0.05	9.87	1.05 (1.02–1.08)	0.002
Platelet count	−0.01	2.90	0.99 (0.9–1.00)	0.089
Total bilirubin	0.01	0.01	1.00 (0.99–1.00)	0.953

AKI, acute kidney injury; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme inhibitor; PPI, proton pump inhibitor; CRRT, continuous renal replacement therapy.

current studies was collected from the same center (i.e., the First Affiliated Hospital of Shandong First Medical University), the populations were different between the two studies. The populations in the previous work were inpatients who received diuretics, while in the present study they were inpatients receiving cefoperazone-sulbactam or mezlocillin-sulbactam. We are therefore confident that these two studies reflect disparate populations. In a retrospective study conducted in a rural Ethiopian hospital (Riley et al., 2013), the authors discerned an AKI incidence of 20% during routine clinical care using the Acute Kidney Injury Network (AKIN) definition of AKI (Bellomo et al., 2004). Over 13 million people still experience AKI annually worldwide, and more than 1.7 million people have died from this disease (Riley et al., 2013), with a mortality rate as high as 50%–80% (Li et al., 2013) in patients with AKI who need dialysis. This phenomenon might reflect the tremendous investitures of time and effort in AKI by different countries and regions worldwide, with the economic pressure on developing countries and regions being particularly prominent.

Recently, Hodgson et al. summarized the efforts of predictive models and AKI alerts reported over recent decades and concluded that the early diagnosis of AKI can only improve outcomes when adequate interventions follow (Kurzhagen et al., 2020). Among the inpatients diagnosed with AKI in our cohort receiving cefoperazone-sulbactam sodium, the elderly group accounted for a large proportion of the entire AKI group (47.31%), while in the mezlocillin-sulbactam sodium cohort, middle-aged patients also accounted for a large proportion (54.34%). These data indicate that older individuals are more likely to develop AKI than younger individuals, potentially because elderly and middle-aged patients often possess multiple underlying diseases or complications during their hospitalization. Moreover, elderly patients often use multiple drugs simultaneously during hospitalization (Formica

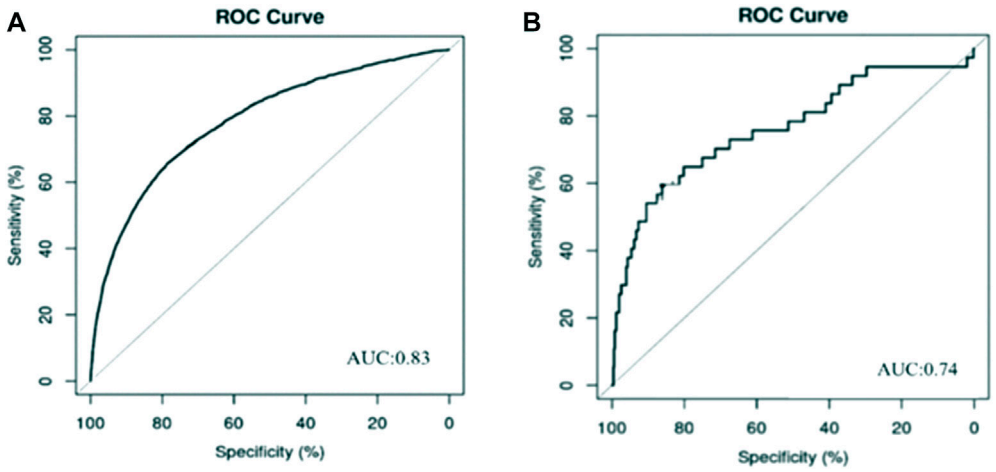

FIGURE 1
Prediction model of AKI associated with cefoperazone and sulbactam sodium and mezlocillin and sulbactam sodium. **(A)** Cefoperazone-sulbactam sodium; **(B)** Mezlocillin-sulbactam sodium Risk factors analysis and predictive model development of acute kidney injury in inpatients with cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium: a single-center retrospective study.

et al., 2018), increasing kidney burden. In contradistinction, the effects could be related to the physiologic decline in organ function, lower kidney reserve function, and lower compensatory capacity in elderly patients (Nash et al., 2002; Xue et al., 2006). The results from both cohorts in our study showed that patients in the AKI group exhibited longer hospital stays than those in the non-AKI group, and that the hospital expenses were also relatively high. These results may be due to the fact that patients with AKI are often more seriously ill, and thus the length of hospital stay is usually longer.

In addition to the effect of drugs on the kidney, the condition of the patients' underlying diseases during hospitalization and the condition of the patients' combined medication during hospitalization will also affect the diagnosis and prognosis of patients with AKI. Among the risk factors that induce AKI in patients, the combination of one or more underlying diseases, or the occurrence of complications during the treatment process are unfavorable for the occurrence and development of acute kidney injury. In our study, patients with hypertension, diabetes, coronary heart disease, heart failure, tumor disease and chronic kidney disease have adverse effects on patients with acute kidney injury caused by target drugs. Congruent with the literature (Pierson-Marchandise et al., 2017), the two drugs we suspected to be associated with AKI risk and analyzed in this study showed that the risk of AKI induction was particularly high in a multi-drug environment and exhibited commensurate increases with the increase in the number of prescription drugs. Cefoperazone-sulbactam sodium may have elevated the risk of AKI in patients with stroke, pneumonia, sepsis, heart failure, or other diseases. In current worldwide epidemiologic surveys conducted on AKI, although most authors have investigated the disease from a macro perspective—elucidating its epidemiologic characteristics and analyzing the risk factors leading to the disease—some specific groups have often been ignored (Dinh et al., 2021). Our results showed that there was a significant difference in kidney function indicators between AKI and non-AKI groups, and we perceived that after the use of target drugs the AKI group patients often manifested a significant increase in laboratory indicators compared with the non-AKI group patients. Therefore, it is important to provide early detection and timely intervention in AKI by paying particular attention to the laboratory indicators of kidney function of inpatients with the aforementioned underlying diseases. In addition to the effect of antibacterial drugs on AKI, our study depicted that the combination of aminoglycosides, diuretics, and proton-pump inhibitors increased the risk of AKI during hospitalization. This effect may have been due to the combined use of multiple drugs, changing the hemodynamics of the kidney and resulting in a reduction in glomerular filtration pressure or renal blood flow (or both) (Prieto-Garcia et al., 2016); this, in turn, culminated in a diminution in GFR, further augmenting the risk of AKI in patients. In previous studies, cephalosporins-related acute kidney injury accounted for 93.04% of all β lactams drugs. The main reason for the occurrence of acute kidney injury is that its metabolites accumulate in cells when excreted by the kidneys, resulting in nephrotoxicity (Bentley et al., 2010). Next are penicillins, which generally do not have direct nephrotoxicity. It causes acute interstitial nephritis by causing allergic reactions, leading to acute kidney injury (Pannu and Nadim, 2008; Bentley et al., 2010). Therefore, with respect to patients with AKI (especially for those individuals administered multiple drugs and possessing underlying disease), we recommend that clinicians give closer attention to enhance patient safety and to optimize pharmacotherapy.

Although there are many AKI-prediction tools offered in previous studies, there are few parallel tools that detect AKI risk in clinical settings. In 2016, Koyner et al. (Koyner et al., 2016) developed a model for AKI risk prediction based on a non-ICU patient cohort, with an AUC ROC of 0.74. However, additional data such as vital signs and laboratory indicators were not included in their study. Our AUC values for the AKI-prediction models associated with cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium were 0.83 (95% CI, 0.82–0.84) and 0.74 (95% CI, 0.71–0.77), respectively. Thus, compared with previous studies, the performance of our model was superior and the variables included were more extensive.

In our previous study, we evaluated AKI in hospitalized patients who underwent diuretic treatment, while in the present study we focused on two other drugs, cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium. Since cefoperazone-sulbactam and mezlocillin-sulbactam are widely used to prevent severe infection caused by lactamase microorganisms worldwide, we posit that it would be of great clinical significance to analyze the risk factors involved in AKI and to develop predictive models for AKI in inpatients receiving these medications.

5 Limitations of this study

There were several limitations for our study. Firstly, these parameters selected in the study are associated with an increased risk of developing acute kidney injury regardless of the etiology. Therefore, it is difficult to distinguish to what extent this model actually predicts the development of AKI. Besides, in this study, the diagnosis of acute kidney injury in our hospital was mostly completed through blood creatinine. Because in clinical practice, continuous long-term urine volume monitoring of patients is not practical and cannot accurately capture urine volume changes that meet the guidelines for acute kidney injury.

6 Conclusion

We herein conducted a single-center retrospective study. The incidence of cefoperazone-sulbactam sodium-related AKI was 12.73% (1116/8767), and the rate for mezlocillin-sulbactam sodium-related AKI was 9.18% (265/2887). We screened out several risk factors for cefoperazone-sulbactam sodium, including the presence of underlying diseases (e.g., cerebral apoplexy, pneumonia, sepsis, and heart failure), and the combined use of PPIs and diuretics. For mezlocillin-sulbactam sodium, several risk factors were also proposed that included older age, combined use of aminoglycosides and diuretics, and the receipt of continuous kidney replacement therapy and mechanical ventilation during hospitalization. Based on the meaningful variables assessed, we developed logistic regression models for AKI risk in hospitalized patients who underwent cefoperazone-sulbactam and mezlocillin-sulbactam sodium treatments. The AUC of the cefoperazone-sulbactam predictive model was 0.83 (95% CI, 0.82–0.84), and the AUC for the predictive model reflecting mezlocillin-sulbactam sodium use was 0.74 (95% CI, 0.71–0.77).

We posit based upon our research results that fully evaluating the risk factors of hospitalized patients before using cefoperazone-sulbactam sodium and mezlocillin-sulbactam sodium would reduce the incidence of AKI. We suggest that it is also necessary to improve the awareness of medical staff and patients regarding AKI.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of First Affiliated Hospital of Shandong First Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XL contributed to conception and design of the work. RZ and LG collected the datasets and carried out the experiments. PC, XH, and WL collated the data and performed the analysis. RZ and LG interpreted the results, performed the analysis and wrote 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.2023.1170987/full#supplementary-material

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Characteristic analysis of adverse reactions of five anti-TNFα agents: a descriptive analysis from WHO-VigiAccess

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Introduction: Tumor necrosis factor (TNF) inhibitors (adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol) have revolutionized the treatment of severe immune-mediated inflammatory diseases, including rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. This study assessed adverse drug reactions (ADRs) after the use of TNFα inhibitors in VigiAccess of the World Health Organization (WHO) and compared the adverse reaction characteristics of five inhibitors to select the drug with the least risk for individualized patient use.

Methods: The study was a retrospective descriptive analysis method in design. We sorted out five marketed anti-TNFα drugs, and their ADR reports were obtained from WHO-VigiAccess. Data collection included data on the age groups, sex, and regions of patients worldwide covered by ADR reports, as well as data on disease systems and symptoms caused by ADRs recorded in annual ADR reports and reports received by the WHO. By calculating the proportion of adverse reactions reported for each drug, we compared the similarities and differences in adverse reactions for the five drugs.

Results: Overall, 1,403,273 adverse events (AEs) related to the five anti-TNFα agents had been reported in VigiAccess at the time of the search. The results show that the 10 most commonly reported AE manifestations were rash, arthralgia, rheumatoid arthritis, headache, pneumonia, psoriasis, nausea, diarrhea, pruritus, and dyspnea. The top five commonly reported AE types of anti-TNFα drugs were as follows: infections and infestations (184,909, 23.0%), musculoskeletal and connective tissue disorders (704,657, 28.6%), gastrointestinal disorders (122,373, 15.3%), skin and subcutaneous tissue disorders (108,259, 13.5%), and nervous system disorders (88,498, 11.0%). The preferred terms of myelosuppression and acromegaly were obvious in golimumab. Infliximab showed a significantly higher ADR report ratio in the infusion-related reaction compared to the other four inhibitors. The rate of ADR reports for lower respiratory tract infection and other infections was the highest for golimumab.

Conclusion: No causal associations could be established between the TNFα inhibitors and the ADRs. Current comparative observational studies of these inhibitors revealed common and specific adverse reactions in the ADR reports of the WHO received for these drugs. Clinicians should improve the rational use of these high-priced drugs according to the characteristics of ADRs.

KEYWORDS

adverse drug reaction, TNFα inhibitors, pharmacovigilance, spontaneous reporting, VigiAccess of the WHO

Introduction

Tumor necrosis factor (TNF)α is a proinflammatory, multifunctional cytokine that is synthesized by various cells, including activated monocytes, macrophages, and T cells (Darrigade et al., 2017). TNFα has been shown to play an essential role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PSA), and ankylosing spondylitis (AS). Therefore, drugs targeting TNF have been developed to neutralize the effects of these pro-inflammatory cytokines (Jang et al., 2021). Anti-TNFα drugs are usually well-tolerated; however, there have been reports of many potentially serious adverse effects. Long-term use of anti-TNFα agents has been associated with the risk of serious infections, malignancies, skin and soft tissue infections, and tuberculosis (Kroesen et al., 2003; Shivaji et al., 2019). A meta-analysis showed that treatment with anti-TNFα agents increased the risk of serious infections (OR: 1.72, 95% CI: 1.56–1.90, $p < 0.00001$) and an increase in cancer risk (OR: 1.36, 95% CI: 1.20–1.53, $p < 0.00001$), whereas the risk of tuberculosis was not significantly different (Li et al., 2021). Although there was no consensus on the risk of infection associated with anti-TNFα treatments in published clinical trials, post-marketing surveillance and retrospective studies have shown an increased risk of tuberculosis and other granulomatous infections (Wallis et al., 2004; Godfrey and Friedman, 2019; Athimni et al., 2022; Doughty et al., 2023). A meta-analysis carried out in 2006 showed an increase in the risk of malignancies and serious infections in patients treated with infliximab and adalimumab, where a higher dose was associated with increased cancer risk (Galloway et al., 2011). Despite the rigor of pre-marketing drug trials, the safety of medicines is not completely understood from pre-authorization clinical trial data as these trials are conducted in controlled settings different from settings of real-world use (Gagliardi et al., 2022). In particular, biological agents such as TNFα inhibitors, which have been on the market for a long time, have a large population base and a wide range of use, so safety research based on a large number of real-world data is more appropriate and valuable. Therefore, adverse drug reactions (ADRs) associated with the TNFα inhibitors need to be further characterized from spontaneous reports in pharmacovigilance databases. More significantly, there are no studies to compare the similarities and differences of ADRs produced by these drugs.

Despite the intrinsic limitations, spontaneous reporting systems represent a valuable source to obtain real-world data about the safety profile of drugs and vaccines, compare therapeutic options, and gain insight into the potential mechanisms of ADRs (Hazell and Shakir, 2006). Spontaneous reporting systems have been the backbone of pharmacovigilance since their introduction in the 1960s. The main aim of spontaneous reporting is the early detection of previously unrecognized ADRs. In addition, spontaneous reporting can also be useful for obtaining information on new aspects of known associations between drugs and ADRs (Srba et al., 2012). The Uppsala Monitoring Center (UMC), on behalf of the World Health Organization (WHO)'s Programme for International Drug Monitoring (PIDM), brings together safety data from all corners of the world. As of the end of 2018, the UMC had received and stored over 20 million ADR reports from more than 170 countries in VigiBase, which is a worldwide voluntary reporting program. Since 2015, data stored in VigiBase can be freely accessed by the public via VigiAccess (Watson et al., 2018; Habarugira and Figueras, 2021). The VigiAccess database supports searching by the trade name of the drug, but the database will identify the active ingredient it contains and display the results of its ADR reports according to the active ingredient. This study searched for five biological TNFα blockers approved by the Food and Drug Administration (FDA): adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol.

The five TNFα inhibitors showed similar efficacy profiles, although recent data show that adalimumab seems to be most effective in geriatric patients, while etanercept is associated with a lower risk of developing *tuberculosis* (Bonek et al., 2021). Therefore, clinicians are often required to tailor treatment decisions based on the risk of adverse events for the individual patient. To compare the differences in the occurrence of these five anti-TNFα-related adverse reactions, we conducted a descriptive study of spontaneous reported adverse reactions in the VigiAccess database and compared the reported rates of adverse reactions caused by these five drugs.

Materials and methods

Drug sample

Table 1 shows the five anti-TNFα agents that we have studied that are available for clinical use. Humanized anti-TNF-α mAbs include Humira® (adalimumab), Simponi® (golimumab), and Cimzia® (certolizumab pegol). Remicade® (infliximab) was the first chimeric anti-TNF-α mAb for the treatment of Crohn's disease. The use of Remicade was then extended to other therapeutic areas, including RA (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, pediatric Crohn's disease, plaque psoriasis, and pediatric ulcerative colitis. The first Ab fusion protein, Enbrel® (etanercept), was approved by the FDA for clinical use in patients with RA in 1998. It comprises the Fc region of Ab conjugated with TNF-receptor 2 (TNFR2). The approval of etanercept opened up the way for the development of several recombinant protein methodologies based on the fusion of various proteins to different antibody regions, including single-chain variable fragments (scFvs), heavy-chain Abs (hcAbs), single-chain Abs (scAbs), and antigen-binding fragments (Fabs) (Leone et al., 2023). It can be seen in Table 1 that their structures are not completely the same, and the sources of synthesis are also different. The earliest launch time of these five drugs is more than 10 years, and they are currently among the world's best-selling drugs, and all of them are marketed in China.

By December 2022, there were thirteen adalimumab biosimilars, seven infliximab biosimilars, and three etanercept

TABLE 1 General information of five anti-TNFα inhibitors.

Drug name and brand name	Structure	Main conditions	First marketing time	Biosimilars
Adalimumab–Humira	Human monoclonal antibodies	Rheumatoid arthritis and ankylosing spondylitis	2002	Amgevita, Cyltezo, Imraldi, Solymbic, Yusimry, Halimatoz, Hefiya, Hyrimoz, Idacio, Kromeya, Hadlima, Abrilada, and Hulio
Infliximab–Remicade	Chimeric monoclonal antibody	Rheumatoid arthritis, ankylosing spondylitis, and ulcerative colitis	1998	Remsima, Inflectra, Flixabi, Renflexis, Ixifi, Zessly, and Avsola
Etanercept–Enbrel	Receptor construct	Psoriasis, rheumatoid arthritis, and ankylosing spondylitis	1998	Erelzi, Benapali, and Eticovo
Golimumab–Simponi	Human monoclonal antibodies	Rheumatoid arthritis, ankylosing spondylitis, and ulcerative colitis	2009	-
Certolizumab pegol–Cimzia	Fab' fragment of humanized monoclonal antibody	Rheumatoid arthritis	2008	-

biosimilars (Table 1). There was no increase in adverse events (AEs) in patients treated with adalimumab biosimilars and concomitant methotrexate (MTX) therapy compared to Humira and MTX therapy in patients with RA (Cohen et al., 2017; Fleischmann et al., 2018). Studies have shown that there are no differences in safety, immunogenicity, and pharmacokinetics between infliximab and infliximab biosimilars (Subedi et al., 2019). Only proven similar efficacy and safety in short- and long-term studies allow switching between originator and biosimilar products. The current time available for comparative research is limited (Agca et al., 2017; Kameda et al., 2020).

Data sources

WHO-VigiAccess was searched on 2 January 2022 for all reported adverse events following the introduction of anti-TNFα agents. The login URL is https://www.vigiaccess.org. All study drugs were identified by the generic name. Data were captured among age groups, sex, report year, and continents of the world by WHO-VigiAccess. Descriptive data were calculated using Excel 2019 version.

WHO-VigiAccess is a free-access portal to the PIDM database allowing retrieval of medicinal products' safety reports received by the UMC. The definition relied on system organ class (SOC) and preferred terms (PTs) by the Medical Dictionary for Regulatory Activities (MedDRA). Thus, records on each anti-TNFα drug were retrieved, and all individual AEs based on MedDRA SOC and PT levels recorded were identified to describe the spectrum of toxicities. Reporting terms used in MedDRA were derived from several dictionaries, including the WHO Adverse Reaction Terminology (WHO-ART), among others (Sultana et al., 2020). A total of 27 items were classified by SOC, of which 20 items directly related to disease symptoms were selected for analysis. In the present study, we focused on the PTs, the level used in the VigiBase database publicly accessible information via WHO-VigiAccess.

To study the outcomes of detected safety signals, we grouped them using outcome code to produce the three severe categories: death, hospitalization, and major events comprising life-threatening events, disability, and congenital anomaly.

Statistical analysis

The study followed a retrospective quantitative study design. Excel descriptive analysis was used to analyze the characteristics of the victims of adverse reactions to the five drugs. The ADR symptom number of each drug divided by the total number of ADR reports was defined as the ADR report rate of the drug. Common ADRs of each drug refer to the symptoms of the top 20 ADR report rate. The rate of reported ADR symptoms for each drug was calculated, and a descriptive comparative analysis was performed. Frequencies and percentages were used to categorize descriptive variables.

Results

Description of the studied cases

The earliest reports of adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol adverse reactions were received in the WHO-VigiAccess database in 2001, 1999, 1999, 2008, and 2003, respectively. By 2021, the WHO had received a total of 591,705, 172,961, 542,647, 38,629, and 57,331 ADR reports for these five drugs, with a total of 1,403,273 reports. The numbers of adverse events covered in these ADR reports were 840,417 cases of adalimumab, 280,811 cases of infliximab, 654,269 cases of etanercept, 4,895 cases of golimumab, and 78,388 cases of certolizumab pegol. Among the 1,403,273 reports related to the five anti-TNFα agents shown in Table 2, except for 73,803 cases in which the sex was unknown, the number of women (916,873) who had ADRs was significantly greater than that of men (412,597), and the female–male ratio was 2.22:1 with a big discrepancy. Excluding the unknown age reports, most of the age groups with the highest reported rates are between 45 and 64 years. Most of the AEs were reported from the Americas (77.94%). Table 2 also lists the reporting years for each of the studied drugs.

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TABLE 2 Characteristics of ADR reports of five anti-TNFα drugs.

	Adalimumab	Infliximab	Etanercept	Golimumab	Certolizumab pegol
Number of ADR reports	591,705	172,961	542,647	38,629	57,331
Female	379,621 (64.2%)	94,131 (54.4%)	376,547 (69.4%)	25,123 (65.0%)	41,451 (72.3%)
Male	191,141 (32.3%)	62,859 (36.3%)	134,050 (24.7%)	11,425 (29.6%)	13,122 (22.9%)
Unknown	20,943 (3.5%)	15,971 (9.2%)	32,050 (5.9%)	2,081 (5.4%)	2,758 (4.8%)
<18	10,908 (1.8%)	7,587 (4.4%)	11,824 (2.2%)	220 (0.6%)	406 (0.7%)
18–44	107,447 (18.2%)	45,770 (26.5%)	73,786 (13.6%)	7,147 (18.5%)	10,948 (19.1%)
45–64	149,288 (25.2%)	42,258 (24.4%)	198,184 (36.5%)	12,867 (33.3%)	12,863 (22.4%)
65–74	47,616 (8.5%)	14,022 (8.1%)	67,265 (12.4%)	4,538 (11.8%)	4,326 (7.6%)
>75	18,482 (3.1%)	5,771 (3.3%)	27,566 (5.1%)	1,904 (4.9%)	1,735 (3.0%)
Unknown	257,964 (43.6%)	57,553 (33.3%)	164,022 (30.2%)	11,953 (30.9%)	27,053 (47.2%)
Africa	1,369 (0.2%)	760 (0.4%)	725 (0.1%)	151 (0.4%)	9 (→)
Americas	445,918 (75.4%)	118,881 (68.7%)	467,392 (86.1%)	21,974 (56.9%)	39,517 (68.9%)
Asia	9,484 (1.6%)	9,962 (5.8%)	5,582 (5.4%)	2,094 (5.4%)	1,241 (2.2%)
Europe	131,479 (22.2%)	40,717 (23.5%)	67,945 (35.7%)	13,804 (35.7%)	16,274 (28.4%)
Oceania	3,455 (0.6%)	2,641 (1.5%)	1,003 (0.2%)	606 (1.6%)	290 (0.5%)
Before 2010	57,603 (9.7%)	35,133 (20.3%)	85,186 (15.7%)	184 (0.5%)	3,313 (5.8%)
2011	21,489 (3.6%)	10,656 (6.2%)	26,142 (4.8%)	537 (1.4%)	5,502 (9.6%)
2012	27,922 (4.7%)	12,051 (7.0%)	35,429 (6.5%)	1,260 (3.3%)	1,123 (2.0%)
2013	7,695 (1.3%)	8,453 (4.9%)	25,420 (4.7%)	1,211 (3.2%)	873 (1.5%)
2014	73,612 (12.4%)	7,371 (4.3%)	55,061 (10.2%)	1,204 (3.1%)	1,696 (3.0%)
2015	49,219 (8.3%)	12,570 (7.3%)	68,668 (12.7%)	4,390 (3.1%)	3,180 (5.6%)
2016	84,741 (14.3%)	25,867 (15.0%)	44,654 (8.2%)	4,654 (11.4%)	5,879 (10.3%)
2017	37,432 (6.3%)	12,761 (7.4%)	59,387 (10.9%)	4,243 (12.1%)	3,525 (6.2%)
2018	61,948 (10.5%)	17,325 (10.0%)	60,154 (11.1%)	6,591 (11.0%)	6,506 (11.4%)
2019	66,396 (11.2%)	13,265 (7.7%)	45,022 (8.3%)	6,623 (17.1%)	6,017 (10.5%)
2020	53,381 (9.0%)	7,158 (4.1%)	18,163 (3.4%)	3,727 (9.7%)	12,012 (21.0%)
2021	48,669 (8.2%)	9,972 (5.8%)	18,168 (3.4%)	3,831 (9.9%)	7,505 (13.1%)

Distribution of 20 SOCs of five anti-TNFα drugs

Table 3 shows the report rates of 20 SOCs of five anti-TNFα drugs. Adalimumab-related nervous system disorders and skin and subcutaneous tissue disorders were significantly higher than the disorders of the other four TNFα inhibitors. The rates of ADR reports of infliximab-related gastrointestinal disorders, cardiac disorders, benign, malignant, and unspecified neoplasms, vascular disorders, and respiratory, thoracic, and mediastinal disorders were significantly higher than those of the other four TNFα inhibitors. Higher rates of ADRs were reported for musculoskeletal and connective tissue disorders in etanercept, as well as infections and infestations in golimumab.

The top five commonly reported AE types of anti-TNFα drugs were as follows: infections and infestations (184,909, 23.0%), musculoskeletal and connective tissue disorders (704,657, 28.6%), gastrointestinal disorders (122,373, 15.3%), skin and subcutaneous tissue disorders (108,259, 13.5%), and nervous system disorders (88,498, 11.0%). The rate of ADRs reported more than 10% in the SOC, and there were four in adalimumab, five in infliximab, three in etanercept, two in golimumab, and four in certolizumab pegol.

Most common ADRs of five anti-TNFα drugs

The 20 most commonly reported ADRs of the five drugs are presented in Table 4, and the manifestations listed were

TABLE 3 ADR number and report rate of 20 SOCs of five anti-TNFα drugs.

System organ classes	Adalimumab (N = 591705)	Infliximab (N = 172961)	Etanercept (N = 542647)	Golimumab (N = 38629)	Certolizumab pegol (N = 57331)
Blood and lymphatic system disorders	9,436 (1.59%)	3,918 (2.26%)	7,403 (1.36%)	566 (1.47%)	739 (1.29%)
Cardiac disorders	14,795 (2.50%)	7,695 (4.45%)	8,920 (1.64%)	831 (2.15%)	1,157 (2.02%)
Congenital, familial, and genetic disorders	1,155 (0.19%)	476 (0.28%)	901 (0.17%)	60 (0.16%)	143 (0.25%)
Ear and labyrinth disorders	5,658 (0.96%)	1,074 (0.62%)	5,239 (0.97%)	252 (0.65%)	393 (0.69%)
Endocrine disorders	1860 (0.31%)	552 (0.32%)	1,182 (0.22%)	103 (0.27%)	116 (0.20%)
Eye disorders	16,608 (2.81%)	4,192 (2.42%)	14,422 (2.66%)	817 (2.11%)	1,228 (2.14%)
Gastrointestinal disorders	95,600 (16.16%)	35,274 (20.39%)	42,005 (7.74%)	3,603 (9.32%)	9,219 (16.08%)
Hepatobiliary disorders	6,616 (1.12%)	3,183 (1.84%)	3,602 (0.64%)	365 (0.94%)	525 (0.92%)
Immune system disorders	13,119 (2.22%)	10,015 (5.79%)	14,347 (2.64%)	857 (2.22%)	1,616 (2.82%)
Infections and infestations	127,859 (21.61%)	42,750 (24.72%)	111,993 (20.64%)	10,796 (27.95%)	15,192 (26.50%)
Metabolism and nutrition disorders	15,241 (2.58%)	4,116 (2.38%)	7,684 (1.42%)	541 (1.40%)	1,025 (1.79%)
Musculoskeletal and connective tissue disorders	100,743 (17.02%)	21,237 (12.28%)	106,799 (19.68%)	5,221 (13.52%)	8,222 (14.34%)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	22,364 (3.78%)	13,143 (7.60%)	16,972 (3.13%)	1,658 (4.29%)	1,773 (3.09%)
Nervous system disorders	68,527 (11.58%)	17,238 (9.97%)	53,879 (9.93%)	2,966 (7.68%)	5,244 (9.15%)
Psychiatric disorders	26,879 (4.54%)	4,591 (2.65%)	19,026 (3.51%)	1,018 (2.64%)	1,866 (3.25%)
Renal and urinary disorders	11,579 (1.96%)	3,900 (2.25%)	6,615 (1.22%)	582 (1.51%)	958 (1.67%)
Reproductive system and breast disorders	7,352 (1.24%)	1,616 (0.93%)	4,108 (0.76%)	272 (0.70%)	545 (0.95%)
Respiratory, thoracic, and mediastinal disorders	48,280 (8.16%)	19,083 (11.03%)	42,051 (7.75%)	2,160 (5.59%)	3,928 (6.85%)
Skin and subcutaneous tissue disorders	84,545 (14.29%)	23,545 (13.61%)	69,874 (12.88%)	3,558 (9.21%)	7,621 (13.29%)
Vascular disorders	17,960 (3.04%)	11,837 (6.84%)	10,631 (1.96%)	964 (2.50%)	1,381 (2.41%)

preferred terms from within the SOC. The common ADRs of all five TNFα inhibitors were rash, arthralgia, rheumatoid arthritis, headache, pneumonia, psoriasis, nausea, diarrhea, and pruritus. Infliximab showed a significantly higher ADR report rate in the infusion-related reaction compared to the other four inhibitors. The rate of ADR reports of lower respiratory tract infection and other infections in golimumab ranks at the top. Most of the AEs in the top 20 commonly reported were minor events that are self-limiting. However, there were some noteworthy events, and these were Crohn's disease, rheumatoid arthritis, and all infections (pneumonia, urinary tract infection, and nasopharyngitis).

Serious AEs of five anti-TNFα drugs

Through WHO-VigiAccess, we can also find major adverse events of anti-TNFα drugs, including life-threatening events, disability, and congenital malformations. The proportion of serious adverse reactions that occurred for certolizumab pegol, infliximab, golimumab, adalimumab, and etanercept was 1.79%, 1.51%, 1.17%, 1.16%, and 1.01%, respectively (Figure 1).

The same and different points of common ADRs of five anti-TNFα drugs

By comparing the top 20 ADRs reported by each anti-TNFα drug in the SOCs, a total of 66 same signals were found at PTs for the five inhibitors. All common signals were sorted into Table 5. The SOC that contained the most adverse signals was infections and infestations, and the top five reports were nasopharyngitis, pneumonia, urinary tract infection, sinusitis, and lower respiratory tract infection. The second was gastrointestinal disorders, and the top five reports were nausea, diarrhea, vomiting, constipation, and Crohn's disease.

When comparing the top 20 ADRs reported for each anti-TNFα drug in the SOCs, all the five TNFα inhibitors had different PTs of

TABLE 4 Top 20 ADRs of anti-TNFα drugs.

Adalimumab (N = 591705)		Infliximab (N = 172961)		Etanercept (N = 542647)		Golimumab (N = 38629)		Certolizumab pegol (N = 57331)	
ADR	Report rate %	ADR	Report rate %	ADR	Report rate %	ADR	Report rate %	ADR	Report rate %
Arthralgia	5.07	Infusion-related reaction	6.05	Arthralgia	5.52	Lower respiratory tract infection	3.44	Rash	3.57
Headache	3.56	Dyspnea	4.71	Rheumatoid arthritis	4.11	Rheumatoid arthritis	3.17	Arthralgia	3.44
Psoriasis	3.33	Crohn's disease	4.07	Psoriasis	3.96	Pneumonia	3.09	Rheumatoid arthritis	3.28
Nasopharyngitis	3.12	Pneumonia	3.75	Pain in extremity	3.53	Arthralgia	2.71	Crohn's disease	3.04
Nausea	3.01	Arthralgia	3.09	Headache	3.36	Nasopharyngitis	2.54	Nausea	2.90
Diarrhea	2.76	Abdominal pain	2.87	Nasopharyngitis	2.98	Infection	2.35	Headache	2.87
Rash	2.58	Nausea	2.85	Sinusitis	2.26	Rash	1.99	Diarrhea	2.84
Crohn's disease	2.58	Rash	2.51	Nausea	2.14	Headache	1.82	Nasopharyngitis	2.80
Pain in extremity	2.56	Pruritus	2.32	Cough	2.10	Urinary tract infection	1.61	Infection	2.71
Rheumatoid arthritis	2.05	Headache	2.23	Joint swelling	1.88	Nausea	1.58	Pneumonia	2.50
Abdominal pain	1.90	Diarrhea	2.14	Pneumonia	1.85	Influenza	1.44	Psoriasis	2.15
Pneumonia	1.87	Flushing	2.05	Rash	1.76	Colitis ulcerative	1.41	Abdominal pain	2.10
Pruritus	1.86	Vomiting	1.97	Lower respiratory tract infection	1.62	Psoriasis	1.40	Urinary tract infection	1.96
Cough	1.79	Hypersensitivity	1.90	Pruritus	1.62	Diarrhea	1.34	Pruritus	1.86
Infection	1.71	Urticaria	1.89	Infection	1.58	Alopecia	1.18	Sinusitis	1.72
Dizziness	1.71	Colitis ulcerative	1.80	Back pain	1.48	Pain in extremity	1.15	Lower respiratory tract infection	1.68
Dyspnea	1.56	Erythema	1.73	Diarrhea	1.39	Pruritus	1.14	Dizziness	1.61
Vomiting	1.56	Psoriasis	1.58	Dizziness	1.38	Dyspnea	1.05	Influenza	1.44
Back pain	1.55	Dizziness	1.34	Musculoskeletal stiffness	1.35	Dizziness	1.02	Dyspnea	1.42
Sinusitis	1.51	Cough	1.24	Influenza	1.23	Joint swelling	0.99	Pain in extremity	1.41

ADR in congenital, familial, and genetic disorders (Table 6). The number of distinctive symptoms for adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol was three, six, five, four, and seven, respectively.

Discussion

The SRS has been utilized in pharmacovigilance for safety assessment of suspected AEs due to inherent limitations of clinical trials, such as stringent trial design, strict enrollment criteria, relatively small sample size, and limited follow-up duration. Furthermore, study data from clinical trials may not fit the real world where patients and comorbidities are heterogenous. The SRS plays a major part in signal identification (Lindquist et al., 2000). At present, research on the safety signals of most drugs mainly comes from three main databases: the EudraVigilance Data Analysis System (EVDAS), Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), and WHO-VigiBase® (Vogel et al., 2020). WHO-VigiAccess was launched by the WHO in 2015 to provide public access to information in VigiBase®, the WHO global database of reported potential side effects of medicinal products. Data mining of the WHO-VigiAccess database would provide previously unknown drug–AE associations and some well-established clinical ones (Yamoah et al., 2022). The present study was conducted to assess the post-market adverse events associated with TNFα inhibitors in the WHO-VigiAccess database.

Data from WHO-VigiAccess show that 70% of AEs associated with the five TNFα inhibitors are reported from the Americas, followed by Europe. Poor reporting of AEs from the African and Oceania continents had been commonly observed in other studies (Alawadhi et al., 2012; Gidudu et al., 2020). In South Africa, the lack

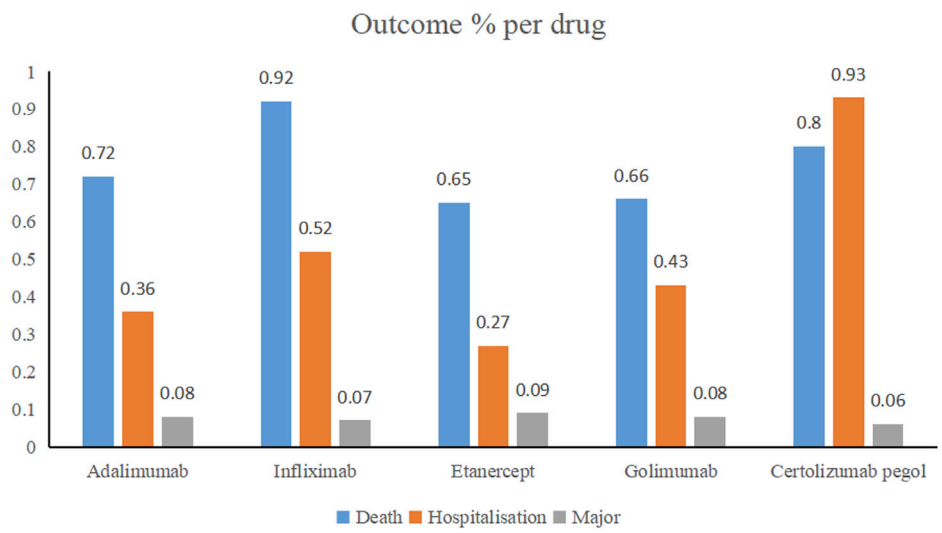

FIGURE 1
Outcomes for serious adverse events associated with anti-TNFα drugs at the level of preferred terms (major events comprising life-threatening events, disability, and congenital anomaly).

TABLE 5 Same ADRs among five anti-TNFα drugs.

System organ classes	ADRs	Signal N
Blood and lymphatic system disorders	Anemia, lymphadenopathy, thrombocytopenia, leukopenia, and neutropenia	5
Cardiac disorders	Myocardial infarction, palpitations, tachycardia, and atrial fibrillation	4
Congenital, familial, and genetic disorders	Atrial septal defect and congenital anomaly	2
Ear and labyrinth disorders	Vertigo and ear pain	2
Endocrine disorders	Hypothyroidism, thyroid disorder, and adrenal insufficiency	3
Eye disorders	Visual impairment, blurred vision, and cataract	3
Gastrointestinal disorders	Nausea, diarrhea, vomiting, constipation, abdominal pain, and Crohn's disease	6
Hepatobiliary disorders	Liver disorder, cholelithiasis, and hepatitis	3
Immune system disorders	Hypersensitivity and immune system disorder	2
Infections and infestations	Nasopharyngitis, pneumonia, urinary tract infection, sinusitis, lower respiratory tract infection, influenza, herpes zoster, and bronchitis	8
Metabolism and nutrition disorders	Decreased appetite, diabetes mellitus, dehydration, and fluid retention	4
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity, back pain, and joint swelling	4
Benign, malignant, and unspecified neoplasms	Skin cancer, breast cancer, basal cell carcinoma, and malignant neoplasm	4
Nervous system disorders	Headache and dizziness	2
Renal and urinary disorders	Nephrolithiasis, renal failure, and dysuria	3
Respiratory, thoracic, and mediastinal disorders	Cough, dyspnea, oropharyngeal pain, and rhinorrhea	4
Skin and subcutaneous tissue disorders	Psoriasis, rash, and pruritus	3
Vascular disorders	Hypertension, hemorrhage, thrombosis, and flushing	4

TABLE 6 Different ADRs among five anti-TNFα drugs.

System organ classes	Adalimumab	Infliximab	Etanercept	Golimumab	Certolizumab pegol
Blood and lymphatic system disorders				Myelosuppression	
Cardiac disorders	Heart valve incompetence	Acute coronary syndrome	Cardiac valve disease		Sinus tachycardia
Congenital, familial, and genetic disorders	Type IV hyperlipidemia	Gilbert's syndrome, congenital foot malformation, and hemophilia	VACTERL syndrome	Osteogenesis imperfecta	Clinodactyly
Endocrine disorders				Acromegaly	
Eye disorders					Swelling of the eyelid and blepharospasm
Gastrointestinal disorders			Toothache		
Pregnancy, puerperium, and perinatal conditions		Placenta previa	Induced labor		Twin pregnancy and placenta previa
Metabolism and nutrition disorders	Reduced fluid intake	Hypomagnesemia	Type 1 diabetes mellitus	Hypovolemia	
Immune system disorders					Iodine allergy

of medical knowledge of biologic medicines among health professionals, coupled with high costs and complex procurement processes, increased barriers to the use of these drugs (Hajjaj-Hassouni et al., 2012; Martelli et al., 2017; Kvamme et al., 2020). Although the use of TNFα inhibitors to treat rheumatoid arthritis is more common among the South African doctors surveyed, accounting for about half of the prescriptions, it can be seen from this study that the number of reported adverse events in Africa is still very low (Mocke-Richter et al., 2021). This may be due to poor quality social mobilization, inadequate accessibility of adverse reaction reporting systems, and low information system coverage.

AEs were more commonly reported in females than males. Except for infliximab, the 45–64 age group had the most adverse reactions after anti-TNFα treatment. The reason for this finding is that the inhibitors of TNFα, such as infliximab, etanercept, and adalimumab, are now second line to methotrexate in RA (Papadopoulos et al., 2019). Golimumab and certolizumab pegol can be combined with methotrexate in the treatment of moderate-to-severe active RA with poor efficacy of disease-modifying anti-rheumatic drugs (DMARDs, including methotrexate) (Smolen et al., 2023). Real-world surveys based on the FAERS database found that more than half of anti-TNF therapy was used to treat rheumatoid arthritis. RA affects at least twice as many women as men, and although it can occur at any age, the peak incidence is at the age of 50 years (Deepak et al., 2013).

An AE with a reporting rate of ≥1% is usually considered common (Chen et al., 2019). Therefore, the serious adverse events, including life-threatening events, disabling, and congenital malformations, of the five anti-TNF α drugs are not common. The most common ADRs for all five TNFα inhibitors were rash, arthralgia, rheumatoid arthritis, headache, pneumonia, psoriasis, nausea, diarrhea, and pruritus.

Both patients with RA and patients with IBD have a higher incidence and severity of infectious diseases compared to the general population. The increased risk of infections in these patients seems to be attributed mainly to immunosuppressive therapies (Calvet et al., 2021). Treatment with systemic corticosteroids is associated with a very high risk of serious infection. The risk of infection also significantly increases when anti-TNFα therapies are combined (Beaugerie and Kirchgesner, 2019; Zabana et al., 2019; Singh et al., 2020). Through a review of the English literature over the last 30 years, experts noted an increased risk of bacterial and mycobacterial infections in patients with arthritis treated with TNF inhibitors compared to non-biologic agents (Chiu and Chen, 2020).

As of November 2016, the FAERS database showed that the top five adverse reactions related to etanercept infections were nasopharyngitis, sinusitis, bronchitis, pneumonia, and influenza, accounting for 13.98%, 10.22%, 6.90%, 6.07%, and 5.54%, respectively. The top five adverse reactions of adalimumab-related infections were nasopharyngitis (15.50%), sinusitis (7.83%), pneumonia (6.23%), bronchitis (5.60%), and influenza (4.45%). The adverse reactions of infliximab-related infections were pneumonia (7.69%), *tuberculosis* (6.15%), herpes zoster (4.72%), pulmonary tuberculosis (2.53%), and sepsis (2.49%) (Chen et al., 2019). However, through the VigiAccess database, we found that the proportion of infection-related adverse reactions in etanercept was nasopharyngitis- 2.98%, sinusitis- 2.26%, pneumonia- 1.85%, lower respiratory tract infection- 1.62%, and infection- 1.60%. The proportion of infection-related adverse reactions in adalimumab was nasopharyngitis- 3.12%, pneumonia- 1.86%, infection- 1.71%, sinusitis- 1.51%, and influenza- 1.27%. Infliximab-related adverse reactions were pneumonia (3.75%), lower respiratory tract infection (1.12%), infection (1.09%), cellulitis (0.91%), and tuberculosis (0.84%). WHO-VigiAccess and FAERS, as the databases to evaluate post-marketing drug vigilance, showed differences in the types and incidence of infection-related adverse reactions caused by anti-TNFα agents. Due to the voluntary reporting of adverse events, the passive-monitoring FAERS database and WHO-VigiAccess database do not represent a complete and comprehensive count

of adverse events and may lack information about reported events. In comparison, the FAERS database can display specific reports of each adverse reaction in most cases and screen eligible case reports more accurately, but professional personnel and intelligent analysis software are needed (Mikami et al., 2021). This may require WHO-VigiAccess to further provide more reporting information to the public to screen for potential links between drugs and adverse reactions in order to avoid incorrect guidance.

Another notable adverse event of anti-TNFα therapy is an increased risk of cancer. An initial meta-analysis showed that the treatment of RA with TNFi was associated with 3.3 times greater odds of cancer when compared to placebo (Bongartz et al., 2006). One published series described 48 cases of malignancy reported to the FDA in children on a TNF inhibitor, half of which were lymphomas (Diak et al., 2010). An analysis of TNFα-inhibitor-treated patients with inflammatory bowel disease (IBD) in the French National Health Insurance database also showed a higher rate of lymphoma (HR 2.41, 95% CI 1.60–3.64) compared with patients with IBD who had no TNF inhibitor exposure (Lemaitre et al., 2017). Furthermore, a study of patients with juvenile idiopathic arthritis, IBD, or psoriasis that used a Medicaid database hinted at a similar, albeit non-significant, increase in the risk of lymphoma in patients receiving TNFα inhibitor treatment (adjusted HR 2.64, 95% CI 0.93–7.51) (Beukelman et al., 2018). However, many register-based cohort studies and systematic reviews of randomized trials had not identified such an increased risk of overall cancer with the use of anti-TNFα, with the exception of an increased risk of squamous cell skin cancer risk in patients treated with abatacept (Xie et al., 2020; Chen et al., 2021; Li et al., 2021). Our results showed that the 10 most common adverse reactions reported were rash, arthralgia, rheumatoid arthritis, headache, pneumonia, psoriasis, nausea, diarrhea, pruritus, and dyspnea, and cancer-related adverse reactions were not included. Based on the definition of an AE, these may be self-limiting or temporal and are, therefore, not a cause for alarm. We also found that common cancer-related adverse reactions of five TNFα inhibitors include skin cancer, breast cancer, and basal cell carcinoma.

We found that the five TNFα inhibitors had different PTs of ADR in congenital, familial, and genetic disorders. It is worth noting that of all the biopharmaceuticals used to treat RA, only TNFα is approved for use during pregnancy and lactation. Prenatal exposure to TNFα has been shown to have no effect on T- or B-cell development (Förger et al., 2019; Kristjansdottir et al., 2019). Yet, there are some safety concerns regarding the risk of developing serious infections, such as tuberculosis, due to detectable anti-TNF antibodies in infants' sera (Romanowska-Próchnicka et al., 2021). Certolizumab pegol and etanercept are approved by the European League Against Rheumatism (EULAR) for use during pregnancy and breastfeeding. Because the concentration of etanercept in breast milk is low and not detectable in neonatal serum, the European registry considers etanercept to be safe, although the level of evidence for etanercept is lower than that for certolizumab pegol (Clowse et al., 2018; Emery et al., 2020). Data on the teratogenic effects of TNFα are limited, and there is no strong evidence of potentially harmful effects if used in the preconception period (Beltagy et al., 2021).

There is increasing data on ocular adverse events associated with anti-TNFα therapy (Nicolela and Pavesio, 2020). Our study found that the most common ocular adverse reactions caused by the five TNFα inhibitors were visual impairment and blurred vision, and the swelling of the eyelid and blepharospasm caused by certolizumab pegol was prominent.

The use of a spontaneous reporting system database has some important implicit limitations because reporting is influenced by factors such as notoriety bias, selection bias, and under-reporting (Faillie, 2019). Missing data, as observed in the results of the current study where some AEs were reported, can neither be attributed to males nor females as well as age groups. In addition, since the VigiAccess database of the WHO is cumulative data, the ADRs of every year cannot be obtained. When drugs are put on the market at different times, the number of ADRs collected is quite different, and the signal difference of all target inhibitors cannot be compared at the same time. Therefore, further data mining will be not possible. In this study, the number of ADRs over the past years and the number of PTs were collected, and the rate of ADR reports of different drugs was compared to avoid the influence of the time of drug marketing. The study results were limited to the relative results of the five TNFα inhibitors.

Conclusion

Anti-TNFα biological agents are an important part of autoimmune diseases. The study showed that WHO-VigiAccess reported more than 1 million adverse reactions to anti-TNF antibody treatment. The ADR of these drugs was mainly concentrated in infections and infestations, gastrointestinal disorders, and blood and lymphatic system disorders. The ADR symptoms of infection and gastrointestinal disorders had been confirmed again. In addition, infusion-related reactions caused by infliximab and lower respiratory tract infections caused by golimumab were very prominent. Even though most of the ADRs were minor and self-limiting, there were some serious ADRs that could lead to hospitalization and even death. Countries should also actively conduct safety studies on biological agents, such as cohort event monitoring, to determine the causal relationship between adverse reactions and drugs. These findings could also be stored in open-access repositories for the general public to enhance their knowledge of AEs associated with biotech drugs.

Data availability statement

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

Author contributions

ML performed statistical analysis of the data from WHO-VigiAccess and wrote the manuscript. RY and YS collected the database from WHO-VigiAccess. HZ contributed to the review and editing of the manuscript. SG planned the study and 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.2023.1169327/full#supplementary-material

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Development and validation of a nomogram for predicting pulmonary infection in patients receiving immunosuppressive drugs

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Objective: Pulmonary infection (PI), a severe complication of immunosuppressive therapy, affects patients' prognosis. As part of this study, we aimed to construct a pulmonary infection prediction (PIP) model and validate it in patients receiving immunosuppressive drugs (ISDs).

Methods: Totally, 7,977 patients being treated with ISDs were randomised 7:3 to the developing (n = 5,583) versus validation datasets (n = 2,394). Our predictive nomogram was established using the least absolute shrinkage and selection operator (LASSO) and multivariate COX regression analyses. With the use of the concordance index (C-index) and calibration curve, the prediction performance of the final model was evaluated.

Results: Among the patients taking immunosuppressive medication, PI was observed in 548 (6.9%). The median time of PI occurrence after immunosuppressive therapy was 123.0 (interquartile range: 63.0, 436.0) days. Thirteen statistically significant independent predictors (sex, age, hypertension, DM, malignant tumour, use of biologics, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, use of methylprednisolone at 40 mg total dose, use of oral glucocorticoids, albumin level, and haemoglobin level) were screened using the LASSO algorithm and multivariate COX regression analysis. The PIP model built on these features performed reasonably well, with the developing C-index of 0.87 (sensitivity: 85.4%; specificity: 81.0%) and validation C-indices of 0.837, 0.829, 0.832 and 0.830 for predicting 90-, 180-,

Abbreviations: C-index, concordance index; CNIs, calcineurin inhibitors; CTX, cyclophosphamide; DCA, decision curve analysis; DM, diabetes mellitus; IQR, interquartile range; ISDs, immunosuppressive drugs; λmin, minimum of λ; LASSO, least absolute shrinkage and selection operator; MMF, mycophenolate mofetil; PI, pulmonary infection; PIP, pulmonary infection prediction; ROC; receiver operating characteristic.

270- and 360-day PI probability, respectively. The decision curve analysis (DCA) and calibration curves displayed excellent clinical utility and calibration performance of the nomogram.

Conclusion: The PIP model presented herein could aid in the prediction of PI risk in individual patients who receive immunosuppressive treatment and help personalise clinical decision-making.

KEYWORDS

immunosuppressive drugs, LASSO, nomogram, pulmonary infection, predictive model

1 Introduction

Immunosuppressive drugs (ISDs) are a class of drugs that exert immunosuppressive effects through various mechanisms and are primarily used to clinically modulate the immune response of patients (Suthanthiran et al., 1996; Barshes et al., 2004; Allison, 2005). Since the establishment of their immunosuppressive action, ISDs have been widely recommended as first-line therapeutics in organ transplantation cases and the treatment of autoimmune disorders (Kasiske et al., 2010; Radhakrishnan and Cattran, 2012; Fanouriakis et al., 2019). With the widespread application of glucocorticoids and other immunosuppressants, an increasing number of latent adverse effects is linked with this class of agents in recent years, and this limits their use (Penfornis and Kury-Paulin, 2006; Htwe and Khardori, 2017; Chotiyarnwong and McCloskey, 2020). Pulmonary infection (PI) is a common comorbidity in immunosuppressed patients and contributes to an exceptionally high mortality rate (Godbole and Gant, 2013; Ahuja and Kanne, 2014), which it has various potential reasons. One reason could be that immunosuppressants inhibit the immune function of patients, which significantly increases their susceptibility to a variety of microbial pathogens and the incidence of infection, especially PI, directly threatening the lives of many patients (Stahn and Buttgereit, 2008). Moreover, the symptoms of infection in patients could be overshadowed by the long-term course of immunosuppressants, which makes it difficult for early diagnosis and treatment, thus rendering rapid progression and a poor prognosis (Poowuttikul et al., 2019). The results of a 10-year cohort study from China revealed that patients with pneumonia who previously received active immunosuppressant therapy had a greater risk of mortality when hospitalised (Yin et al., 2021). Therefore, it is crucial to understand the risk factors and identify patients at a high risk of PI when initiating immunosuppressant therapy. However, there is a lack of visual prediction models that can be applied in broad and large populations.

The nomogram model, as a multi-factor calibrated visualisation tool, has been extensively used to predict various outcomes in clinical practice, and it can provide the rationale for clinicians to develop more effective and individualised therapy regimens (Iasonos et al., 2008). Accordingly, this research was devised to establish a simple and effective nomogram prediction model for PI and validate it in patients receiving immunosuppressive therapy.

2 Materials and methods

2.1 Definitions

The diagnostic criteria for PI in the current research encompassed the following elements: 1) Clinical manifestations comprised the onset of a new cough or expectoration, or the exacerbation of existing respiratory tract symptoms, accompanied by or without purulent sputum, chest pain, dyspnea, hemoptysis, fever, and rales detected during lung auscultation; 2) Leukocyte count exceeding 10×10^9/L or falling below 4×10^9/L (Kalil et al., 2016); 3) Imaging characteristics encompassed the emergence of infiltration, consolidation, ground-glass opacity, or effusion observed in chest plain films or computed tomography scans (Wunderink et al., 1992; Koenig and Truwit, 2006). Patients who satisfied the third criterion, in conjunction with either the first or second criterion, were subjected to a clinical diagnosis of PI. Diagnosis of PI was reviewed and reconfirmed by an experienced specialist in infectious diseases (JZ).

Immunosuppressive agents used in this study were calcineurin inhibitors (CNIs) (tacrolimus and cyclosporine A), cyclophosphamide (CTX), mycophenolate mofetil (MMF), biologics (rituximab, infliximab, etanercept, adalimumab, tocilizumab, abatacept and bortezomib), azathioprine, methotrexate, leflunomide, Tripterygium wilfordii, hydroxychloroquine, and glucocorticoids.

2.2 Eligibility criteria

The inclusion criteria were as follows: 1) patients using ISDs according to electronic medical records; 2) a follow-up period of longer than 14 days after initiating immunosuppressive therapy.

The exclusion criteria were as follows: 1) age less than 18 years old; 2) PI occurred within 14 days of immunosuppressive therapy; 3) patients with pre-existing PI who need to receive ISDs treatment, such as acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and COVID-19.

2.3 Data sources and processing

Demographic characteristics and laboratory data of, and physician's orders for these patients including, but not limited to, sex, age, hypertension, diabetes mellitus (DM), malignant tumour, use of immunosuppressive agents, albumin level, haemoglobin level

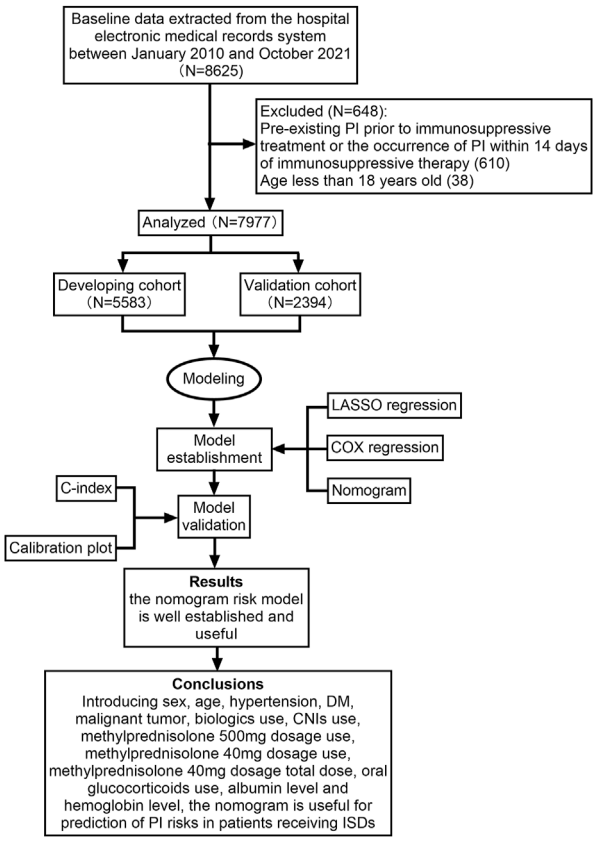

FIGURE 1
Flow diagram of the study design. CNIs, calcineurin inhibitors; DM, diabetes mellitus; ISDs, immunosuppressive drugs; LASSO, least absolute shrinkage and selection operator; PI, pulmonary infection.

and lymphocyte level were excerpted from the hospital's electronic patient management system. The study design flowchart is depicted in Figure 1.

2.4 Statement of human rights and ethics

Keeping in conformity with the Helsinki Declaration (as revised in 2013), our study received ethical permission from the Zhejiang Provincial People's Hospital Ethics Committee (No. 2021QT345) (World Medical Association, 2013).

2.5 Informed consent

Informed consent from the patients was waived as the study was retrospective in nature.

2.6 Statistical analyses

The baseline characteristics of the two cohorts are summarised as frequency count (percentage) for count variables and median (interquartile range [IQR]) for metric variables. To measure between-group differences, count variables were subjected to chi-square or Fisher's exact test, and metric variables were subjected to t-test or Wilcoxon test, depending on the distribution.

Imputation was conducted if missing values were <20%. The LASSO method was adopted to screen significant covariates and prevent the overfitting of the model. In this regression model, the absolute size of the coefficients of a regression model is penalised according to the value of λ, which is a LASSO regularisation parameter. In the presence of larger penalties, the estimates of weaker factors shrink toward zero, resulting in only the strongest factors remaining in the model. The most predictive covariates were chosen based on the minimum of λ (λmin). Thereafter, we incorporated the variables identified via LASSO regression analysis into COX regression models, and the variables that were consistently statistically significant were chosen to construct the nomogram.

A nomogram was constructed based on the final model. To evaluate the predictive performance in terms of discrimination and calibration, validation of the derived nomogram was carried out. An assessment of discrimination was performed using the receiver operating characteristic (ROC) curve and concordance index (C-index). A comparison of the observed PI rates with predictions from the final model was used to evaluate calibration. R software, version 4.1.0 (2021-05-18; R Foundation for Statistical Computing, Vienna, Austria) was employed for the statistical analyses presented. R packages including mice, VIM, missForest, survival, survminer, rms, glmnet, regplot, survivalROC, and survcomp were utilised in the current study. A two-tailed P-value of <0.05 was set to denote statistical significance for all tests.

3 Results

3.1 Baseline characteristics of the developing and validation datasets

In total, 8,625 patients using ISDs between January 2010 and October 2021 were consecutively selected for this study. Among these patients, 610 were excluded because of PI before immunosuppressive treatment or the occurrence of PI within 14 days of immunosuppressive therapy, and 38 patients were excluded as they were under 18 years of age. Ultimately, 7,977 patients were selected for the current analysis. All participants were randomly assigned to either the developing dataset (n = 5,583) or validation dataset (n = 2,394) at a 7: 3 ratio. The detailed study flow was given in Figure 1. There were no statistically significant differences in the demographic factors between the sets (Table 1). The prevalence of PI was 6.9% (384/5,583) in the developing set and 6.9% (164/2,394) in the validation set. The median time of PI after immunosuppressive therapy was 123.0 (IQR: 63.0, 436.0) days.

3.2 Predictor selection

A total of 53 general variables measured at admission to the hospital were included in the LASSO regression analysis. Participants' characteristics were shown in Supplementary Table S1. Based on the LASSO regression analysis results,

TABLE 1 Demographics and baseline characteristics of the study cohort.

	Overall	Developing cohort	Validation cohort	*P*
n	7977	5583	2394	
Follow up time (day)	134.0 (64.0, 495.0)	136.0 (64.0, 501.50)	133.0 (64.0, 469.0)	0.407
Pulmonary infection n(%)	548 (6.9)	384 (6.9)	164 (6.9)	1
Pulmonary infection time (day)	123.0 (63.0, 436.0)	125.0 (63.0, 438.5)	121.0 (63.0, 433.0)	0.476
Sex (female) n(%)	5431 (68.1)	3830 (68.6)	1601 (66.9)	0.136
Age (years)	55 (44, 66)	56 (44, 66)	55 (43, 66)	0.207
Smoking habit n(%)	986 (12.4)	685 (12.3)	301 (12.6)	0.733
Drinking habit n(%)	676 (8.5)	483 (8.7)	193 (8.1)	0.411
Hypertension n(%)	1357 (17.0)	949 (17.0)	408 (17.0)	0.987
Diabetes mellitus n(%)	628 (7.9)	432 (7.7)	196 (8.2)	0.524
Malignant tumor n(%)	2709 (34.0)	1899 (34.0)	810 (33.8)	0.897
Organ transplanation n(%)	172 (2.2)	111 (2.0)	61 (2.5)	0.135
Autoimmune disease n(%)	5056 (63.4)	3546 (63.5)	1510 (63.1)	0.728
Kidney disease n(%)	1676 (21.0)	1146 (20.5)	530 (22.1)	0.112
CTX n(%)	3178 (39.8)	2208 (39.5)	970 (40.5)	0.432
CTX total dose (mg)	3800(2700, 5200)	3800(2700, 5100)	3800 (2800, 5400)	0.378
MMF n(%)	1047 (13.1)	737 (13.2)	310 (12.9)	0.788
MMF duration (day)	140 (48, 533)	146 (47, 548)	140 (49, 471)	0.709
CNIs n(%)	1339 (16.8)	947 (17.0)	392 (16.4)	0.541
CNIs duration (day)	153 (48, 408)	150 (50, 420)	161 (45, 395)	0.486
Biologics n(%)	454 (5.7)	315 (5.6)	139 (5.8)	0.813
Azathioprine n(%)	1825 (22.9)	1309 (23.4)	516 (21.6)	0.07
Azathioprine duration (day)	159 (34, 680)	163 (35, 646)	154 (32, 767)	0.079
Methotrexate n(%)	1203 (15.1)	853 (15.3)	350 (14.6)	0.472
Methotrexate duration (day)	119 (28, 525)	119 (28, 506)	109 (28, 591)	0.451
Leflunomide n(%)	1559 (19.5)	1072 (19.2)	487 (20.3)	0.251
Leflunomide duration (day)	182 (49, 727)	177 (50, 700)	193 (40, 784)	0.236
Tripterygium wilfordii n(%)	2166 (27.2)	1550 (27.8)	616 (25.7)	0.065
TW duration (day)	170 (44, 567)	175 (44, 575)	162 (43, 549)	0.065
Hydroxychloroquine n(%)	1825 (22.9)	1309 (23.4)	516 (21.6)	0.07
Hydroxychloroquine duration (day)	159 (34, 680)	163(35, 646)	154 (32, 767)	0.079
Pred 500 mg n(%)	166 (2.1)	108 (1.9)	58 (2.4)	0.189
Pred 500 mg total dose (mg)	2000 (1500, 2803)	2000 (1500, 2500)	2000 (1500, 3000)	0.159
Pred 40 mg n(%)	1081 (13.6)	739 (13.2)	342 (14.3)	0.223
Pred 40 mg total dose (mg)	640 (280, 1280)	600 (280, 1280)	650 (280, 1283)	0.199
Oral glucocorticoids n(%)	2743 (34.4)	1908 (34.2)	835 (34.9)	0.561
Oral glucocorticoids duration (day)	131 (34, 405)	133 (33, 412)	126 (35, 393)	0.634
SMZ n(%)	626 (7.8)	434 (7.8)	192 (8.0)	0.742

(Continued on following page)

TABLE 1 (*Continued*) Demographics and baseline characteristics of the study cohort.

	Overall	Developing cohort	Validation cohort	*P*
Albumin, g/L	40.2 (36.0, 43.5)	40.3 (36.2, 43.5)	40.1 (35.8, 43.5)	0.575
Globulin, g/L	29.0 (25.8, 32.5)	29.0 (25.8, 32.5)	29.0 (25.9, 32.3)	0.942
Creatinine, μmol/L	71.4 (62.9, 84.9)	71.2 (63.0, 84.8)	71.9 (62.7, 85.0)	0.559
Uric acid, umol/L	295 (238, 366)	295 (238, 366)	297 (238, 366)	0.957
Fasting blood glucose, mmol/L	5.03 (4.63, 5.56)	5.02 (4.63, 5.56)	5.04 (4.62, 5.57)	0.494
Phosphorus, mmol/L	1.18 (1.05, 1.31)	1.18 (1.04, 1.31)	1.18 (1.05, 1.31)	0.267
Monocyte %	5.70 (4.40, 7.20)	5.60 (4.40, 7.10)	5.70 (4.40, 7.20)	0.926
Monocyte, $\times10^9$ /L	0.34 (0.26, 0.48)	0.34 (0.26, 0.48)	0.34 (0.25, 0.48)	0.841
Basophil %	0.30 (0.10, 0.40)	0.20 (0.10, 0.40)	0.30 (0.10, 0.40)	0.365
Basophil	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.656
Eosinophil %	1.20 (0.50, 2.40)	1.20 (0.50, 2.30)	1.30 (0.50, 2.40)	0.262
Eosinophil, $\times10^9$ /L	0.07 (0.03, 0.14)	0.07 (0.03, 0.14)	0.07 (0.03, 0.14)	0.136
Lymphocyte %	28.1 (21.1, 35.0)	28.1 (21.0, 34.9)	28.0 (21.3, 35.1)	0.488
Lymphocyte count, $\times10^9$ /L	1.67 (1.22, 2.20)	1.67 (1.22, 2.20)	1.67 (1.22, 2.20)	0.69
Neutrophil to lymphocyte ratio	2.24 (1.60, 3.33)	2.24 (1.60, 3.35)	2.25 (1.58, 3.28)	0.344
Platelet to lymphocyte ratio	125.8 (90.7, 172.7)	125.9 (90.7, 172.1)	125.4 (90.7, 174.2)	0.992
White blood cell count, $\times10^9$/L	6.11 (4.78, 7.87)	6.10 (4.78, 7.88)	6.14 (4.77, 7.85)	0.793
Hemoglobin, g/L	128.0 (114.0, 139.0)	128.0 (115.0, 139.0)	128.0 (114.0, 139.0)	0.899
Platelets, $\times10^9$ /L	214.0 (167.0, 264.0)	214.0 (166.0, 264.0)	214.0 (169.0, 265.0)	0.507

CTX, cyclophosphamide; MMF, mycophenolate mofetil; CNIs, calcineurin inhibitors; TW, Tripterygium wilfordii; Pred, methylprednisolone; SMZ, sulfamethoxazole.

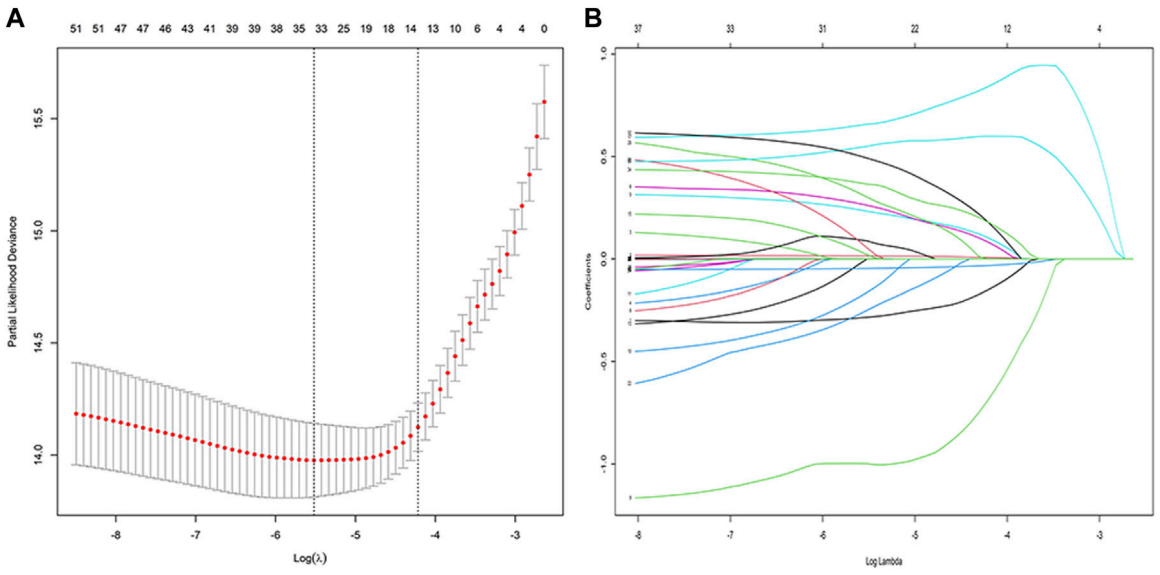

FIGURE 2
Variable selection using the least absolute shrinkage and selection operator (LASSO) regression model: **(A)** LASSO coefficient profiles of the 58 baseline features; **(B)** Tuning parameter (λ) selection in the LASSO model used 10-fold cross-testing via minimum criteria.

15 features were chosen to be potential predictors of PI, including sex, age, hypertension, DM, malignant tumour, CTX total dose, use of biologics, use of MMF, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, total cumulative dose of methylprednisolone at 40 mg, use of oral glucocorticoids, albumin level, and haemoglobin level.

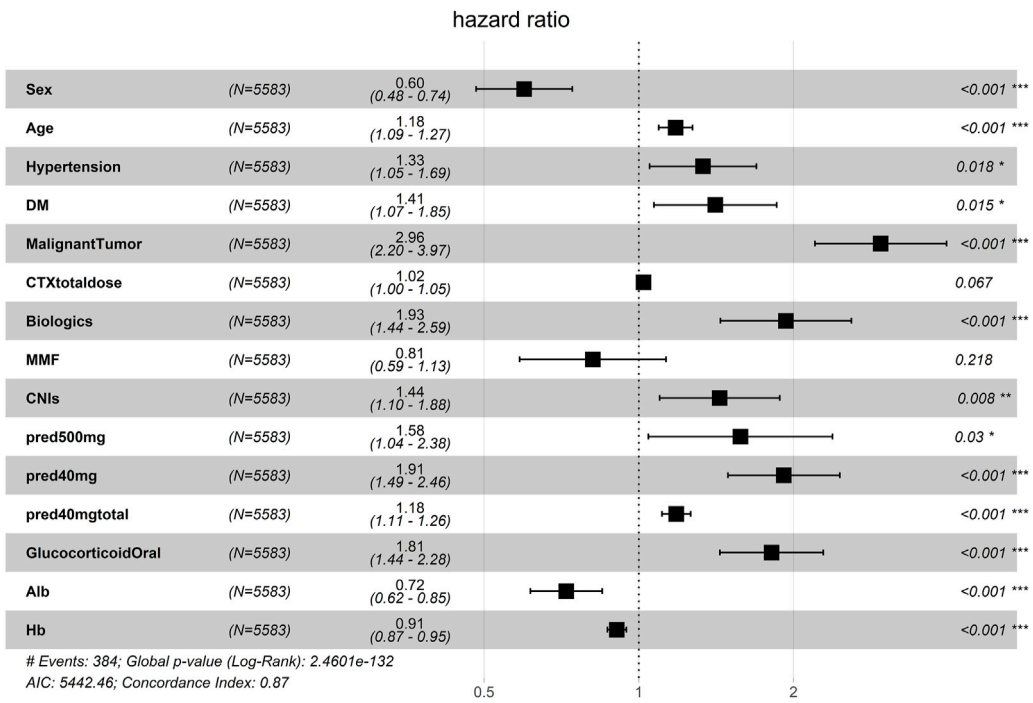

FIGURE 3
Multivariate COX regression analysis of the developing cohort. Alb, albumin; CNIs, calcineurin inhibitors; CTX, cyclophosphamide; DM, diabetes mellitus; Hb, haemoglobin; MMF, mycophenolate mofetil; pred, methylprednisolone.

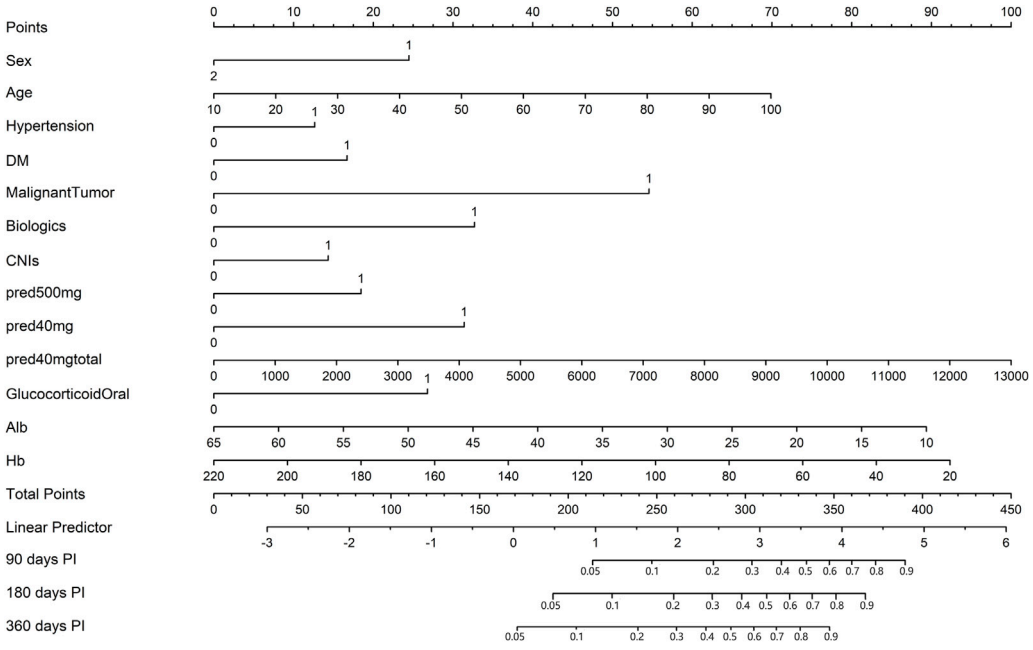

FIGURE 4
The nomogram of the pulmonary infection prediction (PIP) model. In the nomogram, each patient's value is displayed on an axis for each variable, and a line is drawn upward to determine the number of points each variable receives. On the Total Points axis is the sum of these numbers, and a line is drawn downward to the survival axes to determine 90-, 180- and 360-day probability of PI. Alb, albumin; CNIs, calcineurin inhibitors; DM, diabetes mellitus; Hb, haemoglobin; PI, pulmonary infection; pred, methylprednisolone.

The screening for the LASSO analysis is shown in Figure 2. The significant features from LASSO were subsequently chosen for further multivariate COX regression analysis. Thirteen variables were finally screened as statistically significant independent predictors of PI. The results of the multivariate COX regression analysis are presented in Figure 3.

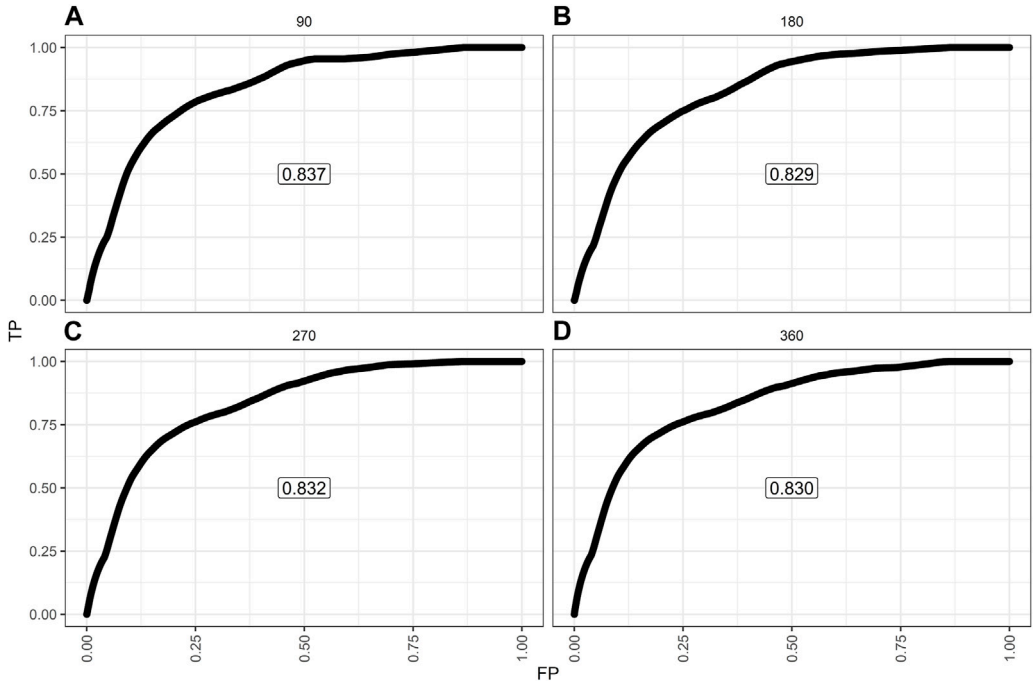

FIGURE 5
The receiver operating characteristic (ROC) curves based on the nomogram in the validation dataset: **(A)** ROC curve predicting 90-day probability of pulmonary infection (PI); **(B)** ROC curve predicting 180-day probability of PI; **(C)** ROC curve predicting 270-day probability of PI; **(D)** ROC curve predicting 360-day probability of PI.

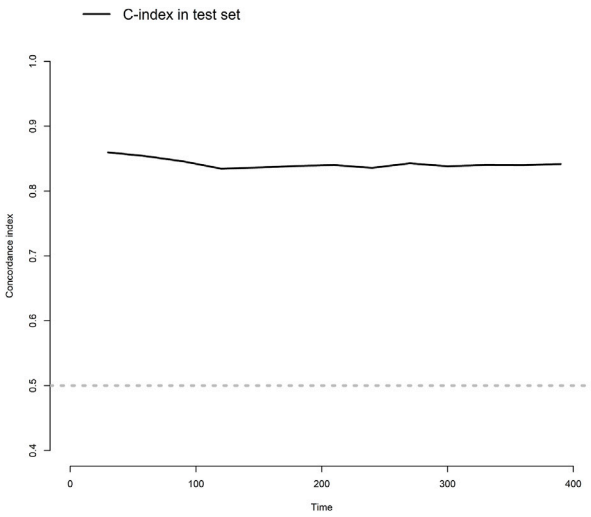

FIGURE 6
The dynamic alterations of concordance index (C-index) for the model in the validation dataset.

3.3 Nomogram construction

Thirteen of the clinical parameters (sex, age, hypertension, DM, malignant tumour, use of biologics, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, use of methylprednisolone at 40 mg total dose, use of oral glucocorticoids, albumin level, and haemoglobin level) were integrated to construct a pulmonary infection prediction (PIP) model in patients receiving ISDs (Figure 4).

Notably, patients with the following features presented a greater probability of developing PI: male, old age, hypertension, DM, malignant tumour, use of biologics, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, high-dose methylprednisolone, use of oral glucocorticoids, and low albumin and haemoglobin levels.

Moreover, the longer the length of the line, the greater the effect of these factors on the risk of developing PI. As found from the nomogram, the use of methylprednisolone at 40 mg total dose had the greatest effect on the occurrence of PI, whereas the presence of hypertension was observed to have the least effect. The top line of the nomogram corresponded to the score for each factor. Scores for each of these parameters were pooled, with higher scores indicating a higher risk of developing PI.

3.4 Nomogram validation

The model showed a high degree of discrimination, with the developing C-index of 0.87 and the validation C-indices of 0.837, 0.829, 0.832 and 0.830 for predicting 90-, 180-, 270- and 360-day PI probability, respectively (Figure 5). The dynamic alterations of the C-indices for the PIP model in the validation cohort are shown in Figure 6. The calibration plot also displayed excellent concordance between the predicted probability of PI and observations, which indicated good calibration of the model in the validation dataset

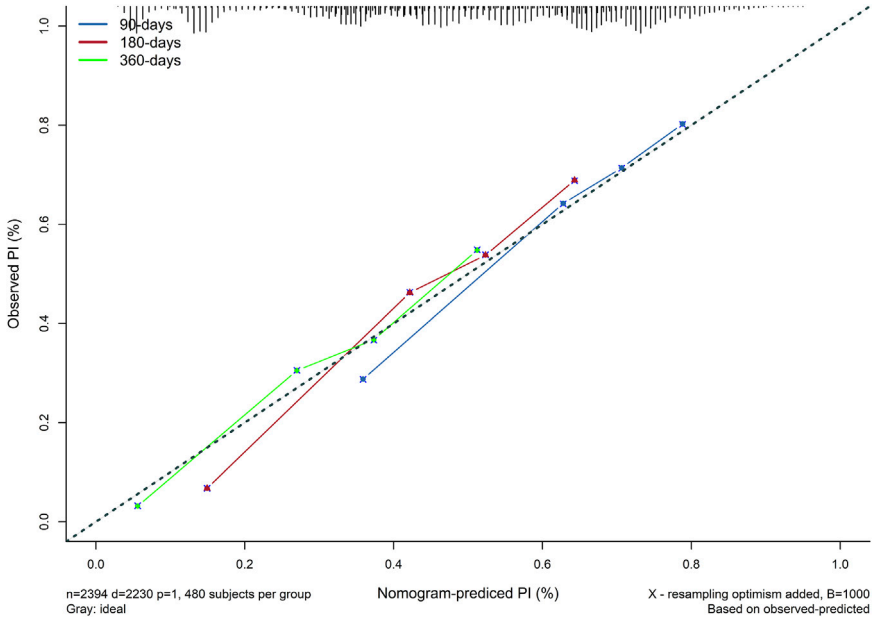

FIGURE 7
The calibration diagram of the model in the validation dataset.

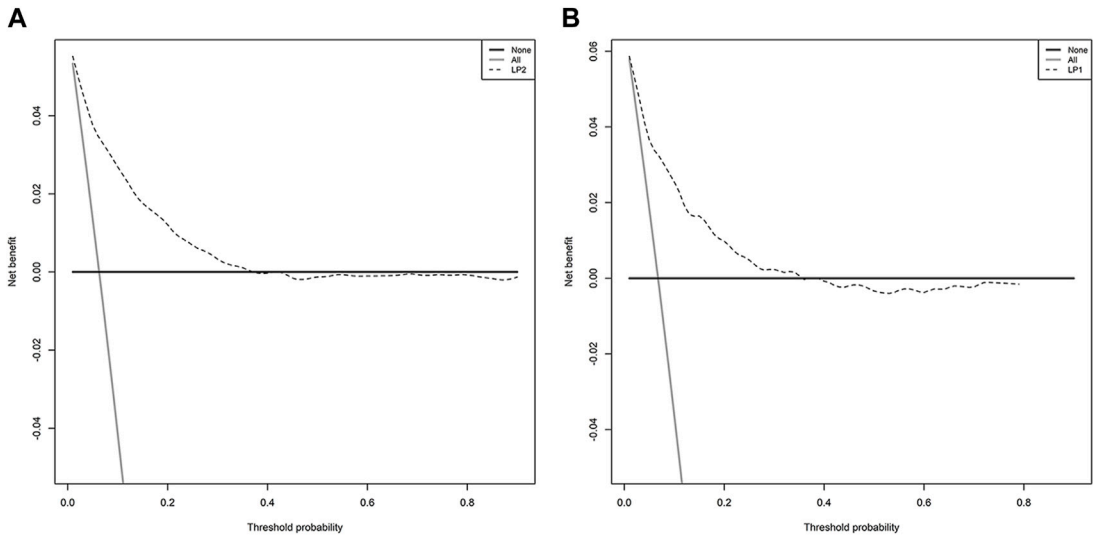

FIGURE 8
The decision curve analysis (DCA) of the model: **(A)** DCA in the developing dataset; **(B)** DCA in the validation dataset.

(Figure 7). The decision curve analysis (DCA) of the developing and validation datasets proved the potential clinical value of the model (Figure 8).

4 Discussion

We built a simplified prediction model based on 13 easily accessible variables selected using LASSO and multivariate regression analyses to facilitate the personalised estimation of the likelihood of PI and validated it in patients who received immunosuppressant medications. The LASSO regression analysis allows the shrinkage of the coefficients of the less contributive variables to be exactly zero, which effectively deals with the multicollinearity problem in the model and the enormous number of clinical factors (Hepp et al., 2016). The nomogram provides a simple pictorial representation of sophisticated mathematical calculations, and it has been recognised as a reliable and valuable predictive tool for clinical use (Xie et al., 2015). However, it must be clarified that the relatively large

number of parameters involved in this model did not affect its usefulness and feasibility. This is because the combination of two or three ISDs is the most commonly used therapy, and it is seldom that all of the listed ISDs are simultaneously prescribed in clinical practice. Further, all patients receiving immunosuppressant therapy were included in our study, regardless of hospital departments. As a result, our predictive model seemed to have a better generalizability to some extent. In 2019, Wang et al. (2019), utilising clinical data of 333 patients, proposed using the AIM-7C score for the early evaluation of the risk of developing PI after the initiation of a cyclosporine regimen. Nevertheless, this score was only applicable to patients with primary membranous nephropathy, and not to all patients receiving immunosuppressive therapy. To our understanding, this is the inaugural instance of a visual nomogram model designed explicitly for the early detection of PI in all patients treated with ISDs.

In this study, we found that the prevalence of PI was 6.9% (548/7,977), illustrating that patients receiving immunosuppressive therapy are a high-risk population for PI. Furthermore, the results showed that the incidence rate of PI among males was 11.9% (302/2,546), whereas that among females was 4.2% (246/5,431), demonstrating that male patients were more vulnerable to PI than females. The reason for this phenomenon could not be elucidated. One possible reason is the different effects of sex hormones on the immune response. Previous studies have reported that testosterone has an immunosuppressive effect, whereas oestrogens tend to reinforce immunological hyper-response (Beery, 2003). Additionally, the majority of males have a history of smoking and alcohol consumption (Fujii et al., 2021; Shrestha et al., 2021). Smoking and alcohol consumption can aggravate underlying diseases and reduce cardiopulmonary function, which is another possible reason for this observation. Another independent risk factor that we found was the age of the patients. There is increasing evidence that the lung immune system declines with age, increasing the risk of developing infections and chronic inflammatory diseases, as well as the mortality rate (Larbi et al., 2008). Moreover, we found low albumin and haemoglobin levels to be independent risk factors for PI development, and this was consistent with the findings of previous research (Levy et al., 2005; Wang et al., 2019). As a well-established marker of malnutritional status, a low serum albumin level strongly suggests poor dietary choices in patients. Long-term immunosuppressive therapy can further affect nutrient balance, which in turn reduces the body's immunity to pathogens. Patients receiving immunosuppressive therapy who have anaemia may experience weakened immune systems, further increasing their risk of infection. Furthermore, we found that malignant tumours, and the use of biologics and CNIs, were significantly associated with the occurrence of PI. It is generally known that patients with malignant tumours often experience complications with infection owing to their immunocompromised status (Azevedo et al., 2020). Infection is frequently cited as an adverse effect in the administration of biologics and CNIs (Thaunat et al., 2004; Evens et al., 2011; Kelesidis et al., 2011; Sułkowska et al., 2012; High and Olivry, 2020). The pathogenic microorganisms identified in patients with infection included viruses, bacteria, fungi, and virus-bacteria co-infection. Besides the above clinical parameters, we found that the use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, total cumulative dose of methylprednisolone at 40 mg, and use of oral glucocorticoids were independent predictors of PI development. Long-term use of glucocorticoids can inhibit the antigen-antibody reaction in the human body, thereby leading to the development of infection (McEwen, 2008). A previous animal study confirmed the relationship of glucocorticoid use with the development of PI (Reis e Sousa, 2001). As such, rational clinical use of glucocorticoids appears to be particularly valuable. In addition, DM and hypertension were correlated with an elevated risk of developing PI. Indeed, DM has been considered a significant risk factor for lower respiratory tract infections in susceptible patients (Klekotka et al., 2015). Chronic hypertension damages blood vessels, resulting in pulmonary oedema, pulmonary congestion, systemic hypoxia, and even PI (Ponte et al., 2013).

Based on 13 independent risk factors (male, age, hypertension, DM, malignant tumour, use of biologics, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, total cumulative dose of methylprednisolone at 40 mg, use of oral glucocorticoids, and low albumin and haemoglobin levels) established from a large cohort with sufficient sample size, we constructed the first practical nomogram model and demonstrated that it was advantageous for the individualised risk stratification of PI in patients taking immunosuppressants. Our nomogram model demonstrated satisfactory prediction ability, with C-indices of 0.837, 0.829, 0.832, and 0.830 for the 90-, 180-, 270- and 360-day probability of PI in the validation set, respectively, which demonstrated the model's favourable discriminative ability to differentiate patients who were at a risk of developing PI from those who were not. Furthermore, the calibration plot demonstrated a strong agreement between the calibration and standard curves in the validation cohort, suggesting that the predicted occurrence of PI was close to the observed data. In addition to acknowledging uncontrolled factors, such as sex, age, and malignant tumours, medical staff should strengthen the management of controllable factors. In this prediction model, we consider a value greater than 0.5 as high risk and a value less than 0.5 as low risk. If the value is greater than 0.5, we will not only increase the frequency and content of follow-up, but also communicate with the patient about the risk of infection and adjust the treatment plan if necessary. Once high-risk cases are detected, aggressive preventive interventions should also be undertaken at the earliest opportunity to reduce the morbidity rate of PI. For instance, it is imperative to strongly advocate smoking cessation for all patients receiving immunosuppressants who are still smoking. And nursing staff should assume the responsibility of instructing patients in respiratory function exercises to enhance lung function. Moreover, regular nutritional screening and management should be reinforced as a fundamental element of preventive measures, ensuring efficient support in maintaining optimal patient health.

A number of limitations were identified in the current study. In the first place, due to its retrospective nature, its generalizability was limited by the fact that it was restricted to a single site. Yet, our study enrolled all patients treated with ISDs in a single center irrespective of disciplines, which might somewhat compensate for the aforementioned drawback. Second, our nomogram has not yet undergone external validation, and

thus, the extrapolation of our nomogram to other cohorts remains unknown. Further independent external validation using additional large datasets to verify these findings has been planned. Third, some patients were administered more than one ISD during the study, which unavoidably introduced bias into the study. Consequently, further studies should take into account the potential interactions among multiple drugs. Last but not least, our study did not grade the risk of developing PI in patients with immunosuppressive therapy. Accordingly, we plan to explore this issue in our future research.

5 Conclusion

To summarize, sex, age, hypertension, DM, malignant tumour, use of biologics, use of CNIs, use of methylprednisolone at 500 mg, use of methylprednisolone at 40 mg, total cumulative dose of methylprednisolone at 40 mg, use of oral glucocorticoids, and albumin and haemoglobin levels were independent predictors of the occurrence of PI in patients who were receiving immunosuppressant therapy. The nomogram model established in this study has the potential to assist in the development of an optimal therapeutic intervention for this condition, thereby effectively reducing the occurrence of PI. This suggests that our nomogram model holds promise for widespread implementation 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 Zhejiang Provincial People's Hospital Ethics Committee. 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 study was retrospective in nature.

Author contributions

CL: Writing–original draft. YZ: Writing–original draft. JZ: Writing–original draft. CJ: Writing–original draft. XY: Writing–original draft. YR: Writing–original draft. HS: Writing–original draft. MC: Writing–original draft. YL: Writing–original draft. QH: Writing–review and editing. GX: Writing–review and editing. LS: 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.2023.1255609/full#supplementary-material

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