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# Rising stars in drugs outcomes research and policies 2023

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# Rising stars in drugs outcomes research and policies: 2023

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# The price and affordability of essential medicines, progress and regional distribution in China: a systematic review

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**Background:** Essential medicine is a vital component to assure universal access to quality healthcare. However, the trend of affordability to essential medicines in China and its regional differences were not yet fully understood. This study aimed to systematically evaluate the price and affordability of essential medicines, their progress, and regional distribution in China in the last decades.

**Methods:** We searched seven databases and three websites for potentially eligible studies from inception until March 2022. Studies on the price and affordability of essential medicines investigated in China were included. Median and interquartile range (IQR) was used to describe the price and affordability of essential medicines, and compared in three periods, before 2009, from 2009 to 2014, and from 2015 to 2019. Subgroup analysis was performed to examine the price and affordability by regions, health facilities, and ATC categories of medicines. The study was registered with PROSPERO (CRD42022310173).

**Results:** A total of 65 studies including 11,639 health facilities investigated between 2006 and 2019 were included in this review. Median price ratios (MPR) and affordability of essential medicines were reported in 44 studies and 50 studies, respectively. The median MPRs of essential medicines in China was 1.59 (IQR: 5.39), with a tendency to rise first and then fall from 2006 to 2019. And the median affordability was equal to 0.88 (IQR: 2.58) days' wage of the lowest paid unskilled government worker, but steadily rose from 2006 to 2019. Subgroup analysis showed that the affordability in the western region (1.40, IQR: 2.88), urban area (0.95, IQR: 2.80), private sector (0.90, IQR: 2.30), of originator brands (OB) (2.90, IQR: 6.68), and antineoplastic and immunomodulating agents (5.68, IQR: 56.47) were worse than their counterparts.

**Conclusion:** The prices of essential medicine were higher than international level, the overall affordability of essential medicines in China is acceptable but poor in

the western region, for OB drugs and anti-cancer medicines. Further national essential medicine policies are needed to reduce regional disparities and improve the affordability of expensive drugs.

**Systematic Review Registration:** https://www.crd.york.ac.uk/PROSPERO/#recordDetails

KEYWORDS

**affordability, China, essential medicines, median price ratio, systematic review**

# 1 Introduction

Essential medicines are those that satisfy the priority healthcare needs of the population and should be available in the context of functioning healthcare systems. It should be in sufficient supply, appropriate dosage forms, consistent quality, adequate information, and at a price that the individual and the community can afford (World Health Organization, 2002). Access to safe, effective, quality and affordable essential medicines and vaccines for all to achieve universal health coverage is one of the Sustainable Development Goals (SDGs 3.8) of the United Nations (Sustainable Development, 2020). However, according to the report by World Health Organization (WHO) (World Health Organization, 2017), it is estimated that nearly two billion people have no access to essential medicines, causing a cascade of misery and suffering that can be easily and inexpensively prevented or treated through simple and affordable interventions. It was reported that about 10 million lives a year could be saved by the implementation of the National Essential Medicines Policy (World Health Organization, 2008).

WHO had published the first model list of essential medicines in 1977 and revised it every 2 years for adapting to the circumstances in more than one hundred countries. Meanwhile, A standard methodology for measuring medicine prices, availability, and affordability was developed by the WHO and Health Action International, 2021 (World Health Organization, 2008) and has been applied in more than 60 countries. (HAI) However, global access to essential medicines is facing formidable challenges. A survey investigated in 25 countries between 2008 and 2019 showed a substantial variation in access, with a range of 0%–69% (median of 15%) of health facilities providing an available and affordable set of essential medicines for the treatment, prevention, and management of acute and chronic diseases, and no facility offered all these essential medications in over one-quarter (28%) of the nations (World Health Organization, 2022). The price barrier was the main reason hindering access to essential medicines. The high price and cost of medicines have impaired the ability of many healthcare systems to provide population-wide access (World Health Organization, 2020). Especially, in the absence of insurance coverage, patients and their families often experience significant financial burdens when in need of medications (Cohen and Kirzinger, 2014).

As in many developing countries, the lack of access to essential medicines has caused growing concern in China and a series of measures have been taken to meet the public's basic healthcare needs. Since 1982, China had officially issued the first edition of the national essential medicine list (NEML) and revised it eight times. The latest edition was updated in 2018 and involved 685 medicines, among which the top three medicines in the highest proportion are used for cardiovascular diseases, endocrine diseases, and anti-microbial (Zuo et al., 2020). Up to now, several studies were carried out to evaluate the price and affordability of essential medicines across China, which found that the affordability of some medicines was still challenging (Zhu et al., 2019; Dong et al., 2020; Wang et al., 2021). However, most studies focused on specific regions or provinces at a single time point. Long-term national monitoring and evaluation of the progress of affordability of essential medicines in China are lacking, and its geographic variations among regions and provinces are unclear. Thus, this study aimed to systematically evaluate the price and affordability of essential medicine, their progress and regional distribution in China, to inform evidence-based policy-making to improve the affordability and equitable access to essential medicines in China.

# 2 Materials and methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), and was registered at the International Prospective Register of Systematic Reviews (CRD42022310173).

## 2.1 Search strategy and selection criteria

We searched PubMed, EMBASE (Ovid), CENTRAL (Ovid), Web of Science (WOS), The Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature Database (CBM), and the official websites of World Health Organization (WHO), International Pharmaceutical Federation (FIP), and Health Action International, 2021 from inception until 1 March 2022. We used the following combined text and MeSH terms: "essential medicine*" and "China." The detailed search strategies were provided in Supplementary Appendix SA1. Additionally, the reference lists of included studies were reviewed for more eligible studies. The language was restricted to English and Chinese.

We included studies if they investigated the affordability of essential medicines in hospitals, pharmacies, or drug supply enterprises in China; were cross-sectional studies, interrupted time series studies, controlled or uncontrolled before-after studies; reported outcomes of median price, median price ratios (MPR), or affordability. A study was excluded if it was a duplicate publication or the full text was not available. Based on WHO/HAI standard methodology, the MPR is defined as the ratio of the median local unit price of a medication to the median international reference

unit price, in which the price of a medicine is lower than the international level if the value was less than 1; and the affordability is defined as the ratio of the monthly treatment cost of a medication to the daily wage of the lowest paid unskilled government worker, in which a medicine is considered affordable if the value was less than 1 (World Health Organization, 2008).

## 2.2 Study selection and data extraction

Two reviewers (ZL and MZ) independently screened the title and abstract for potential studies in available records using Endnote X9 (Clarivate Analytics, United Kingdom), and the final included studies were determined after reading the full text according to the inclusion criteria.

A standardized table was designed for extraction and a pre-test with 10% of the included studies was conducted to revise the table and formulate instructions for filling it. The following information of included studies was independently extracted using Microsoft Excel (Microsoft Corporation, United States) by two reviewers (ZL and MZ): i) basic information of literature including title, first author, publication year, and study design; ii) research details including data collection period, investigation region (eastern/central/western/northeastern region, and province Supplementary Appendix SA2), area (urban/rural), health facility (public/private, tertiary/secondary/primary hospital, pharmacy or enterprise), sample size, methodology, and medicine list (generic name, characteristic and category of medicine); iii) outcome measures including median prices, MPR, and affordability. Disagreements were resolved through discussion with the third reviewer (KZ).

## 2.3 Risk of bias assessment

According to the Joanna Briggs Institute (JBI) appraisal tools, two reviewers (ZL and MZ) evaluated the methodological quality and risk of bias of studies included in our systematic review independently. The checklist consists of 9 items across four domains: i) sampling methods; ii) research objects; iii) data collection, and iv) analysis methods (Munn et al., 2015). Each item was rated "yes" (one point), "no" (zero points), "unclear" (zero points), or "not applicable" (one point), and the methodological quality of each study was graded into low (0–3), moderate (4–6), and high (7–9) (Wilairatana et al., 2021). Disagreements were resolved by consulting the third reviewer (KZ).

## 2.4 Statistical analysis

Descriptive statistics were conducted, in which the summary measures of the price and affordability reported in included studies were expressed as median and interquartile range (IQR). We examined the price and affordability of essential medicines in three periods based on the time of the survey, namely, before 2009, from 2009 to 2014, and from 2015 to 2019, to explore the changes over time before and after the implementation of national essential medicines policy. Then, we performed subgroup analysis, if the data available, to further examine the price and affordability of essential medicines during three periods by: i) regions (eastern, central, western, or northeastern region); ii) provinces; iii) areas (urban or rural); iv) types of health facilities (public or private sector); v) levels of health facilities (tertiary, secondary or primary); vi) characteristic of medicines [originator brand (OB) or lowest priced generic equivalent (LPG)]; and vii) category of medicines of the anatomic therapeutic chemistry (ATC) classification. Statistical analyses were performed using Stata, version 17.0 (Stata Corp., United States).

# 3 Results

## 3.1 Search results

We identified 6,935 citations from seven databases and registers and 3,406 records from three websites. After the removal of duplicates ($n$ = 2796), 4,139 titles and abstracts were screened, 112 of which were selected for full-text review. The records from the websites were also screened but no eligible study was found. Following the assessment of 101 potentially eligible articles, 65 studies were eventually included in this review. The flow diagram of study selection is shown in Figure 1.

## 3.2 Characteristics of included studies and risk of bias

The included 65 studies were all cross-sectional studies, involving a total of 11,639 health facilities (except nine studies that not reported the number of investigated health facilities), and were conducted from 2006 to 2019. Of these 65 studies, 25 studies (38.46%) were conducted in eastern China, 13 (20.00%) were in central China, 14 (21.54%) were in western China, 2 (3.08%) were in the northeastern region, and 12 studies (18.46%) were cross-regional survey. Among them, 23 studies (35.38%) investigated in urban areas, 9 studies (13.85%) investigated in rural areas, and 33 studies (50.77%) investigated both urban and rural areas simultaneously. As regard survey methods, 61 studies (93.85%) adopted the WHO/HAI standardized methodology to investigate the affordability of essential medicines, while 4 studies (6.15%) used non-WHO/HAI methods but adopted the same definition of measured outcomes. The detailed characteristics of the included studies are shown in Supplementary Appendix SA4 and the number of reported studies of each subgroup is shown in Supplementary Appendix SA5 in detail.

Among the 65 studies, 12 studies attained a score of 8, 12 studies a score of 7, 14 studies a score of 6, 9 studies a score of 5, 13 studies a score of 4, 4 studies a score of 3, and 1 study a score of 2. Overall, 24 studies (36.92%) were assessed as high quality, 36 studies (55.38%) were of moderate quality, and 5 studies (7.69%) were of low quality. The results of the quality assessment in this review are presented in Supplementary Appendix SA6.

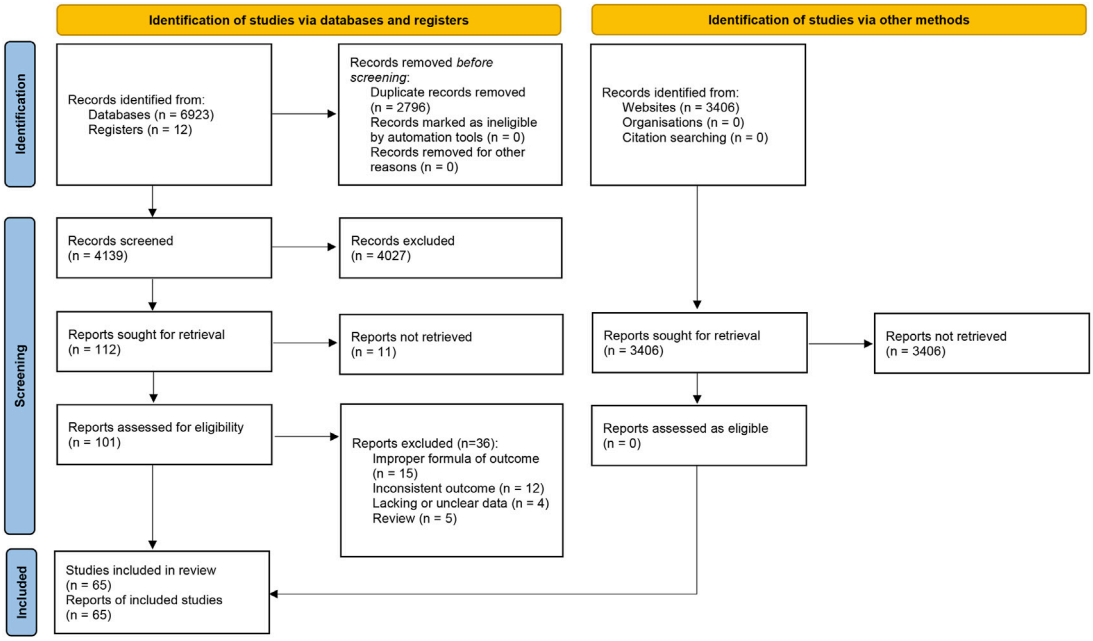


FIGURE 1
PRISMA flow diagram of study selection.

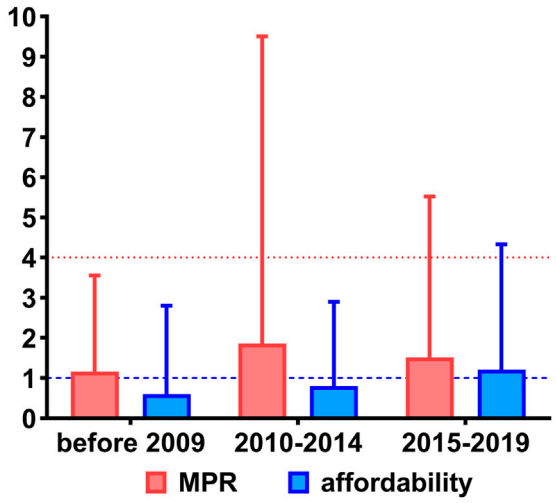


FIGURE 2
The overall price and affordability of essential medicines in China. Notes: Red indicates the MPRs of essential medicines with a red dotted line as the threshold, and blue indicates the affordability of essential medicines with a blue dotted line as the threshold. MPR, median price ratio.

## 3.3 Price of essential medicines in China

A total of 44 studies reported the MPR of essential medicines. The median MPRs of essential medicines nationwide of all included studies was 1.59 (IQR: 5.39), with the trend of rising first and then falling before 2009 (1.15, IQR: 2.40), from 2010 to 2014 (1.86, IQR: 7.65), and from 2015 to 2019 (1.51, IQR: 4.01). The overall trend of the prices is presented in Figure 2.

Subgroup analysis showed that medicine prices in the western region (2.50, IQR: 8.29) were higher than in other regions. It varied largely from the highest in Zhejiang province (9.31, IQR: 9.06) to the lowest in Jiangsu province (0.71, IQR: 2.52). The MPRs of urban area (1.50, IQR: 4.03), private sector (2.24, IQR: 6.97), tertiary and secondary health facilities (3.69, IQR: 5.17), and OB drugs (10.29, IQR: 18.68) were higher than their counterparts. The top three ATC types of essential medicines with the highest prices were blood and blood-forming organs drugs (B) (6.33, IQR: 17.15), antiparasitic products, insecticides and repellents (P) (5.33, IQR: 5.93), and musculoskeletal system drugs (M) (3.69, IQR: 17.84). The results of subgroup analysis of the prices are presented in Figure 3A, among which the provincial characteristics are shown in Figures 4A–C. The detailed results are listed in Supplementary Appendix SA7.

## 3.4 Affordability of essential medicines in China

A total of 50 studies reported the affordability of essential medicines. The median affordability of essential medicines nationwide was equal to 0.88 (IQR: 2.58) days' wage, with the trend of gradual growth before 2009 (0.60, IQR: 2.20), from 2010 to 2014 (0.80, IQR: 2.10), and from 2015 to 2019 (1.20, IQR: 3.13). The overall trend of affordability is presented in Figure 2.

Subgroup analysis showed that the cost of medicines of day's wages in the western region (1.40, IQR: 2.88) was higher than in

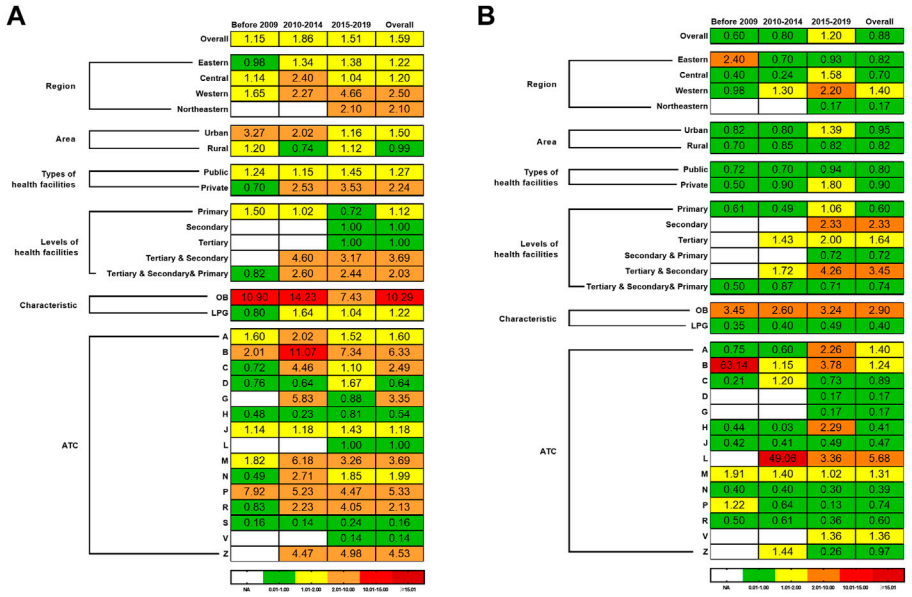


FIGURE 3
The price and affordability of essential medicines in China. Notes: **(A)** the median MPRs of essential medicines in China; **(B)** the median affordability of essential medicines in China. MPRs, median price ratios; OB, originator brand; LPG, lowest priced generic equivalent; ATC, anatomic therapeutic chemistry; A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; D, dermatologicals; G, genito urinary system and sex hormones; H, systemic hormonal preparations, excl. sex hormones and insulins; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides and repellents; R, respiratory system; S, sensory organs; V, various; Z, unknow.

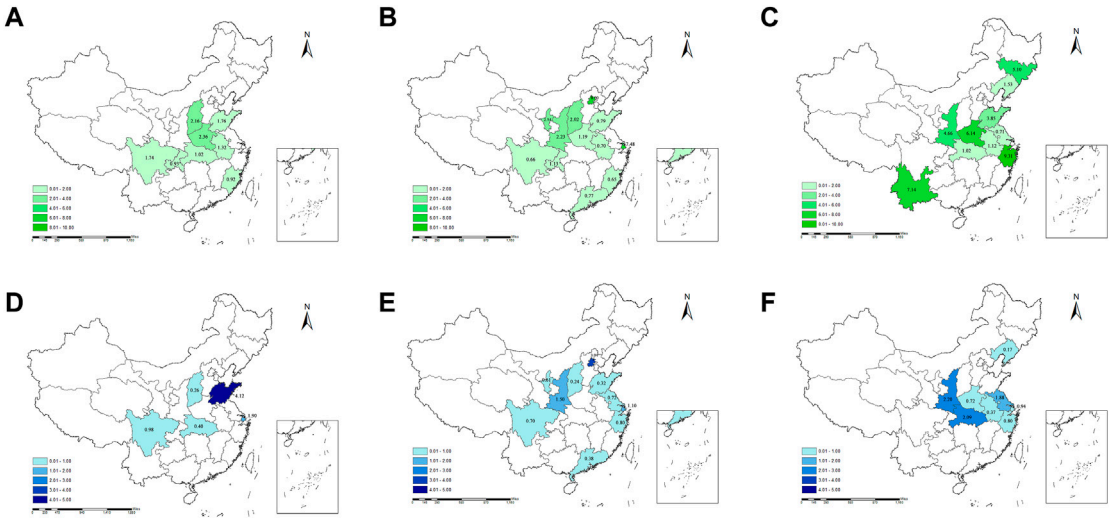


FIGURE 4
The provincial characteristics of the price and affordability of essential medicines in China. Notes: i) the upper pictures show the MPRs of essential medicines of each province in China before 2009 **(A)**, from 2010 to 2014 **(B)**, and from 2015 to 2019 **(C)**; ii) the bottom pictures show the affordability of essential medicines of each province in China before 2009 **(D)**, from 2010 to 2014 **(E)**, and from 2015 to 2019 **(F)**. MPRs, median price ratios.

other regions, which varied largely from the highest in Beijing province (3.04, IQR: 3.24) to the lowest in Shanxi province (0.24, IQR: 0.92). The affordability of urban area (0.95, IQR: 2.80), private sector (0.90, IQR: 2.30), tertiary and secondary health facilities (3.45, IQR: 20.39), and OB drugs (2.90, IQR: 6.68) was higher than their counterparts. The antineoplastic and immunomodulating agents (L) with 5.68 days' wages required (IQR: 56.47) were higher than other categories of medicines. The results of subgroup analysis of affordability are presented in Figure 3B, among which the provincial characteristics are

shown in Figures 4D–F. The detailed results are listed in Supplementary Appendix SA8.

## 4 Discussion

To our knowledge, this is the first systematic review that evaluated the overall price and affordability of essential medicines, their time trends, regional distribution, and health system distribution in China for the last decade. It shows that the price of essential medicines in China is close to and a little higher than the international level, with a tendency to rise first and then fall from 2006 to 2019. In addition, essential medicines are generally affordable in China, though the drug prices compared to the lowest daily wages of government workers increased gradually from 2006 to 2019.

Since 2009, the Chinese government has issued a series of healthcare system reforms aimed to provide equitable basic healthcare for all people and achieve universal health coverage, including the national essential medicine policy. As one significant component of the healthcare system reforms in China, the national essential medicine system had comprehensive and deepen reforms in terms of selection, production, distribution and procurement, reasonable pricing, quality assurance, and evaluation policies, to facilitate the accessibility of essential medicines with the concerted efforts (Tao et al., 2020).

With the persistently high prices than international reference, it is noteworthy that the affordability of essential medicines had modestly risen to more than 1 after 2015, which suggested that the growth rate of medicine price is faster than that of *per capita* income in China in the last decades, and the affordability potentially get worse in the future if without any measures. There are complex factors and issues that trigger the change in medicine prices, such as drug rebates, reimbursement ratio, price deviation and inflation (Long et al., 2022). Establishing a reasonable pricing mechanism for essential medicines is one of the approaches to curb the deterioration, such as reference pricing policy applied in many countries (Acosta et al., 2014). The findings remind us that continued efforts are needed to keep the balance between supply and demand of medicines, and coordinate the price relations to avoid larger deviation from international reference and maintain affordable prices.

The results of subgroup analysis showed that prices of essential medicines in the western region were higher and their affordability (as times of lowest wage per day) was inferior to other regions. Affected by many factors such as historical, social, and natural conditions, its economic development is at the lowest level in China, which is significantly correlated with the shortage of health resources in the western region (Li et al., 2021). The lower economic development level also contributes to the lower residents' income, and their ability to pay for medications is poorer than that of the developed coastal eastern and central regions (Wang et al., 2022). On the other hand, the western region where far from the coast has more complex geographical conditions and increases the transportation costs for the supply side, which may result in the high price of medicines for this region as well. Therefore, tailored financing policies for medicines, such as relaxing reimbursement, reducing copayment or tiered fixed co-payment of essential medicines may be further needed to lower the out-of-pocket payment of medicines and improve their affordability in those regions (Green et al., 2010; Luiza et al., 2015).

Despite the higher price of essential medicines can be observed in the urban than the rural area, the overall gap of affordability was not significantly widening between urban and rural areas. This might be because residents in urban areas had higher incomes than those who lived in rural areas, allowing them to afford more expensive medicines. On the other hand, the medical insurance system in China plays an important role in reducing people's burden of using essential medicines, such as the new cooperative medical scheme (NCMS) for rural residents. The reimbursement ratio for medical expenses is more generous in rural areas, and it controls the costs within their affordable ability, which narrow the disparity with the urban area (Xie et al., 2018; Luo et al., 2021).

Furthermore, we found that the public sector provided more affordable prices for essential medicines. Similar findings have been reported in several studies (Guan et al., 2013; Guan et al., 2018; Guan et al., 2018), and it appeared that the private sector also had higher pricing than the public sectors in other low- and middle-income countries (LMICs).(M. Ewen et al., 2017). Previously, the Chinese government allowed public sectors to have a 15% profit margin on medicines, which introduced incentives of over-prescribed, especially expensive medicines (The Central People's Government of the People's Republic of China, 2009). Recognizing the caveats, China has implemented two important pharmaceutical policies, namely, zero markup drug policy and centralized drug procurement policy for public health institutions, which have successfully changed the prescribing practice and curbed the rate of increasing expenditure of medicines in China (Liu et al., 2021a; Yuan et al., 2021a). These became significant policy-related factors associated with affordable medicines in public sectors. As national data reported, the growth rate of medicine expenditure has been slowing down in 2019, with an average annual growth of 4.20% lower than that in 2015 (9.89%) (Li et al., 2022). The decreased proportion of medicine costs for patients reduced their financial stress, and previous studies also showed that the incidence of catastrophic health expenditure in China in recent years displayed a downward trend (Liu et al., 2021b; Yuan et al., 2021b).

Additionally, generic medicines presented better affordable than originator products in our review, which was similar to the level among upper-middle-income countries as reported in a previous study (M. Ewen et al., 2017). Affordable pricing for medicines has long been a controversial topic, especially for OB. High profits generated by innovative originator products and patent markets for pharmaceutical manufacturers are the primary reason behind the high prices, which makes counterproductive effects on access to these life-saving medicines (Gronde et al., 2017). On the other hand, generic medicine can be purchased at a low price in the market as its low risk in research and development, accordingly protecting equitable opportunities for patients. In order to further improve the quality and bioequivalent recognition, the National Medical Products Administration (NMPA) of China has issued consistency assessment policy for quality and efficacy of generic medicines in 2016 (State Council of the People's Republic of China, 2016), which promotes generic substitution and assists to decrease medicine expenditure. Further work could be focused on the scope

extension of policy implementation to improve the affordability of more medicines.

Our review also indicated that the prices and affordability of essential medicines varied substantially between different ATC categories. It can be seen from the data that although the blood and blood-forming organs drugs (B), antiparasitic products, insecticides and repellents (P), and musculoskeletal system drugs (M) were the top three categories with the highest prices in China compared with the international reference, the affordability of most medicines was less than or close to the daily wage of the lowest paid unskilled government worker, except for antineoplastic and immunomodulating agents (L). The price of most anti-cancer medicines is still in a high position due to the irreplaceability of innovative originator products. Another possible reason for this is the lengthy period of chemotherapy required in cancer patients, which together leads to high total medicine costs. A similar result was reported in a previous study that the anti-cancer medicines with less affordability in LMICs, and it considered that might be associated with the high medicine cost, limited insurance coverage, or non-inclusion in the national essential medicine list (Ocran Mattila et al., 2021). Besides, current systematic reviews indicated that the affordability of essential medicines for asthma, chronic obstructive pulmonary disease, and cardiovascular disease was poor in LMICs, however, which was acceptable in China in our analysis (Babar et al., 2013; Husain et al., 2020; M. Stolbrink et al., 2022). In recent years, China has carried out several rounds of the national-level pricing negotiations and gradually expand the coverage of national health insurance, assisting in the improving accessibility of most medicines, and the patients who required these innovative anti-cancer medicines also got the benefit from the policy (Sun et al., 2022).

This study has several limitations. Firstly, there is insufficient data on the affordability of essential medicine available in China. The coverage of investigation on essential medicines currently performed unbalanced that only 18 provinces (18/31, 58.06%) provided specific data. Further studies are warranted for some provinces where the data is lacking, such as Tibet, Guizhou, Guangxi, Jiangxi, Hainan, Hebei, and Tianjin. Besides, the number of survey studies varied among different investigated provinces and information from individual studies was used to represent the whole group, which may introduce bias in the overall estimates. Moreover, the medicine lists surveyed differed among included studies, which may introduce further heterogeneity of included studies. Unified investigation methods and essential medicine lists of investigation are needed for consistent and long-term monitoring studies in China.

In conclusion, essential medicines were generally affordable in China but remained concerning in the western region, OB drugs, and anti-cancer medicines. This emphasizes the need for concerted national efforts to reduce the disparity of affordability of essential medicines among geographic regions and ATC categories. Evidence-based pricing and purchasing strategies can be exercised to address these issues and improve equitable access to affordable essential medicines in China toward universal health coverage.

## Data availability statement

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

## Author contributions

ZL and KZ designed the study. ZL, MZ, and YS did the literature searches. ZL and MZ screened the literature, extracted data and assess quality independently. DL, ZC, BL, and XC verified the data. ZL and KZ analysed the data. ZL and KZ wrote the draft. DL, HL, LZe, YT, SZ, IC, and YJ revised the manuscript. LZh had oversight of the study design and reviewed the final manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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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.2023.1153972/full#supplementary-material

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# Cost-effectiveness of adding empagliflozin to the standard of care for patients with heart failure with reduced ejection fraction from the perspective of healthcare system in Malaysia

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**Objective:** The aim of this study was to determine the cost-effectiveness of adding empagliflozin to the standard of care *versus* SoC alone for the treatment of patients with heart failure (HF) with reduced ejection fraction (HF*r*EF) from the perspective of the Ministry of Health of Malaysia.

**Methods:** A cohort-based transition-state model, with health states defined as Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) quartiles and death, was used to determine the lifetime direct medical costs and quality-adjusted life years (QALYs) for both treatment groups. The risks of all-cause death, cardiovascular death, and health state utilities were estimated from the EMPEROR-Reduced trial. The incremental cost-effectiveness ratio (ICER) was assessed against the cost-effectiveness threshold (CET) as defined by the country's gross domestic product *per capita* (RM 47,439 per QALY) to determine cost-effectiveness. Sensitivity analyses were conducted to assess the key model parameters' uncertainty in respect to the incremental cost-effectiveness ratio. A scenario analysis was performed using health states as defined by the New York Heart Association classes.

**Results:** Compared to SoC alone, empagliflozin + SoC for the treatment of HF*r*EF was more expensive (RM 25,333 vs. RM 21,675) but gained more health utilities (3.64 vs. 3.46), resulting in an ICER of RM 20,400 per QALY in the KCCQ-CSS model. A NYHA-based scenario analysis generated an ICER of RM 36,682 per QALY. A deterministic sensitivity analysis confirmed the robustness of the model in identifying the empagliflozin cost as the main driver of cost-effectiveness. The ICER was reduced to RM 6,621 when the government medication purchasing prices were used. A probabilistic sensitivity analysis with a CET of 1xGDP *per capita* reached 72.9% probability for empagliflozin + SoC against SoC being cost-effective.

**Conclusion:** Empagliflozin + SoC compared to SoC alone for the treatment of HF*r*EF patients was cost-effective from the perspective of the MoH of Malaysia.

KEYWORDS

**empagliflozin, heart failure, cost-effectiveness, cost-utility, economic evaluation**

# 1 Introduction

Heart failure (HF) is the terminal form of various cardiovascular (CV) disorders (i.e., acute coronary syndrome, cardio-rhythm disorder, valvular diseases, hypertension, and congenital heart diseases). The estimated worldwide prevalence of HF was about 60 million cases, with 50% of them having severe HF defined as symptomatic HF at rest (Lippi and Sanchis-Gomar, 2020) or reduced ejection fraction (Virani et al., 2020). HF is associated with frequent worsening of symptoms, thus substantially reducing quality of life and eventually leading to frequent hospitalisation and death (Savarese and Lund, 2017). The HF registry of Malaysia reported that the 30-day risk of all-cause readmission was 13% and went up to 45% within 1 year (National Heart Association Malaysia, 2021). After a worsening HF event, patients are more likely to have another episode of readmission than stable patients (Butler et al., 2020). The first prospective multinational Asian registry of patients with symptomatic HF (stage C), the ASIAN-HF Registry, reported that the overall mortality of patients with HF in the Southeast Asia region is 13.6% (MacDonald et al., 2020), which is comparable to developed countries (13%–18%) (Maggioni et al., 2013; Virani et al., 2020). In Malaysia, the estimated total cost of HF in 2012 was RM 785 million (National Heart Association of Malaysia, 2019). Inpatient cost is the main cost driver of the healthcare cost of HF in Malaysia and accounts for about 90% of the total healthcare costs of HF (Shafie et al., 2019).

The primary goals of treatment in HF patients are to reduce hospitalisation due to heart failure (hHF), CV death, and to improve symptoms and health-related quality of life (HRQoL) (McDonagh et al., 2021). Evidence-based therapy can avert CV death and hHF in HF patients with reduced ejection fraction (HF*r*EF) (Yancy et al., 2017; McDonagh et al., 2021), which accounts for two-thirds of patients with this syndrome (National Heart Association Malaysia, 2021). Currently, the available treatments for patients with HF*r*EF are pharmacological therapy and device implantation in selected patients only. Optimal pharmacological therapy includes renin–angiotensin–aldosterone system inhibitors, beta-blockers, mineralocorticoid inhibitors (MRA), and sodium–glucose cotransporter type 2 inhibitors (SGLT2i) (Yancy et al., 2017; McDonagh et al., 2021). Empagliflozin is a medication from SGLT2i that reduces the risk of primary composite outcomes of CV death or hHF by 25% when compared to the standard of care (SoC) (Packer et al., 2020). The clinical benefit of empagliflozin on the primary composite outcome is driven by the reduction in the risk of hHF by 30% among HF*r*EF patients receiving empagliflozin.

Empagliflozin is employed as a cost-effective treatment in patients with HF*r*EF in Taiwan, Japan, South Korea, Australia, Singapore (Liao et al., 2021), and China (Jiang et al., 2021). However, the cost-effectiveness of empagliflozin in addition to SoC for treating HF*r*EF patients is not readily available in Malaysia. This analysis is essential for decision-makers to justify allocating scarce resources to adopting empagliflozin as part of the treatment regimen for HF*r*EF. Therefore, the study's objective is to determine the cost-effectiveness of adding empagliflozin to SoC in patients with HF*r*EF from the perspective of the Ministry of Health (MoH) of Malaysia.

# 2 Methods

## 2.1 Model description

A validated cohort-based transition-state Markov model was adopted from the cost-effectiveness model (CEM) of empagliflozin + SoC vs SoC monotherapy submitted to the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence, 2022). The CEM was conducted from the perspective of the Malaysian Ministry of Health as the payer for the Malaysian healthcare system. The Markov model simulated the clinical course of HF*r*EF patients through health states based on the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) quartiles (Figure 1). As the KCCQ-CSS health states are a patient-centric approach that is better aligned with clinical symptoms and survival, it is preferred over the New York Heart Association (NYHA) classification (McEwan et al., 2020; National Institute for Health and Car e Excellence, 2021). The progression of HF*r*EF was simulated using five health states with health state-specific values: KCCQ-CSS quartile 1 (0–54), KCCQ-CSS quartile 2 (55–74), KCCQ-CSS quartile 3 (75–89), KCCQ-CSS quartile 4 (90–100), and death. The patient cohort in CEM was based on the baseline KCCQ-CSS quartiles distribution in the EMPEROR-Reduced trial. Patients could either transition to a higher quartile (less disease burden) or a lower quartile (more disease burden), remain in the same health state, or die. The model used a lifetime horizon with a monthly cycle length and half-cycle correction to account for the chronic and progressive nature of the disease, consistent with previous HF economic models (National Institute for Health and Care Excellence, 2012; National Institute for Health and Care Excellence, 2016; Di Tanna et al., 2019).

The model captured the incidence of hHF and adverse effects related to treatment as transient events. Patients in each KCCQ-CSS quartile experienced a monthly risk of hHF, CV death, or non-CV death. The transition probability matrix for transitions between the different KCCQ-CSS quartiles was applied to the remaining number of patients in the 'alive' health states to calculate the health state distribution in the next cycle. Patients could discontinue treatment with empagliflozin in each cycle. After discontinuation, patients received SoC treatment until death or the end of the modelled time horizon. Patients who discontinued treatment with empagliflozin experienced the same event rates and health state transition probabilities as those receiving SoC. Multiple admissions for HF were permitted over the entire model's time horizon for a more realistic representation of the clinical journey. The adverse events modelled were urinary tract infection, genital mycotic infection, acute renal injury, hepatic injury, hypotension, hypoglycaemic event, and bone fracture.

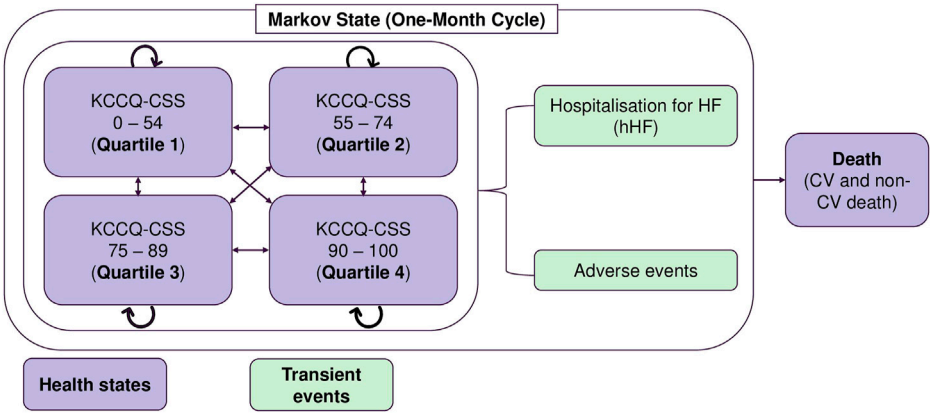


FIGURE 1
Markov model structure. AE: adverse events; CSS: clinical summary score; CV: cardiovascular; hHF: hospitalisation due to heart failure; ICER: incremental cost-effectiveness ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; RM: Ringgit Malaysia.

Only direct medical costs were included in the model. These were associated with medication acquisition, CV death, hHF, disease management, and treating adverse effects. Utilities were accrued based on the duration spent in each KCCQ-CSS quartile, adjusted for disutilities associated with hHF and adverse events.

A 3% discount rate was applied to future costs and outcomes (Pharmaceutical Services Programme, 2019). The Markov model development and analyses were performed using Microsoft Excel® (Microsoft, USA). Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health of Malaysia (NMRR ID-21-02,128-9 KR).

## 2.2 Cohort population

The modelled patient population was the intention-to-treat (ITT) population from the EMPEROR-Reduced trial, which corresponded to the anticipated licensed indication of empagliflozin for the treatment of HF*r*EF. The initial distribution of patients according to the KCCQ-CSS quartiles was as follows: KCCQ-CSS quartile 1 (24.3%), KCCQ-CSS quartile 2 (25.1%), KCCQ-CSS quartile 3 (27.2%), and KCCQ-CSS quartile 4 (23.4%) (Supplementary Appendix A Table A1). Adult participants (aged ≥18 years) who had been diagnosed with HF with left ventricular ejection fraction (LVEF) ≤ 40% and NYHA functional classes II-IV were simulated in CEM. The majority of the patients were male (76%), and about three-quarters (75.1%) of the modelled patients were classified as NYHA class II (Supplementary Appendix A Table A1). Patients with HF originating from an ischaemic aetiology were 51.7%. HF*r*EF patients with type 2 diabetes mellitus (T2DM) were about half (49.8%) of the total population. The mean [standard deviation (SD)] starting age of the cohort was 60 (13.6) years, which was the mean age of HF patients reported in the Malaysian Heart Failure Registry (MyHF) (Abidin et al., 2021). The details of the inclusion criteria and demographic characteristics of the trial patients are provided in the published article (Packer et al., 2020).

## 2.3 Intervention and comparator

The intervention was empagliflozin at a dose of 10 mg once daily in addition to the SoC for the HF*r*EF patients. The comparator of this study was SoC only. The SoC comprised renin–angiotensin–aldosterone system blockers (either angiotensin receptor–neprilysin inhibitor [ARNi], angiotensin-converting enzyme inhibitor [ACEi], or angiotensin receptor blocker [ARB]), beta-blockers, MRA, ivabradine, diuretics, and cardiac devices when indicated. The utilisation patterns were estimated based on the EMPEROR-Reduced trial. Each medication in the SoC was assumed to have the same utilisation rate across all KCCQ-CSS quartiles. In the model, empagliflozin acted to delay disease progression and reduce the incidence of hHF and CV death in patients with HF*r*EF. The treatment effect of empagliflozin was assumed to be unaffected by different combinations of background therapies. This assumption was supported by the findings of the EMPEROR-Reduced trial *post hoc* analysis, which found that the clinical benefits of empagliflozin were independent of background therapies (Packer et al., 2020).

## 2.4 Input parameters

### 2.4.1 Clinical data

The model also considered improvement (ascent) or progression (descent) of disease *via* the transition of patients between KCCQ-CSS quartiles. Separate transition probabilities for movement between different KCCQ-CSS health states were obtained from the EMPEROR-Reduced trial for each treatment group. There were three transition probability matrices: baseline to week 12 (months 1–3), week 12 to week 32 (months 4–8), and week 32 to week 52 (months 9+). These reflected the different inflexion points observed in the data (Supplementary Appendix A Table A2).

Data obtained from the EMPEROR-Reduced trial were statistically analysed to derive the rates and risk of events and the efficacy of empagliflozin. The EMPEROR-Reduced trial was selected as the primary source for the clinical benefits of

empagliflozin because the trial was a multinational phase III trial that investigated the efficacy of empagliflozin and SoC against SoC alone on the composite outcomes of hHF or CV death in approximately 3,370 HF patients with LVEF<40%. In addition, the management of HF with medical therapies and devices is consistent with local and international clinical practice guidelines; thus, it is highly relevant to the actual clinical practice in the hospital setting. Statistical analyses of data from the EMPEROR-Reduced trial produced separate equations for all-cause death, CV death, hHF, and treatment discontinuation with the KCCQ-CSS quartile as the time-varying predictor (Supplementary Appendix A Table A3). Furthermore, the treatment effects of empagliflozin were included as a covariate in the hHF, death (CV and all-cause), and treatment discontinuation equations.

The risk equation for hHF events was derived using the ITT population of the EMPEROR-Reduced trial. The rate of first and recurrent hHF was estimated from a model constructed using a Poisson model fitted to patient-level data with generalised estimating equations to account for the repeated measures on patients. The model included treatment and time-varying KCCQ-CSS quartiles as predictors.

A parametric survival analysis using a Weibull distribution allowed for extrapolation of time to all-cause death and CV-related death as a function of treatment. KCCQ-CSS quartiles health states were used to estimate disease progression beyond the EMPEROR-Reduced trial duration. The Akaike information criterion values for various distributions were compared to determine the best distribution fitted to the equations (with lower values indicating better fit)—in this case, Weibull. This distribution enables a more accurate estimation of the survival benefit of empagliflozin beyond the duration of the clinical trial. An alternative distribution (exponential) was considered in the sensitivity analysis. The clinical events in a clinical trial, such as time-to-events (e.g., mortality), are often censored; therefore, not all the events of interest will be noticed for all the participants at the end of a trial. Generally, data censoring occurs because some participants did not experience the event of interest when the trial ended or were lost to follow-up. Data extrapolation for time to events will better estimate the efficacy of a new intervention beyond the trial period (Latimer, 2013). Deaths attributable to non-CV causes during each model cycle were calculated based on the difference between the all-cause death and CV death rates, which were estimated using the parametric equations or the difference between the rates of age- and sex-specific all-cause death and CV death for the general Malaysian population, whichever was the highest. This adjustment ensured that the non-CV death in the CEM was at least as high as it was in the general Malaysian population.

Parametric survival analysis was applied to estimate the time to empagliflozin treatment discontinuation (using exponential distribution). The alternative distribution (Weibull) was observed in the EMPEROR-Reduced trial. The treatment and time-varying KCCQ-CSS quartiles were considered predictors for empagliflozin discontinuation in the analysis. After discontinuing empagliflozin + SoC, patients were assumed to receive SoC and thus experience the same risk of clinical events, costs, and utility decrements as patients on SoC.

The CEM included the probability of experiencing adverse events from the treatment of HF and was modelled assuming a constant incidence rate. The model included the adverse events associated with empagliflozin with SoC and SoC monotherapy, and their respective rates were obtained from the EMPEROR-Reduced trial (Supplementary Appendix A Table A4).

### 2.4.2 Cost

This study adopted the perspective of the Malaysian healthcare system, whereby only direct medical costs were included. All costs are presented in 2021 Malaysian Ringgits (RM).

Drug costs for empagliflozin 10 mg and SoC therapies were obtained from the IQVIA dataset that had the market sale prices for Malaysia. The indicated strength and dosage for each drug were based on the Ministry of Health (MoH) Medication Formulary, which includes information on medications licensed to be used in MoH facilities. The monthly acquisition costs of SoC were based on the recommended doses of each active ingredient as confirmed by the cardiologists from the MoH facilities. The weighted average costs of each active ingredient were calculated using the percentage of utilisation (Supplementary Appendix A Table A5) from the in-house local study (Ong et al., 2022). Then, the weighted average cost of SoC was computed using the utilisation rate of HF medication classes reported in the EMPEROR-Reduced trial (at baseline) and the weighted average monthly costs of each class. Finally, the cost associated with each treatment regimen (i.e., empagliflozin + SoC and SoC monotherapy) in the model was computed (Supplementary Appendix A Table A6). The drug acquisition costs for empagliflozin + SoC and SoC monotherapy were RM 285.83 and RM 175.17, respectively.

The cost of hHF per admission was obtained from the in-house local study (Ong et al., 2022) (Supplementary Appendix A Table A7). The cost of hHF consisted of hospitalisation care, medication, diagnostic tests, and procedures. The cost of CV death was estimated from the cost analysis of the management of T2DM in the Action in Diabetes and Vascular Disease (ADVANCE) study using only the data for Malaysia (Clarke et al., 2010). The cost of CV death was defined as the cost of fatal events due to major coronary, cerebrovascular, and HF; it was first derived separately for male and female people. The weighted cost of each fatal event was weighted by the proportion of male and female people among the HF population obtained from the Malaysia Heart Failure Registry (National Heart Association Malaysia, 2021). The average cost of CV death was then weighted by the number of patients who died due to each fatal event in 2020. Appendix B provides additional details on how the cost of CV death was derived. The non-CV death cost was assumed to be the same between the comparator and intervention groups, thus incurring no additional cost for the MoH of Malaysia.

The HF-related disease management costs and frequencies associated with HF clinic follow-up visits were obtained from the in-house local study (Ong et al., 2022). The resources (frequency of visits and cost) utilised by patients with HF*r*EF were converted from an annual to monthly frequency and assumed to be the same for all KCCQ-CSS quartiles. Then, the disease management costs for all KCCQ-CSS quartiles were computed based on the frequency of visits and unit cost.

The costs of managing adverse events were calculated as weighted average costs based on the proportion of the type of care received (inpatient vs. outpatient visit), as estimated by the

cardiologists from the MoH facilities, and the unit cost of each visit (Supplementary Appendix A Table A8). The cost of inpatient care was obtained from the Malaysia Disease-Related Group (DRG) case-mix database. The cost of outpatient care was derived from the resource utilisation during outpatient visits as determined by experts' opinions on the treatment algorithm.

The costs were adjusted using the consumer price index (CPI) health domain to the 2021 Malaysian Ringgit value (Department of Statistics Malaysia, 2022).

### 2.4.3 Utility

The utility values were used to evaluate the impact of health states and clinical events on the HRQoL. The quality-adjusted life years (QALYs) accrued for each cycle were determined by subtracting utility reductions attributable to hHF and adverse events from the health state utilities.

Due to the unavailability of utility data for Malaysian HF patients, utility values associated with KCCQ-CSS quartiles and disutility values associated with adverse events and hHF were obtained from the ITT population pooled analysis in the EMPEROR-Reduced trial. The EQ-5D-5L questionnaire responses of patients were mapped to EQ-5D-3L (Alava et al., 2017) scores and converted into utility index scores using the appropriate value sets for the United Kingdom (Dolan, 1997). A linear mixed regression model was fitted to account for repeated utility measurement on the same patients, baseline demographic characteristics, comorbidities, health states, and clinical events (Supplementary Appendix A Table A9).

The impact of hHF and adverse events on HRQoL was captured as a one-off decrement in the proportion of the cohort who had experienced the events in each cycle. Decrements associated with the clinical event (hHF) and adverse events were applied over a duration equal to that of the model cycle length. The disutility values associated with urinary tract infection, genital mycotic infection, acute renal failure, and hypotension were obtained from Sullivan et al (Sullivan and Ghushchyan, 2006; Sullivan and Ghushchyan, 2016). Disutility values for other adverse events (hepatic injury, volume depletion, and bone fracture) were generated from a patient-level analysis of the EMPEROR-Reduced trial because the trial values were deemed to be more reflective of the population of interest compared to the values reported in the literature. The disutility value for hypoglycaemic events was obtained from the CEM of empagliflozin previously submitted to NICE (National Institute for Health and Care Excellence, 2011).

## 2.5 Outcome measures

The primary outcomes of this study were the total cost, total QALYs, incremental cost, incremental QALYs, and incremental cost-effectiveness ratio (ICER). The secondary outcomes of the CEM were the number of hHF, CV death, non-CV death, life years gained, and incremental cost per life year gained. The ICER was defined as the ratio of the difference in the total healthcare cost between the two treatment groups to the healthcare outcomes; it was expressed as cost per life year gained or cost per QALY gained. The ICER was compared to the cost-effectiveness threshold (CET) to determine the cost-effectiveness of empagliflozin. Adding empagliflozin to SoC in HF patients was deemed to be cost-effective when the ICER generated from this study was below the CET. The CET based on one-time GDP *per capita* in 2021was RM 47,439 per QALY (The World Bank, 2022).

## 2.6 Sensitivity analyses

Deterministic sensitivity analysis (DSA) was performed to determine the impacts of varying model inputs within the plausible range on the ICER and to identify model drivers. A tornado diagram displayed the results of the one-way sensitivity analyses.

A multivariate probabilistic sensitivity analysis (PSA) was conducted to examine how the ICER was affected by simultaneous variations in different model inputs within their feasible ranges based on the assumed probability distributions. The parameters included in the PSA are summarised in Supplementary Appendix A Table A10. The simulation was repeated 1,000 times to generate a range of ICERs for a given set of model inputs. The generated ICERs were then summarised and plotted on a cost-effectiveness plane. Finally, a cost-effectiveness acceptability curve was plotted to illustrate the cost-effectiveness probability of the addition of empagliflozin to the SoC at a given CET.

## 2.7 Scenario analyses

Scenario analyses were performed to evaluate certain scenarios that significantly impacted the ICER. A scenario analysis was conducted using the NYHA functional class as the health state instead of the KCCQ-CSS quartiles. The NYHA functional classification is commonly used in routine clinical practice to classify HF patients according to the severity of clinical symptoms and physical functionality. The CEM included four health states in this scenario: NYHA I, NYHA II, NYHA III/IV, and death. NYHA class III and class IV were combined due to the low number of patients in class IV. Similarly to the CEM model using KCCQ-CSS quartiles, HF patients could transfer between different health states and were subjected to the health state probability of experiencing hHF and death (CV and non-CV) during each cycle. Appendix C reports the transition matrices, risk equation for all-cause death, CV death, hHF, treatment discontinuation, utility, and disease management costs for the NYHA-based model. In accordance with the EMPERIOR-Reduced trial, the starting age of the cohort was increased from 60 years in the base case to 67 years. In addition, a different time horizon was explored to determine the uncertainties caused by the duration of treatment. Lastly, the effects of using the medication acquisition costs of MoH-funded hospitals on the ICER were also explored. The costs were obtained from the average acquisition costs by the procurement unit of a fully funded MoH hospital.

All patient subgroups in the EMPEROR-Reduced trial benefited from treatment with empagliflozin + SoC compared to SoC alone. The reduction in the risk primary composite outcome (hHF or CV death) was shown to be consistent across multiple subgroups, including baseline T2DM status, age (<65 years or ≥65 years),

**TABLE 1 Base-case results for the cost-effectiveness of adding empagliflozin to the standard of care.**

| Outcome | Empagliflozin + SoC | SoC | Incremental |
|---|---|---|---|
| Total Cost (RM) | 25,333 | 21,675 | 3,658 |
| Total LYs | 4.98 | 4.84 | 0.14 |
| Total QALYs | 3.64 | 3.46 | 0.18 |
| ICER, Cost per LY gained (RM/LY) | 26,268 | | |
| ICER, Cost per QALY gained (RM/QALY) | 20,400 | | |

ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years; RM: ringgit malaysia; SoC: standard of care.

sex race, baseline body mass index, and prior ARNi used (Packer et al., 2020). Thus, only the ITT population was considered in the CEM.

# 3 Results

## 3.1 Base-case cost-effectiveness analysis result

Table 1 displays the discounted results of the base-case analysis of adding empagliflozin to SoC against SoC alone for treating HF*r*EF over a lifetime horizon. SoC monotherapy was associated with 4.84 life years, 3.46 QALYs, and a total cost of RM 21,675 per patient. Adding empagliflozin to SoC increased the accrued life years and QALYs by 0.14 and 0.18 per person, respectively, but at an additional cost of RM 3,658 per person. Treatment of HF*r*EF patients with empagliflozin as an add-on to SoC was cost-effective against SoC monotherapy, with an ICER of RM 20,400 per QALY. The ICER generated from the CEM was well below the CET of 1xGDP *per capita* (RM 47,439/QALY). Essentially, the treatment with empagliflozin + SoC against SoC alone was cost-effective.

Treatment with empagliflozin + SoC was associated with a reduction in hHF and CV death incidence by 19.3% and 5.8% compared to SoC (Table 2). In addition, HF patients treated with empagliflozin + SoC had higher QALYs (+0.18) compared to SoC monotherapy. The incremental QALYs gained were driven by the increased life years and longer time spent in the alive state, particularly among patients in KCCQ-CSS quartile 4 (+0.20 life years and +0.17 QALYs). Furthermore, the incidence of hHF averted by the treatment of empagliflozin + SoC contributed to 0.04 QALYs gained. Treatment with empagliflozin + SoC was also associated with a lower risk of developing acute renal failure, hepatic injury, and hypoglycaemic events compared to SoC monotherapy. Conversely, treatment with empagliflozin + SoC led to a higher rate of adverse events such as urinary tract infection, genital mycotic infection, volume depletion, hypotension, and bone fracture.

The main cost driver of incremental costs associated with empagliflozin + SoC treatment was the drug acquisition cost of empagliflozin. This was partially offset by cost savings from the reduction in the incidence of CV death and hHF relative to SoC. The costs of adverse event management were nearly equivalent for both arms. Treatment with empagliflozin + SoC increased the incidence of volume depletion and hypotension. However, the increased costs associated with these adverse events were partially offset by the decreased incidence of acute renal failure and hepatic injury, which are more expensive to treat than in the other modelled adverse events. The life years gained from the treatment of empagliflozin + SoC translated to a higher disease management cost in the intervention arm. This is because the disease management cost was calculated based on the survival duration. Furthermore, patients treated with the intervention arm remained in quartile 4 for a longer duration, leading to the highest incremental disease management cost in this health state.

## 3.2 Deterministic sensitivity analysis

Figure 2 displays the DSA results. The drug acquisition cost of empagliflozin was the main driver of the cost-effectiveness of adding empagliflozin to SoC against SoC alone. The ICER changed by 35.2% when the acquisition cost of empagliflozin changed by 30%. The second most impactful parameter was the treatment effect of empagliflozin + SoC in preventing CV death. The ICER increased by 22.3% to RM 24,949 per QALY when the effect of empagliflozin + SoC associated with CV death was assumed to be the same as SoC alone, but the ICER dropped to RM 14,346 per QALY at the upper value (Supplementary Appendix D Table D1). The other drivers of the CEM were the treatment effect associated with hHF, the discount rate on health, and disutility for a hHF event.

## 3.3 Probabilistic sensitivity analysis

The results of the PSA are summarised in the cost-effectiveness plane (Figure 3) and the cost-effectiveness acceptability curve (Figure 4). Of 1,000 iterations, 82.8% were located in the north-east quadrant of the cost-effectiveness plane, thus indicating that adding empagliflozin to the SoC was more costly but more treatment effective than SoC alone. In addition, among these, 72.9% of the simulation's replications produced an ICER value below the 1xGDP *per capita* (RM 47,439 per QALY). Furthermore, the average ICER from the PSA analysis was RM 20,266, similar to the ICER generated from the base-case scenario of RM 20,400 (Supplementary Appendix D Table D2). The small difference between the ICER derived from the base-case scenario and the PSA reflect the robustness of the CEM.

**TABLE 2 Summary of clinical and cost outcomes for the base-case scenario.**

| Clinical outcomes | Empagliflozin + SoC | SoC | Incremental |
|---|---|---|---|
| Event rates (per 100 patient years) | | | |
| HF hospitalisation | 17.02 | 21.10 | −4.08 |
| CV death | 9.58 | 10.17 | −0.59 |
| Non-CV death | 8.06 | 8.03 | 0.04 |
| Adverse events | | | |
| Urinary tract infection | 3.99 | 3.76 | 0.23 |
| Genital mycotic infection | 1.06 | 0.53 | 0.53 |
| Acute renal failure | 8.46 | 9.02 | −0.56 |
| Hepatic injury | 3.58 | 3.83 | −0.25 |
| Volume depletion | 9.07 | 8.76 | 0.31 |
| Hypotension | 8.02 | 7.69 | 0.33 |
| Hypoglycaemic event | 1.22 | 1.25 | −0.03 |
| Bone fracture | 1.97 | 1.89 | 0.08 |
| Time on treatment (undiscounted), LYs, and QALYs (discounted) per patient | | | |
| Time receiving empagliflozin (years) | 3.55 | N/A | |
| **Total LYs** | **4.98** | **4.84** | **0.14** |
| KCCQ-CSS Quartile 1 | 0.77 | 0.84 | −0.07 |
| KCCQ-CSS Quartile 2 | 1.02 | 0.99 | 0.03 |
| KCCQ-CSS Quartile 3 | 1.32 | 1.34 | −0.02 |
| KCCQ-CSS Quartile 4 | 1.88 | 1.67 | 0.20 |
| **Total QALYs** | **3.64** | **3.46** | **0.18** |
| KCCQ-CSS Quartile 1 | 0.46 | 0.51 | −0.04 |
| KCCQ-CSS Quartile 2 | 0.73 | 0.71 | 0.02 |
| KCCQ-CSS Quartile 3 | 1.04 | 1.06 | −0.02 |
| KCCQ-CSS Quartile 4 | 1.61 | 1.44 | 0.17 |
| Loss due to hHF | −0.207 | −0.252 | 0.04 |
| Loss due to AEs | −0.005 | −0.005 | 0.00 |
| **Cost Outcomes** | **Empagliflozin + SoC** | **SoC** | **Incremental** |
| Cost outcomes (discounted), per patient | | | |
| **Drug acquisition cost (RM)** | **14,753** | **10,168** | **4,585** |
| **Clinical event management cost (RM)** | **5,600** | **6,596** | **−996** |
| HF hospitalisation | 4,414 | 5,369 | −955 |
| CV death | 1,186 | 1,227 | −41 |
| **AE management cost (RM)** | **3,291** | **3,269** | **22** |
| Urinary tract infection | 34 | 31 | 3 |
| Genital mycotic infection | 17 | 8 | 9 |
| Acute renal failure | 1,331 | 1,382 | −51 |
| Hepatic injury | 571 | 595 | −24 |
| Volume depletion | 443 | 416 | 28 |
| Hypotension | 510 | 475 | 36 |
| Hypoglycaemic event | 42 | 42 | 0 |
| Bone fracture | 343 | 320 | 23 |
| **Disease management cost (RM)** | **1,689** | **1,642** | **47** |
| KCCQ-CSS Quartile 1 | 260 | 285 | −24 |
| KCCQ-CSS Quartile 2 | 345 | 334 | 11 |
| KCCQ-CSS Quartile 3 | 446 | 455 | −8 |
| KCCQ-CSS Quartile 4 | 637 | 568 | 69 |
| **Total cost (RM)** | **25,333** | **21,675** | **3,658** |

AE: adverse events; CSS: clinical summary score; CV: cardiovascular; HF: heart failure; hHF: hospitalisation due to heart failure; LY: life year; KCCQ: kansas city cardiomyopathy questionnaire; QALY: quality-adjusted life year; RM: ringgit malaysia; SoC: standard of care.

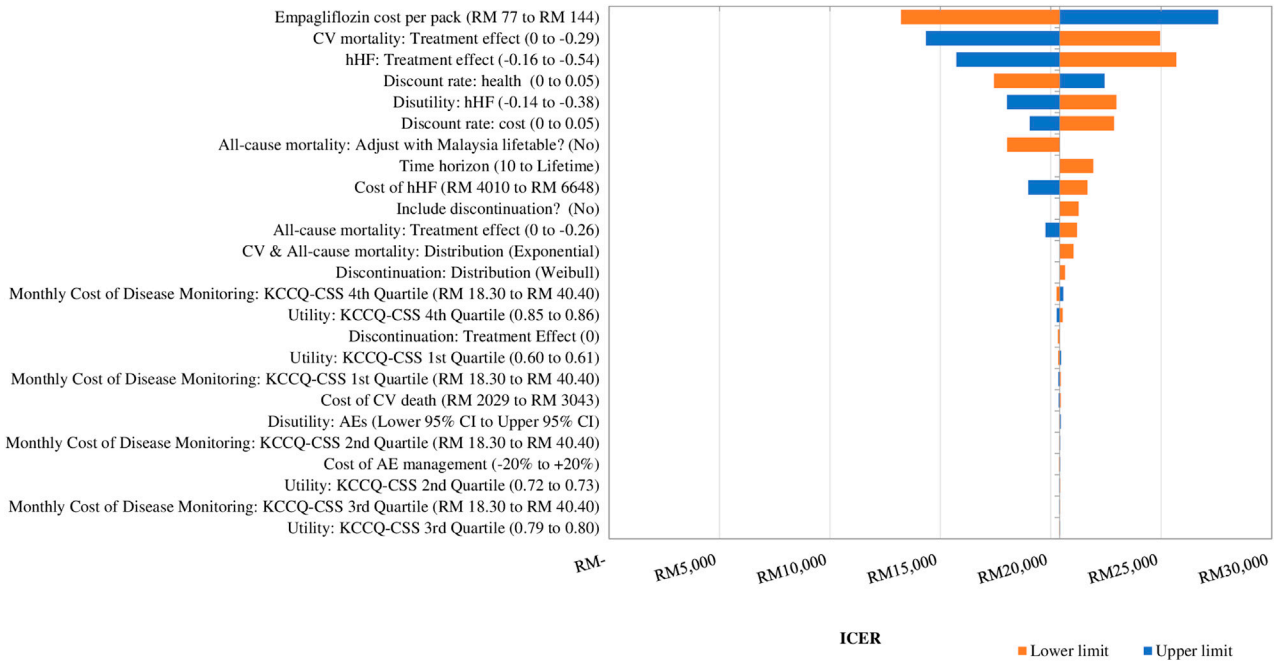


FIGURE 2
Tornado diagram showing the deterministic sensitivity analysis of the cost-effectiveness model simulation. GDP: gross domestic product; QALY: quality-adjusted life year; RM: Ringgit Malaysia; SoC: standard of care. 1xGDP *per capita* is RM 47,439 per QALY.

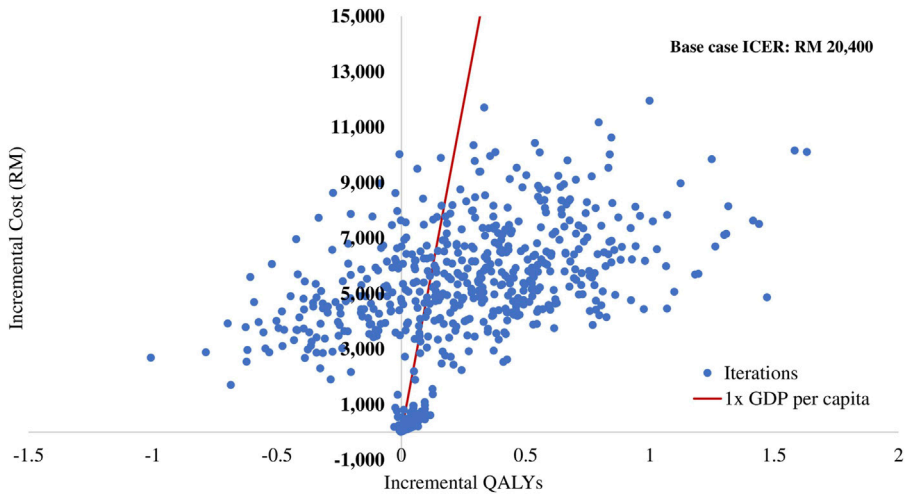


FIGURE 3
Scatter plot of incremental cost and incremental quality-adjusted life year for empagliflozin + SoC vs SoC. QALY: quality-adjusted life year; RM: Ringgit Malaysia; SoC: standard of care.

## 3.4 Scenario analysis

A scenario analysis was conducted wherein the health states were defined as NYHA functional classes instead of KCCQ-CSS quartiles. In the NYHA-based model, the total cost for empagliflozin + SoC was RM 23,970 per patient, which was RM 3,395 higher than the SoC alone over the lifetime horizon (Supplementary Appendix E Table E1). Similarly, the empagliflozin add-on to the SoC resulted in increased life years (+0.05) and QALYs (+0.09) against SoC alone. As a result, the deterministic analysis based on the NYHA model generated an ICER of RM 36,682 per QALY, which was below the CET.

The empagliflozin + SoC arm was associated with a reduction in hHF and CV death incidence rates but a slight increase in the

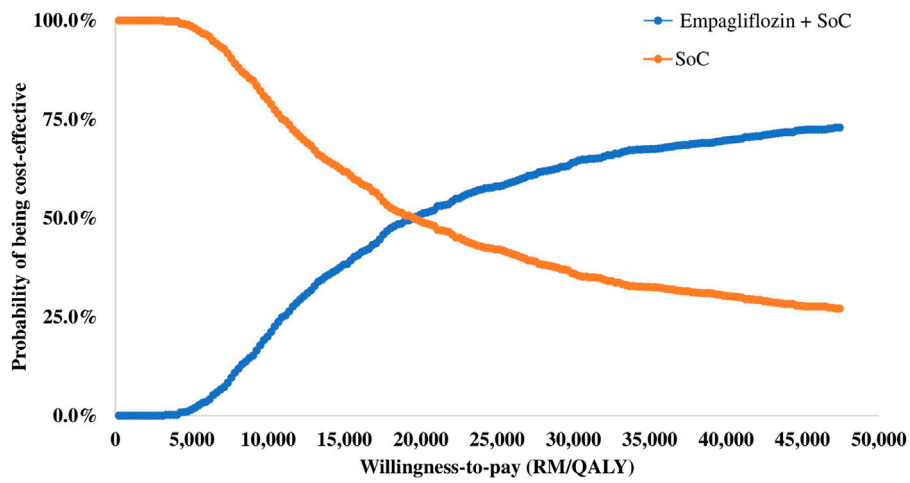


FIGURE 4
Cost-effectiveness acceptability curve for empagliflozin + SoC vs SoC.

**TABLE 3 Findings of scenario analyses presented as ICER.**

| Scenarios | Incremental cost (RM) | Incremental QALYs | ICER (RM/QALY) |
|---|---|---|---|
| **Base case** | 3,658 | 0.18 | 20,400 |
| **Time horizon** | | | |
| 1 year | 819 | 0.02 | 34,365 |
| 5 years | 2,679 | 0.10 | 25,903 |
| 10 years | 3,440 | 0.16 | 21,922 |
| **Source of medication cost** | | | |
| **IQVIA** | | | |
| NYHA | 3,395 | 0.09 | 36,682 |
| **MoH acquisition cost** | | | |
| KCCQ-CSS | 1,188 | 0.18 | 6,627 |
| NYHA | 1,128 | 0.09 | 12,188 |
| **Cohort starting age** | | | |
| 67 years | 3,125 | 0.14 | 22,268 |

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; RM: ringgit malaysia.
CSS: clinical summary score; CV: cardiovascular; KCCQ: kansas city cardiomyopathy score.
*Adverse events: urinary tract infection, genital mycotic infection, acute renal injury, hepatic injury, hypotension, hypoglycaemic event, and bone fracture.

non-CV death rate (Supplementary Appendix E Table E2). Furthermore, the clinical benefits of empagliflozin in reducing the incidence of hHF and CV death translated in cost saving; these partially offset the cost of acquiring empagliflozin in the intervention arm. However, the disease management cost of the intervention arm increased by RM 18 per patient due to the increased lifespans of HF*r*EF patients.

The ICER decreased from RM 34,365 per QALY to RM 21,922 per QALY when the time horizon was increased from 1 year to 10 years (Table 3). In addition, when the cohort's starting age was 67 years (60 years for the based-case analysis), the ICER increased to RM 22,268 per QALY. When the MoH acquisition cost was applied, the ICER for KCCQ-CSS and NYHA health states decreased to RM 6,627 per QALY and RM 12,188 per QALY, respectively.

## 4 Discussions

This study is the first cost-utility study that investigated the addition of empagliflozin to the SoC in the treatment of HF*r*EF in Malaysia. It was performed based on the clinical efficacies of

empagliflozin derived from the EMPEROR-Reduced trial and localised cost data. The base-case analyses indicated that empagliflozin + SoC was cost-effective compared to SoC alone. The prevention of hHF primarily drove the cost-effectiveness of empagliflozin, resulting in more life years and QALYs gained among patients treated with empagliflozin. Moreover, the cost-savings from the prevention of hHF partially offset the acquisition cost of empagliflozin.

Cost-utility analyses of empagliflozin + SoC against SoC alone were conducted in Thailand (Krittayaphong and Permsuwan, 2022), Taiwan (Liao et al., 2021), the United Kingdom (National Institute for Health and Care Excellence, 2022), and China (Jiang et al., 2021; Lin et al., 2022; Sang et al., 2022; Tang and Sang, 2022). Although these studies reported that empagliflozin + SoC was more cost-effective than SoC alone, a localised country-based economic evaluation need to be conducted in Malaysia due to concerns about the applicability and generalisability of findings from other cost-utility analyses. The ICER generated from the studies performed in other countries studies cannot be applied to the local setting because of the differences in the i) resources and associated costs, ii) acquisition costs of medications, iii) healthcare system, iv) health utilities valuations, v) analysis perspective, and vi) discount rate.

Liao *et al.* performed a cost-effectiveness evaluation using a two health states model (stable HF and death) with hospitalisation as a transient event from the healthcare payer perspective of Taiwan (Liao et al., 2021). The study reported that the ICER generated for the add-on empagliflozin against SoC alone was USD 20,508 per QALY, below the country's 1x GDP *per capita* of USD 25,000. Subsequently, the author also examined the cost-effectiveness of adding empagliflozin to the SoC for different countries from the Southeast Asia–Pacific region using localised cost data. The ICERs generated in the study were consistently below these countries' 1xGDP *per capita* WTP threshold, except for Thailand. Using the two-states model to simulate the analysis in the CEM posed a few concerns, as mentioned in the health technology assessment reports submitted to NICE (National Institute for Health and Care Excellence, 2012; National Institute for Health and Care Excellence, 2016). The critical concerns highlighted were the calculated risk of clinical events by considering the cohort's baseline characteristics during randomisation and the assumption that the constant rate of hHF would overestimate the long-term efficacy of the medication. In addition, using the multi-state model over the two-state model would allow the clinical outcomes to be modelled using different stages of disease severity. The benefit of the treatment effect on disease progression can also be considered in the multi-state model.

The CEAs modelled from the Chinese medical and health system perspective reported that the ICER for empagliflozin + SoC compared to SoC alone was below the country's 1xGDP *per capita* (Jiang et al., 2021; Lin et al., 2022; Tang and Sang, 2022). These studies simulated the CEM using the NYHA functional classification as the health state (Jiang et al., 2021; Lin et al., 2022; Tang and Sang, 2022). The problems associated with using the NYHA functional classification as a proxy for disease severity and progression were its non-reproducibility and subjectivity, as the NYHA assessment is not patient-centric and is subjected to interpersonal variation during evaluation by cardiologists (Raphael et al., 2007; Kosiborod et al., 2020). Together with the advantages mentioned in the methodology section, KCCQ is a more suitable tool to measure the progression of HF status.

The DSA results of the current study were robust to variation in the key model parameters and their plausible ranges. All the ICERs generated from the DSA were below the CET. The most impactful parameter that determined the cost-effectiveness of empagliflozin + SoC against SoC alone was the cost of empagliflozin. In the scenario analysis when the MoH acquisition costs of empagliflozin and other drugs were applied (i.e., lower than the average market price derived from the IQVIA database), the ICER reduced markedly from RM 20,400 per QALY in the base case to RM 6,627 per QALY. Thus, empagliflozin is highly cost-effective from the perspective of the MoH of Malaysia. The model also found that ICER was sensitive to CV death risk, and a slight change in this parameter would have a significant impact on the ICER (Jiang et al., 2021; Tang and Sang, 2022). The treatment effect of empagliflozin in preventing hHF was also the key driver that drove the cost-effectiveness of empagliflozin + SoC against SoC alone. The clinical efficacy of empagliflozin on the primary composite outcome was primarily driven by the reduction in the risk of hHF (Packer et al., 2020). Furthermore, hospitalisation severely impacts the HRQoL of HF patients because of the symptoms experienced by patients during the acute decompensated state, such as shortness of breath and lethargy (Albuquerque de Almeida et al., 2020). In addition, the risk of mortality has been shown to increase after each subsequent hHF (Lin et al., 2017). Thus, the clinical benefit of empagliflozin in averting hHF translates into more life years and QALYs gained, which significantly impact the ICER. These findings further explain the key parameters, such as the disutility associated with hHF, that drove the cost-effectiveness of empagliflozin + SoC relative to SoC alone. Apart from decreasing in a younger cohort, the ICERs also decreased when the time horizon increased. This indicates that the addition of empagliflozin to SoC has more pharmacoeconomic incentives, which result from the greater quantity of clinical events prevented and more life years and QALYs gained throughout HF patients' lifespans. Following these scenarios, the ICERs were sensitive to the variations in the discount rate of costs and health outcomes. However, the findings from DSA and PSA confirmed that the ICERs were robust with respect to changes in key model parameters in the CEM.

In the scenario analysis, the ICER increased to RM 36,682 per QALY when the disease progression was modelled using the NYHA functional classes (RM 20,400 per QALY in the base-case scenario using KCCQ-CSS quartiles). The marked difference between the ICER for both models was primarily contributed by the distribution of patients based on the NYHA class relative to those in the KCCQ-CSS quartiles. In the NYHA model, about three-quarters of the patients entered the model with NYHA class II, and the remaining patients were split between NYHA class III and class IV (Supplementary Appendix A Table A1). In comparison, the distribution of patients was evenly spread across different degrees of disease severity when the disease progression was captured by the KCCQ-CSS quartiles. In addition, the monthly probability of transitioning out from NYHA class II starts low and decreases over time (Supplementary Appendix C Table C1), resulting in most patients remaining in the NYHA class II until the end of the

simulation. Thus, fewer patients benefited from the treatment effect of empagliflozin + SoC in the NYHA class model, as captured in the risk equations for the clinical events (i.e., all-cause death, CV death, and hHF) and the improvement in health states. This finding is further confirmed by the fact that the life years and QALYs gained in the NYHA model were primarily contributed by patients in NYHA class II.

Despite clinical trials demonstrating the efficacies of SGLT2i in improving clinical outcomes in HFrEF patients (McMurray et al., 2019; Packer et al., 2020) and international guidelines advocating SGLT2i as part of guideline-directed medical therapy (GDMT) for HFrEF patients (McDonagh et al., 2021; Heidenreich et al., 2022), the SGLT2i prescribing rates reported in multiple observational studies are still low (Canonico et al., 2022; Chakrala et al., 2023; Okoroike et al., 2023). One potential barrier that prevents prescribing GDMT, including SGLT2i, is the medication acquisition costs (Canonico et al., 2022). Adding empagliflozin to SoC resulted in higher monthly medication costs and a longer life expectancy than SoC monotherapy, which increased lifetime medication and disease management costs even further. These additional costs, however, were partially offset by cost savings from avoiding hHF. The trade-offs between additional benefits gained and higher lifetime costs captured by ICER were well below the CET, indicating that empagliflozin + SoC was more cost-effective than SoC monotherapy. Adopting a cost-effective intervention, such as empagliflozin in this study, can improve the overall health of a population. Hence, the finding from this study confirms the economic effectiveness of empagliflozin in treating HF*r*EF and supports the decision to enlist the medication in the National Medicines Formulary. Consequently, this will improve access to the cost-effective medication and increase its prescribing rate.

The primary strength of the current study is that it is based on the EMPEROR-Reduced trial, wherein the background HF treatments in the comparator groups were reflective of the most recent HF treatment guidelines and closely resembled the suggested treatment regimen of HF*r*EF in Malaysia. This may increase the relevance of the results of this analysis. Secondly, the disease progression was captured by the patients' self-reported KCCQ-CSS outcomes, which are both sensitive and reproducible in detecting changes in HF health status (Green et al., 2000; Spertus et al., 2005; Joseph et al., 2013) and a crucial secondary outcome in the EMPEROR-Reduced trial (Packer et al., 2020). This allows the granularity of the trial data to be captured. The risk of hHF can then be modelled based on the KCCQ-CSS health states.

The results of the analysis should be interpreted with its several limitations in mind. First, the long-term treatment effects of empagliflozin + SoC and SoC alone were extrapolated from the median follow-up duration of the EMPEROR-Reduced trial, resulting in uncertainty in the long-term estimates. Nevertheless, this is a limitation inherent to any CEM. The results of the sensitivity analyses suggest that the choice of parametric distribution for important clinical outcomes did not significantly influence the ICER. Therefore, it is unlikely that the uncertainties would change the conclusion of the study. Second, the treatment effects of empagliflozin on clinical events were estimated from the ITT population of the EMPEROR-Reduced trial. The uptake of medications could be different in the Malaysian clinical settings, especially the utilisation of ARNi (19.5% in the trial vs 6% in the Malaysia Heart Failure Registry (Ghazi et al., 2021)). Even so, the sub-group analysis of the EMPEROR-Reduced trial showed that the treatment effects of empagliflozin on the primary composite outcome (hHF or CV death) were consistent and independent of the baseline use of ARNi. Third, the CEM did not include diabetic ketoacidosis as one of the rare and recognised adverse effects of SGLT2i medications. This exclusion was supported by the fact that diabetic ketoacidosis was not observed in the EMPEROR-Reduced trial. Additionally, there was no imbalance in the incidence rates between the two treatment groups in the EMPA-REG OUTCOME trial involving T2DM patients with established CV diseases (Zinman et al., 2015). Fourth, the majority of the ITT population in the EMPEROR-Reduced trial was of Caucasian ethnicity, with Asian patients comprising approximately 18% of the total population. Moreover, the subgroup analysis showed that the risk reduction of the primary composite outcome was greater in the Asian population. Thus, the ICER values generated in the current study may represent a conservative estimate. Finally, we could not obtain data regarding the health utility of each health state in the Malaysian population, which may have potentially introduced some bias to the CEM outcomes. However, the ICERs were well below the CET even when the lower estimates of utility and disutility values were used in the one-way sensitivity analyses. In addition, the PSA was simulated using a wide range of health utilities to account for this difference. This further confirms the robustness of this finding as nearly all iterations were below the CET.

## 5 Conclusion

In conclusion, the CEM provided objective evidence that the addition of empagliflozin to SoC compared to SoC alone for the treatment of HF*r*EF was associated with improved clinical outcomes and HRQoL of patients with HF*r*EF at a reasonable upfront cost to pay. In the current study, empagliflozin + SoC was cost-effective from the perspective of the MoH of Malaysia. Considering the increasing prevalence of HF and especially the HFrEF population, cost-effective treatments such as empagliflozin could be important to the healthcare system.

## Data availability statement

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

## Author contributions

SCO and JZL: conceptualisation, data curation, formal analysis, methodology, and project administration. SCO: funding acquisition and supervision. SCO, JZL, and SL: resources and software JL: writing—original draft. SCO, JZL, and SL: validation and writing—review and editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

SL was employed by Boehringer Ingelheim International GmbH.

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

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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.2023.1195124/full#supplementary-material

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# Cost-effectiveness of empagliflozin for the treatment of heart failure: a systematic review

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**Objective:** This study aims to synthesize evidence on the cost-effectiveness of empagliflozin for heart failure (HF).

**Methods:** MEDLINE, Embase, the Cochrane Library, EconLit, CNKI, Wanfang Data and Chongqing VIP were searched to identify original articles on cost-effectiveness of empagliflozin for HF, and literature surveillance ended on 20 November 2022. The reporting quality of the included articles was determined using the Consolidated Health Economic Evaluation Reporting Standards statement.

**Results:** Of 97 articles identified, 11 studies published from 2020 to 2022 met the inclusion criteria, and the overall quality was accepted. The studies were conducted in 8 countries (China, Japan, Korea, Singapore, Thailand, Australia, United States, and United Kingdom). This body of evidence suggested that add-on empagliflozin was cost effective for HF with reduced ejection fraction (HFrEF) patients compared to standard of care alone in all the related studies including China, Japan, Korea, Singapore, Thailand, and Australia. For HF with preserved ejection fraction (HFpEF) patients, add-on empagliflozin was cost effective in China and Australia, but not in United States and Thailand. For HF with diabetes, add-on empagliflozin was cost effective in United Kingdom. Moreover, the incremental cost-effectiveness ratios (ICER) were lower for patients with diabetes than without in subgroup analysis. In the uncertainty analysis of all included studies, the ICERs were most sensitive to the cost of empagliflozin and cardiovascular mortality, followed by the cost of the standard treatment, hazard ratio of HF hospitalization.

**Conclusion:** add-on empagliflozin for HFrEF might be cost-effective or dominant compared with standard of care alone. However, for HFpEF patients, add-on empagliflozin might be cost-effective in China and Australian, but not cost-effective in United States and Thailand.

KEYWORDS

**empagliflozin, heart failure, economic evaluation, cost-effectiveness, systematic review**

## Introduction

Heart Failure (HF), a heterogeneous syndrome characterized by significant morbidity and mortality, poor functional capacity and quality of life, and high costs, affects more than 64 million people worldwide (James et al., 2018; Baman and Ahmad, 2020; Savarese et al., 2022). The overall lifetime healthcare costs due to HF per patient was estimated to be USD

$126,819 by a systematic review including 16 international studies from 2004 to 2016 (Lesyuk et al., 2018). Due to the raising prevalence of HF, the economic burden of the disease on healthcare expenditures worldwide is even expected to increase. In the US, the total cost for HF was estimated to be USD $30.7 billion in 2012, with projections suggesting a significant increase in costs to USD $69.8 in 2030 (Virani et al., 2021). Therefore, it is imperative to undertake economic evaluation of the therapies for HF to reduce its social and economic burden.

Treatment for HF depends on its cause, symptoms, and ejection fraction, a measure of the heart's squeezing function. Historically, the standard of care (SoC) for HF is standard heart failure device and drug therapy, which included diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers. Recently, several clinical trials have confirmed that sodium-glucose cotransport 2 (SGLT2) inhibitors could reduced the risk of cardiovascular (CV) death or hospitalization for heart failure (Packer et al., 2020; Packer et al., 2021; Santos-Gallego et al., 2021). Empagliflozin, a SGLT2 inhibitor, is the newest medication approved by the US Food and Drug Administration for HF in 2021 and by the Chinese National Medical Products Administration in 2022. The empagliflozin outcome trial in patients with chronic heart failure (EMPEROR) evaluated that empagliflozin reduced CV mortality or HF hospitalization in patients with HFrEF or HFpEF independently of their glycemic status (Anker et al., 2021; Packer et al., 2021). It is currently the only drug that has been proven to improve the outcome of patients with HFpEF by a large randomized controlled trial. Therefore, empagliflozin is recommended not only for HFrEF, but also for HFpEF by 2022 AHA/ACC/HFSA guideline for the management of HF (Heidenreich et al., 2022).

The clinical effects of empagliflozin for patients with HF are demonstrated. Due to the limitation of healthcare resources, the cost effectiveness of empagliflozin for HF must be considered. Several studies from different countries have evaluated the cost effectiveness of empagliflozin for HF, but there were differences in the study methods and results. Therefore, it is necessary to synthesize these studies so that researchers can quickly obtain more comprehensive economic data. This study is the first systematic review to appraise and synthesize the economic evidence of empagliflozin for HF patients. Our results would provide valuable information to administrators and health workers in making the best decisions.

# Methods

## Literature search

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021). Eligible studies were identified from the following databases: MEDLINE, Embase, the Cochrane Library, and EconLit databases with no language restrictions, and CNKI, Wanfang Data and Chongqing VIP for Chinese-language studies. We restricted the analysis to original articles on cost-effectiveness of empagliflozin for HF, and literature surveillance ended on 20 November 2022. The detailed search strategy was presented in Supplementary Table S1.

## Eligibility criteria

Articles meeting the following criteria were included: 1) target population was patients with HF; 2) empagliflozin intervention was included and comparison was not limited; 3) the original economic evaluation, examined costs with their consequences, and reported incremental cost-effectiveness ratios (ICERs) or incremental cost-utility ratios; 4) complete full-text formats were available. Duplicated literature, reviews, commentaries, conference abstracts, expert opinions, and other secondary research were excluded.

## Study selection

Titles and abstracts were screened against the eligibility criteria and then full-text formats of all potentially relevant publications were obtained and reviewed to decide whether they met the inclusion criteria by two authors. Another discussion could be conducted to resolve discrepancies.

## Reporting quality assessment

The 28-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al., 2022) was used to appraise the reporting quality of studies. Each item was scored as having met the criteria in full ("1"), not at all ("0"), or not applicable (NA). According to the scores, studies were categorized as good (>75%), moderate (50%–75%), and low (<50%).

## Data extraction and synthesis

We made standardized forms to extract relevant information such as basic information (i.e., authors' name, target population, intervention and comparison), methods and the main results. A narrative synthesis was used to evaluate the aims, methods, settings, and results of the included studies. If possible, we undertook horizontal comparison of modeling technique, cost perspective, measures of benefit used, ICERs, and results of uncertainty analysis across the studies. For better comparing the results of economic analysis between different currencies, all reported ICERs are converted in US$ for the common price year 2022 using the "CCEMG-EPPI-Centre Cost Converter" Version 1.6 (CCEMG-EPPI-Centre Cost Converter, 2019).

# Result

## Studies identified

Of the 97 potential publications retrieved, 25 were excluded for repetitive publications, and 53 were excluded based on title and abstract. The remaining 19 were retrieved for full-text screening, and 8 were excluded for reasons such as review articles ($n = 1$), not heart failure ($n = 1$), and meeting abstracts ($n = 6$). Finally, 11 publications (Reifsnider et al., 2020; Jiang et al., 2021; Liao et al., 2021; Wan et al., 2022a; Jiang and Xie, 2022; Krittayaphong and Persuwan, 2022;

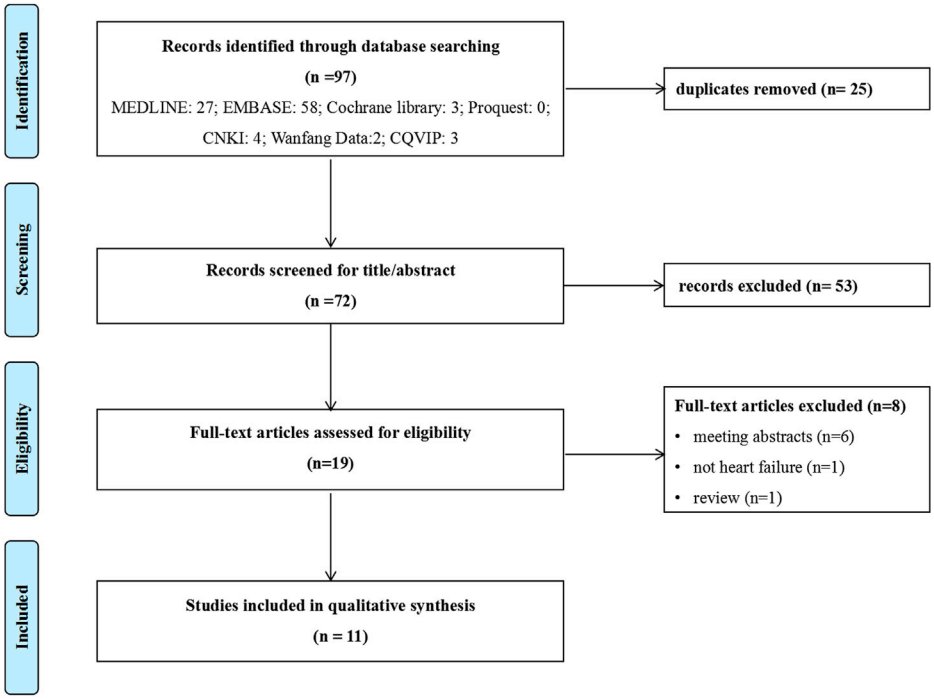


FIGURE 1
Flowchart of literature search. CNKI: China National Knowledge Infrastructure database; CQVIP: Chongqing VIP database.

Lin et al., 2022; Lou et al., 2022; Tang and Sang, 2022; Zheng et al., 2022; Zhou et al., 2022) were included in this review, and more details about studies identified were reported in Figure 1.

## Basic characteristics

The general characteristics of the included studies were reported in Table 1. The included studies were conducted in 6 developed countries (United Kingdom, United States, Australia, Korea, Japan, and Singapore) and 2 developing countries (China and Thailand). The Markov model was used in 10 studies, and discrete-event simulation model was used in 1 study. The populations simulated in all the models were based on the basic characteristics of those in the EMPEROR-Preserved study or the EMPEROR-Reduced study. All the included studies compared empagliflozin plus SoC with SoC alone from the healthcare perspective. The time horizons were applied for 10 years or more. Four studies used 1-month Markov cycles, and 6 studies used 3-month Markov cycles.

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## Reporting quality assessment

All studies have not mentioned three items, which were health economic analysis plan, approach to engagement with patients and others affected by the study, and effect of engagement with patients and others affected by the study respectively. Four studies failed to report characterizing distributional effects (Wan YM. et al., 2022; Jiang and Xie, 2022; Zhou et al., 2022; Reifsnider et al., 2020). The four items mentioned above have been added in the CHEERS statement updated in 2022, therefore the studies did not report well. However, the remaining 24 items were reported sufficiently in all of the included studies, and the included studies were all evaluated as of good quality. More details were summarized in Table 2.

## Cost-effectiveness analysis

Four studies provided economic evaluation for HFrEF, 4 studies for HFpEF, 2 studies for HFrEF and HFpEF, 1study for HF with type 2 diabetes. The overview of the economic evaluation outcomes are summarized in Table 3.

Six studies provided economic evaluation for HFrEF. Four studies conducted in China indicated that adding empagliflozin to SoC was proven to be more cost-effective for HFrEF from a healthcare system perspective. One study conducted in Thailand have the same results as the above studies in China. One study was conducted in China (Taiwan), Australia, Korea, Singapore, Japan, and Thailand. The results showed that adding empagliflozin to SoC

**TABLE 1 General characteristics of the included studies.**

| References | Country | Perspective | Model | Target population | Age | Intervention | Comparison | Cost components | Length of cycle | Time horizon | Discount rate (%) | Health outcomes | Source of effectiveness |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liao et al. (2021) | China (Taiwan), Japan, Korea, Singapore, Thailand, Australia | Healthcare System | Markov | HFrEF | 67 | EMPA + SoC | SoC | medical costs | 1 month | 15 years | 3 | QALY | RCT |
| Lou et al. (2022) | China | Healthcare system | Markov | HFpEF | 72 | EMPA + SoC | SoC | direct medical costs | 3 months | 30 years | 5 | QALY | RCT |
| Jiang and Xie (2022) | China | Healthcare system | Markov | HFpEF | 66 | EMPA + SoC | SoC | the cost of hospitalization for HF, standard therapy, and empagliflflozin | 3 months | 10 years | 5 | QALY | RCT |
| Jiang et al. (2021) | China | Medical and health system | Markov | HFrEF | 66 | EMPA + SoC | SoC | direct medical costs | 3 months | 10 years | 5 | QALY | RCT |
| Zhou et al. (2022) | Australia | Healthcare system | Markov | HFpEF | 72 | EMPA + SoC | SoC | direct medical costs | 1 month | lifetime | 5 | QALY | RCT |
| Lin et al. (2022) | China | Healthcare system | Markov | HFrEF | 65 | EMPA + SoC | SoC | direct medical costs | 3 months | 15 years | 5 | QALY | RCT |
| Zheng et al. (2022) | United States | Healthcare system | Markov | HFpEF | 72 | EMPA + SoC | SoC | direct healthcare costs | 1 month | lifetime | 3 | QALY | RCT |
| Reifsnider et al. (2020) | United Kingdom | Healthcare system | Discrete-event simulation | HF with T2D | - | EMPA + SoC | SoC | direct healthcare costs | - | lifetime | 3.5 | QALY | RCT |
| Krittayaphong and Permsuwan (2022) | Thailand | Healthcare system | Markov | HFrEF and HFpEF | 60 | EMPA + SoC | SoC | direct medical costs | 3 months | lifetime | 3 | QALY | RCT |
| Tang and Sang (2022) | China | Healthcare system | Markov | HFrEF and HFpEF | 65 | EMPA + SoC | SoC | direct medical costs | 3 months | 10 years | 5 | QALY | RCT |
| Wan et al. (2022a) | China | Healthcare system | Markov | HFrEF | 67 | EMPA + SoC | SoC | direct medical costs | 1 month | 20 years | 5 | QALY | RCT |

*HFrEF,* heart failure with reduced ejection fraction; *HFpEF,* heart failure with preserved ejection fraction; *HF,* heart failure; *T2D,* Type 2 diabetes; *EMPA,* empagliflozin; *SoC,* standard of care; *QALY,* quality-adjusted life-year; *RCT,* randomized controlled trial; *DAPA,* dapagliflozin.





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**TABLE 2 Reporting quality of the economic evaluations (as assessed by the CHEERS statement).**

| Item no. | Section/item | Liao et al. (2021) | Lou et al. (2022) | Jiang and Xie (2022) | Jiang et al. (2021) | Zhou et al. (2022) | Lin et al. (2022) | Zheng et al. (2022) | Reifsnider et al. (2020) | Krittayaphong and Permsuwan (2022) | Tang and Sang (2022) | Wan et al. (2022a) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Title | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | Abstract | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3 | Background and objectives | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | Health economic analysis plan | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | Study population | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 6 | Setting and location | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 7 | Comparators | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 | Perspective | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | Time horizon | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10 | Discount rate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 11 | Selection of outcomes | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 12 | Measurement of outcomes | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 13 | Valuation of outcomes | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 14 | Measurement and valuation of resources and costs | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 15 | Currency, price date, and conversion | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 16 | Rationale and description of model | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 17 | Analytics and assumptions | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 18 | Characterizing heterogeneity | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 19 | Characterizing distributional effects | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| 20 | Characterizing uncertainty | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 21 | Approach to engagement with patients and others affected by the study | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 22 | Study parameters | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

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TABLE 2 (*Continued*) Reporting quality of the economic evaluations (as assessed by the CHEERS statement).

| Item no. | Section/item | Liao et al. (2021) | Lou et al. (2022) | Jiang and Xie (2022) | Jiang et al. (2021) | Zhou et al. (2022) | Lin et al. (2022) | Zheng et al. (2022) | Reifsnider et al. (2020) | Krittayaphong and Permsuwan (2022) | Tang and Sang (2022) | Wan et al. (2022a) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | Summary of main results | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 24 | Effect of uncertainty | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 25 | Effect of engagement with patients and others affected by the study | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 26 | Study findings, limitations, generalisability, and current knowledge | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 27 | Source of funding | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 28 | Conflicts of interest | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Overall quality | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |

Note: "1" meets the quality assessment criteria; "0" does not fully conform to the quality assessment criteria; CHEERS, consolidated health economic evaluation reporting standards.

for HFrEF was expected to be a cost-effective option, and the probabilities were highest in Korea, lowest in Thailand.

Six studies provided economic evaluation for HFpEF. Three studies were conducted in China, and suggested that the adding empagliflozin to SoC for HFpEF was cost-effective in healthcare systems. One study in Australian suggested that adding empagliflozin is likely to be cost-effective in the healthcare setting. One study in USA suggested that adding empagliflozin provides low economic value compared with SoC for HFpEF. However, the ICER was lower for HFpEF with CV mortality reduction than without. The last study was conducted in Thailand, and suggested that empaglifozin was not a cost-effective add-on treatment for HFpEF. In total, the ICERs were higher for HFpEF than for HFrEF.

## Subgroup analysis

Subgroup analysis was performed according to the different states of diabetes in 3 studies (Jiang et al., 2021; Lin et al., 2022; Zheng et al., 2022), revealing that empagliflozin had similar cost-effectiveness among patients with and without diabetes, and empagliflozin was more cost effective in HErEF patients with diabetes. The details were shown in Table 4. Subgroup analysis was also performed across EF strata and HF-related health status among HErEF patients in 1 study (Zheng et al., 2022), indicating that the ICER was slightly lower for patients with EF less than 50%, and similar for mildly impaired HF and moderately impaired HF.

## Uncertainty analysis

One-way sensitivity analysis and probabilistic sensitivity analyses (PSA) were applied in all the included studies. Six studies indicated that the major factor affecting the ICER was the cost of empagliflozin. Three studies (Reifsnider et al., 2020; Lin et al., 2022; Lou et al., 2022) showed when the cost increased to its upper limit, the ICER was still lower than the WTP threshold. One study (Jiang and Xie, 2022) showed when the cost increased to its upper limit, the ICER was higher than one-time GDP but lower than three-time GDP. One study (Zheng et al., 2022) showed that the monthly cost of empagliflozin would need to drop from $326.69 to $153.56 to meet a WTP threshold of $180 000 per quality-adjusted life-year (QALY). One study (Zhou et al., 2022) showed that empagliflozin was no longer cost-effective if its cost exceeded AUD$110 per month.

Six studies displayed the CV mortality to be the most influential parameter. With the decrease of CV mortality in SoC or the increase of CV mortality in adding empagliflozin, the ICERs got higher. One study (Jiang et al., 2021) showed that the CV mortality in adding empagliflozin and SoC had a great impact on the ICER value, which was far more than three-time GDP. Another study (Tang and Sang, 2022) showed the CV mortality in SoC had similar effect. Two studies (Liao et al., 2021; Jiang and Xie, 2022) showed when the CV mortality increased to its upper limit, the ICERs were higher than one-time GDP but lower than three-time GDP. One study (Zhou et al., 2022) showed that adding empagliflozin was no longer cost-effective if the hazard ratio for CV mortality exceeded 0.99.

**TABLE 3 Overview of economic evaluation outcomes of included studies.**

| References | Country | Target population | Discount year | Costs (original currency; mean) | | QALY | | △Cost | △QALY | ICER | ICER (2022 US$ per QALY) | PSA | Uncertainty analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | I | C | I | C | | | | | WTP (Iterations cost-effectiveness) | |
| Liao et al. (2021) | China (Taiwan) | HFrEF | 2020 | $79141 | $71739 | 9.66 | 9.30 | $7402 | 0.36 | $20508 | $21367.37 | $25000 (63.4%) | The probability of CV death influenced ICER the most, followed by the probability of non-CV death, monthly costs and utility of stable HF. |
| | | | | | | | | | | | | $75000 (93.7%) | |
| | Japan | HFrEF | 2020 | $45210 | $37664 | 8.37 | 8.06 | $7546 | 0.31 | $24046 | $25053.62 | $40137.8 (77.9%) | |
| | | | | | | | | | | | | $120413.4 (95.6%) | |
| | Korea | HFrEF | 2020 | $15934 | $13158 | 8.37 | 8.06 | $2776 | 0.31 | $8846 | $9216.68 | $31494.9 (93.6%) | |
| | | | | | | | | | | | | $94484.7 (96.3%) | |
| | Singapore | HFrEF | 2020 | $148751 | $130602 | 9.02 | 8.68 | $18149 | 0.34 | $53379 | $55615.79 | $59819.0 (58.1) | |
| | | | | | | | | | | | | $179457 (94.2%) | |
| | Thailand | HFrEF | 2020 | $21805 | $15247 | 8.11 | 7.81 | $6558 | 0.30 | $21543 | $22445.74 | $7371.4 (%0) | |
| | | | | | | | | | | | | $22114.2 (51.9%) | |
| | Australia | HFrEF | 2020 | $56356 | $49573 | 8.63 | 8.31 | $6783 | 0.32 | $20982 | $21861.23 | $53022.5 (89%) | |
| | | | | | | | | | | | | $159067.5 (95.9%) | |
| Lou et al. (2022) | China | HFpEF | 2021 | $5423 | $4189 | 4.80 | 4.68 | $1234 | 0.12 | $9881 | $10085.41 | $37654 (80%) | The cost of EMPA has the largest impact on the ICER. |
| Jiang and Xie (2022) | China | HFpEF | 2021 | $5916.50 | $4645.23 | 4.81 | 4.70 | $1271.27 | 0.11 | $11292.06 | $11525.67 | $12652.5 (52.7%) | The probability of CV death influenced ICER the most, followed by the cost of EMPA, the cost of hospitalization for heart failure, NYHA functional classes, and time horizon |
| | | | | | | | | | | | | $37957.5 (67.6%) | |
| Jiang et al. (2021) | China | HFrEF | 2020 | $5021.93 | $4118.86 | 3.66 | 3.53 | $903.07 | 0.13 | $6946.69 | $7237.78 | $11008.07 (55.2%) | The probability of CV death influenced ICER the most, followed by the cost of hospitalization, diabetes status, and time horizon |
| Zhou et al. (2022) | Australian | HFpEF | 2021 | A$63218 | A$58478 | 4.97 | 4.81 | A$4740 | 0.16 | A$29202 | $20727.20 | A$50000 (85%) | The probability of CV death influenced ICER the most, followed by the cost of EMPA and HR of HF hospitalization |

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**TABLE 3 (*Continued*) Overview of economic evaluation outcomes of included studies.**

| References | Country | Target population | Discount year | Costs (original currency; mean) | | QALY | | △Cost | △QALY | ICER | ICER (2022 US$ per QALY) | PSA | Uncertainty analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | I | C | I | C | | | | | WTP (Iterations cost-effectiveness) | |
| Lin et al. (2022) | China | HFrEF | 2020 | $5220.98 | $4873.96 | 4.86 | 4.68 | $347.02 | 0.18 | $1893.59 | $1972.94 | $31510.57 (100%) | The major factors affecting the ICER were the cost of EMPA, the cost of the standard treatment, the CV mortality rate in the standard group |
| Zheng et al. (2022) | United States | HFpEF without CV mortality reduction | 2021 | $197615 | $171357 | - | - | $26258 | 0.06 | $437633 | $446686.57 | $180000 (2.7%) | The results were most sensitive to the monthly cost, quality-of-life benefit, and mortality effect of EMPA. |
| | | HFpEF with CV mortality reduction | 2021 | $199183 | $169438 | - | - | $29745 | 0.17 | $174970 | $178589.71 | $180000 (57.7%) | |
| Reifsnider et al. (2020) | United Kingdom | HF with T2D | 2018 | £18,197 | £16,829 | 6.27 | 5.62 | £1368 | 0.65 | £2104 | $2124.80 | £20,000 (91%) | Variations in the discount rate to costs, the price of EMPA, and the discount rate to QALYs were most influential on the ICER. |
| Krittayaphong and Permsuwan (2022) | Thai | HFpEF | 2021 | $929.20 | $306.71 | 4.52 | 4.47 | $622.49 | 0.05 | $12449.8 | $12707.36 | $4773.27 (11%) | The major factors affecting the ICER were the risk of non-hospitalized CV death, risk of hospitalization in standard treatment, and cost of EMPA. |
| | | HFrEF | 2021 | $1049.50 | $639.68 | 3.79 | 3.59 | $409.82 | 0.20 | $2049.1 | $2091.49 | $4773.27 (98%) | The major factors affecting the ICER were the risk of non-hospitalized CV death and cost of EMPA, followed by the risk of non-hospitalized non-CV death |
| Tang and Sang (2022) | China | HFpEF | 2021 | $5916.20 | $4645.23 | 4.96 | 4.85 | $1270.97 | 0.11 | $11554.27 | $11793.30 | $12652.5 (53.1%) | The major factors affecting the ICER were the risk of CV death, followed by the cost of EMPA and the cost of hospitalization for HF. |
| | | | | | | | | | | | | $37957.5 (72.2%) | |
| | | HFrEF | 2021 | $5501.48 | $4673.96 | 4.27 | 4.12 | $827.52 | 0.15 | $5616.80 | $5733.00 | $12652.5 (59.4%) | |
| | | | | | | | | | | | | $37957.5 (72.6%) | |
| Wan et al. (2022a) | China | HFrEF | 2020 | ¥34,177.91 | ¥25,864.93 | 5.74 | 5.52 | ¥8 312.98 | 0.22 | ¥37,995.94 | $11253.80 | ¥72,447 (58.8%) | The steady-state hospitalization rate of 2 groups was the most important factor affecting the ICER. |
| | | | | | | | | | | | | ¥217,341 (63.8%) | |

*I*, intervention; *C*, comparator; *QALY*, quality-adjusted life year; *ICER*, incremental cost effectiveness ratios; *PSA*, probabilistic sensitivity analyses; *WTP*, willingness-To-pay; *HFrEF*, heart failure with reduced ejection fraction; *CV*, cardiovascular; *HF*, heart failure; *HFpEF*, heart failure with preserved ejection fraction; *EMPA*, empagliflozin; *NYHA*, new york heart association; *HR*, hazard ratio; *T2D*, Type 2 diabetes; *DAPA*, dapagliflozin; *AEs*, Adverse events.





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**TABLE 4 Subgroup analyses of diabetes status.**

| References | Country | ICER(US$ per QALY) | |
|---|---|---|---|
| | | With diabetes | Without diabetes |
| Jiang et al. (2021) | China | 5016.44 | 10,844.36 |
| Lin et al. (2022) | China | Dominant | 2568.15 |
| Zheng et al. (2022) | United States | Without CV: 419,739 | Without CV: 454,942 |
| | | With CV: 162,334 | With CV: 188,464 |

ICER, incremental cost effectiveness ratios; QALY, quality-adjusted life year; CV, cardiovascular.

However, there was a study (Krittayaphong and Permsuwan, 2022) showed that the CV mortality did not change the economic outcome.

## Discussion

Eleven economic evaluations of empagliflozin for the treatment of HF from 8 countries were identified in our systematic review, where turns out that add-on empagliflozin is cost effective in most countries, especially for HFrEF patients. The results are similar to the economics of dagliflozin for HF (Krittayaphong and Permsuwan, 2021; Cohen et al., 2023). Unfortunately, there is currently few economic comparison between SGLT2 for the treatment of HF, and it is difficult to determine which SGLT2 is more economical.

In this review, all reported ICERs of different regional backgrounds were adjusted to 2022 USD and the results of PSA were summarized in Table 3 for more convenient comparison. According to the results, the ICERs varied greatly in different studies and different countries. For HFrEF patients, add-on empagliflozin was cost effective in all of the included countries. However, the highest ICER was in Singapore, which was $55615.79 per QALY (Liao et al., 2021), and the lowest ICER was in China, which was $1972.94 per QALY (Lin et al., 2022). It was mainly because of the huge cost difference. For HFpEF patients, with the exception of the USA (Zheng et al., 2022) and Thailand (Liao et al., 2021), it was considered that empagliflozin was cost effective in the remaining countries. It means that the economic results of one country cannot be applied to another, and several economic evaluations have already demonstrated the variability of cost-effectiveness estimates for drugs in different countries (Mac et al., 2019; Li et al., 2021).

It is worth mentioning that the results still varied despite the studies coming from the same country. The ICERs ($22445.74 per QALY vs. $2091.49 per QALY) differ by 10-fold in two studies (Liao et al., 2021; Krittayaphong and Permsuwan, 2022) for HFrEF patients from Thailand. Since Liao et al. did not list specific cost data, there was no way to analyze the reasons for the difference. There were similar situations in Chinese studies. The ICERs of five studies for HFrEF patients varied greatly. One came from Taiwan, China, with the ICER of $21367.37 per QALY (Liao et al., 2021), and the other four were from Chinese mainland with the lowest ICER of $1972.94 per QALY (Lin et al., 2022). The possible reasons for heterogeneity were mainly derived from differences in costs as well as time horizon. Wu et al. (Wu et al., 2022) got similar results in an economic systematic review of dapagliflozin for HF. Therefore, we should consider the heterogeneity in different regions of the same country when evaluating the economics of empagliflozin for HF patients.

Uncertainty analysis showed that the cost of empagliflozin was the major factor affecting the ICERs. With the implementation of centralized procurement of drugs in China, a lower price of empagliflozin is negotiable, hence empagliflozin in treatment for HF patients will be more cost effective from a Chinese healthcare system perspective.

Similar to the previous studies, some critical elements of economic evaluation were also found in our studies (Wan Y. et al., 2022; Liu et al., 2022). Firstly, the election of the target population is crucial, and it could lead to different economic outcomes. For instance, add-on empagliflozin was evaluated to be dominant for HFrEF patients, but not cost-effectiveness for HFpEF patients in the same study (Krittayaphong and Permsuwan, 2022). Furthermore, subgroup analysis performed in 3 studies indicated that empagliflozin was more cost-effectiveness in HErEF patients with diabetes or HF with CV mortality reduction. Hence, the selection of target population is one of the most critical structures of economic evaluation. Secondly, the comparator is a very important element. One study (Jiang et al., 2021) from China showed that add-on empagliflozin was more cost-effectiveness compared with SoC, but led to more costs and less QALY compared with dapagliflozin. We have previously reached the similar results in an economic systematic review of elbasvir/grazoprevir for chronic hepatitis C (Liu et al., 2022). Thirdly, the country or region selected is extremely crucial. The included analyses were mainly for a certain country, so the economic outcomes must be markedly affected by the healthcare system, and economic levels of the country. Therefore, the applicability and extrapolation of research is limited. It will be necessary to improve the methods, such as constructing multi-level models and identifying a series of appropriate covariates to enhance the applicability and extrapolation. Furthermore, There are some other elements that need to be considered (Vandepitte et al., 2021; Yang et al., 2021).

Despite scientific and systematic methods used to minimize deviations, several limitations should be acknowledged. First, The CHEERS statement used in the systematic review is a guideline reporting tool that can help determine whether the study is well reported, but it is not a methodological quality assessment tool. Second, it is extremely difficult to synthesize these studies due to the possible divergences in backgrounds and methodology such as length of cycle, time horizons, target populations, healthcare systems, and cost components, *etc.* For example, although all the studies considered only the direct medical costs, some studies specified the cost details and others did not, which created a limitation to quantitative

analysis or horizontal comparison of the studies. Therefore, we summarized the evidence qualitatively and then interpreted the outcomes cautiously. Third, all the included studies have only considered direct medical costs. In fact, HF will cause tremendous social and economic burden if not treated in time. Therefore, it is necessary to carry out further research from the perspective of the whole society. Last but not least, the populations simulated in all the models were based on the EMPEROR study, which means that the reliability of outcomes may be influenced by publication bias.

## Conclusion

In conclusion, this study is the first systematic review on the cost-effectiveness of empagliflozin for HF. Based on the available evidence, add-on empagliflozin for HFrEF might be dominant or cost-effective compared with SoC, and add-on empagliflozin for HFpEF might be cost-effective in China and Australian, but not cost-effective in USA and Thailand. The ICERs were most sensitive to the cost of empagliflozin and CV mortality. In further economic evaluations of empagliflozin for HF patients, the country epidemiological real-world data should be taken into account in model building and sensitivity analysis.

## Data availability statement

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

## Author contributions

JL and RY: study design and study conduct. JL and AW: data collection. RY, AW, XG, and JL: data interpretation. JL and RY: data analysis and drafting manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1186579/full#supplementary-material

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# Efficacy and safety of ciprofol for long-term sedation in patients receiving mechanical ventilation in ICUs: a prospective, single-center, double-blind, randomized controlled protocol

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**Introduction:** Critically ill patients who receive mechanical ventilation after endotracheal intubation commonly experience discomfort and pressure. The major sedative drugs that are currently used in clinical practice present with many complications, such as hypotension, bradycardia, and respiratory depression. Ciprofol (HSK3486), which is a newly developed structural analog of propofol, is a short-acting gamma-aminobutyric acid (GABA) receptor agonist, and its mechanism of action is sedation or anesthesia by enhancing GABA-mediated chloride influx. The high efficacy of ciprofol for short-term sedation is comparable to that of propofol, and it has a relatively low incidence of adverse effects and high level of safety, which has been confirmed by multiple clinical studies. However, few studies have examined its safety and efficacy for long-term sedation. The purpose of the study is to evaluate the efficacy and safety of ciprofol for long-term sedation in mechanically ventilated patients.

**Methods:** A prospective, single-center, double-blind, randomized, propofol-controlled, non-inferiority trial is proposed. The study will enroll 112 mechanically ventilated patients hospitalized in the intensive care unit (ICU) of the Shanghai Fourth People's Hospital affiliated with Tongji University based on the inclusion and exclusion criteria of the study, and randomly assign them to a group sedated with either ciprofol or propofol. The primary outcome is the percentage of time spent under target sedation, and secondary outcomes include drug dose, number of cases requiring additional dextrometropine, incidence of systolic blood pressure <80 or >180 mmHg, incidence of diastolic blood pressure <50 or >100 mmHg, incidence of heart rate <50 beats per minute (bpm) or >120 bpm, inflammatory indicators, blood lipid levels, liver and kidney functions, nutritional indicators, ventilator-free days within the 7-day period after enrollment, 28-day mortality, ICU stay duration, and hospitalization costs.

**Discussion:** We hypothesize that the efficacy and safety of ciprofol for long-term sedation in mechanically ventilated ICU patients will not be inferior to that of propofol.

**Trial registration:** Chinese Clinical Trials Registry identifier ChiCTR2200066951.

KEYWORDS

ciprofol, endotracheal intubation, long-term sedation, mechanical ventilation, propofol

## 1 Introduction

Critically ill patients on mechanical ventilation after endotracheal intubation are commonly admitted to intensive care units (ICUs) and typically experience stress states, such as pain, anxiety, and irritability. Such discomfort can stimulate the sympathetic nervous system and increase the risk of the patient removing their endotracheal tubes and intravascular catheters (Pun et al., 2019; Prabhakar et al., 2021; Temesgen et al., 2021). Guidelines recommend that mechanically ventilated patients should receive moderate analgesia and sedation to reduce anxiety and decrease their discomfort and psychological pressure (Devlin et al., 2018). Sedation and analgesia can reduce patient-machine disharmony events as well as decrease oxygen consumption and cardiovascular events, thereby reducing the incidence of secondary complications (Guerin, 2020). The study by Brook et al. (1999) showed that goal-directed sedation reduces the duration of mechanical ventilation and ICU stay as well as the need for tracheotomy in critically ill patients with acute respiratory failure. Therefore, moderate analgesic and sedative treatment must be used for patients in clinical practice.

The drugs that are most commonly used for sedation in clinical practice include benzodiazepines, propofol, and dexmedetomidine (Moller et al., 2022), and the most common complications include hemodynamic instability such as hypotension, bradycardia, and delirium; respiratory depression; bowel obstruction; renal impairment; venous return stasis; and immunosuppression (Zaal et al., 2015; Foster, 2016; Devlin et al., 2018; Duprey et al., 2021). Propofol is a gamma-aminobutyric acid (GABA) receptor agonist that acts as a sedative. It has a rapid onset of action and metabolism, and the most common adverse effects of propofol include loss of airway reflexes, hypoventilation, apnea, and hypotension. When the infusion of propofol is prolonged, "propofol infusion syndrome" may occur, which is a rare but serious adverse effect that includes severe metabolic acidosis, rhabdomyolysis, hyperkalemia, and cardiovascular failure that is usually fatal (Sahinovic et al., 2018). Ciprofol (HSK3486), a newly developed structural analog of propofol, is a short-acting GABA receptor agonist. Its mechanism of action is sedation or anesthesia by enhancing GABA-mediated chloride influx (White, 1989). It can be used in patients during invasive endoscopy and intensive care due to its sedative effects (Teng et al., 2021a). A clinical trial in Australia (Teng et al., 2021b) showed that ciprofol was safe at doses of 0.15–0.90 mg/kg, and most of the adverse effects of ciprofol were mild to moderate. In another clinical trial (Teng et al., 2021a), ciprofol was found to be safe at doses of 0.4–0.9 mg/kg, and it showed similar onset and duration of action as propofol, along with 4–5 times the potency of propofol. Studies have also found that in elderly patients undergoing painless gastroscopy, 0.2 mg/kg ciprofol could provide a sedative effect similar to that of 1 mg/kg propofol; moreover, it showed no significant differences in the induction and recovery times, and had fewer adverse reactions such as hypotension, respiratory depression, and injection pain as compared to the propofol group (Chen X. et al., 2022; Chen B. Z. et al., 2022; Li et al., 2022). Owing to its high efficacy, the dose used for clinical application as well as the incidence of adverse effects are lower than those for propofol. In conclusion, the efficacy of ciprofol for short-term sedation was comparable to that of propofol, and a relatively lower incidence of adverse effects was observed, as confirmed by an increasing number of clinical studies.

However, clinical studies on the efficacy and safety of the long-term use of sedatives in patients admitted to the ICU are limited. Based on previous findings, this study aims to investigate the efficacy and safety of ciprofol for long-term sedation over 7 days in patients undergoing mechanical ventilation and light sedation [Richmond Agitation-Sedation Scale (RASS) −3~0].

## 2 Study design

This is a prospective, single-center, double-blind, randomized, propofol-controlled, non-inferiority study (Chinese Clinical Trials

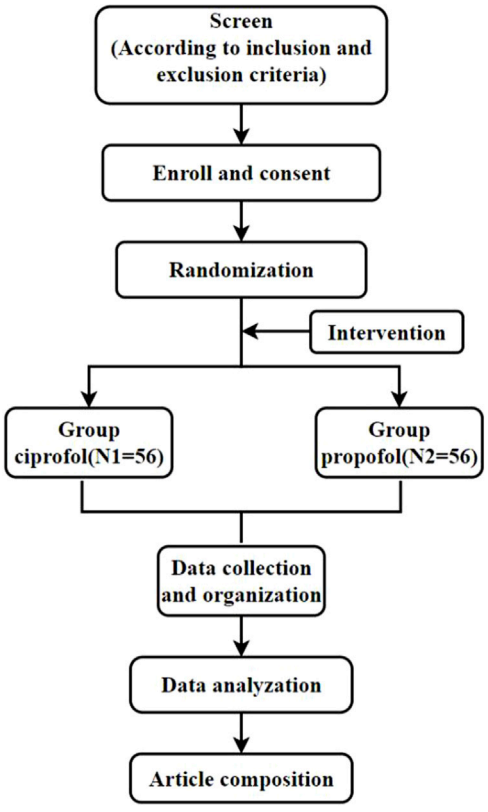


FIGURE 1
Technical route.

Registry identifier: ChiCTR2200066951) that will be conducted in accordance with clinical trial protocols (and any amendments), the Declaration of Helsinki (as currently revised), Chinese adult ICU analgesic and sedative treatment guidelines, and Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the ICU.

## 2.1 Study setting

The study will enroll 112 patients undergoing mechanical ventilation and hospitalized in the ICU of Shanghai Fourth People's Hospital affiliated with Tongji University, based on the inclusion and exclusion criteria of the study. These patients will then be randomly assigned to either ciprofol or propofol sedation groups. The technical scheme is shown in Figure 1.

## 2.2 Inclusion criteria

The inclusion criteria are as follows.

(1) Age, ≥18 years and ≤85 years; BMI, ≥18 kg/m$^2$ and ≤30 kg/m$^2$; either gender.
(2) Before enrollment, the patients would have been intubated and mechanically ventilated for no more than 96 h, and would have been scheduled to receive sedation for ≥24 h. The target sedation goal of patients will be within the range of RASS: −3~0.
(3) The patients' families must fully understand the purpose and significance of the trial, participate voluntarily, and sign an informed consent form.

## 2.3 Exclusion criteria

The exclusion criteria are as follows.

(1) Acute severe neuropsychiatric disease and various conditions that interfere with RASS.
(2) Systolic blood pressure at less than 90 mmHg with high doses of a single vasoactive drug to maintain blood pressure or two or more vasoactive drugs to maintain blood pressure.
(3) Heart rate less than 50 bpm, second- or third-degree atrioventricular block, and no pacemaker.
(4) Cardiac function class IV (NYHA Association) or severe cardiomyopathy.
(5) Severe liver dysfunction or acute liver failure (Child-Pugh class C).
(6) Chronic alcohol or drug use (benzodiazepines, opioid or heroin).
(7) Known allergies to eggs, soy products, or propofol and contraindications to propofol, opioids, and their relief medications.
(8) Contraindications to deep sedation (moribund state or myasthenia gravis) or previous sedation accident.
(9) Pregnancy or lactation in women.
(10) Unsuitability for inclusion in the study for various reasons based on the investigator's judgement.

## 2.4 Randomization and blinding

The patients will be uniformly coded as 1, 2, , 112 based on their names, and a seed number would be set as 20221031. Random numbers would be generated using the Stata 17.0 software uniform() function, and the patients will be sorted by these numbers. Thereafter, the patients would be divided into the ciprofol or propofol group using the group() function, and a grouping data file will be generated.

Since patients in the ICU are often critically ill, keeping the researcher blinded may be difficult. Therefore, the patients, research evaluator, and dedicated nurses would be blinded for this study and not allowed to communicate drug-related information of the study with each other. The researcher would calculate the patients' initial and supplemental doses prior to dosing based on the grouping, and the research evaluator would be primarily responsible for the timing of dosing initiation, dose adjustment, and medication discontinuation and provide the investigator with appropriate information in a timely manner. During this process, the researcher would not disclose any drug-related information.

## 2.5 Study drug and timelines

All patients will be given a loading dose of ciprofol (Haisco Pharmaceutical Group Co., Ltd., China) or propofol (AstraZeneca, United Kingdom). The total time of drug administration (including loading dose and maintenance dose) will be at least 24 h ± 30 min, and the longest time would be no more than 7 days.

## 2.6 Intervention

The patients will be randomized 1:1 to receive sedation with either ciprofol or propofol. At baseline, the delirium status would be assessed using the Confusion Assessment Method (CAM)-ICU scale. The lung-protective ventilation strategy would be adopted as follows (Hafiz and Stahl, 2019): 1) VT: 6~8 ml/kg [ideal body weigh (IBW)]; 2) plateau pressure: <30 cm$H_2O$; 3) stress pressure: <15 cm$H_2O$; and 4) reasonable positive end-expiratory pressure (PEEP): 5~10 cm$H_2O$.

Prior to drug administration, analgesics would be continuously administered according to a standardized procedure. During the maintenance period, the analgesic dose would be adjusted according to the Critical-Care Pain Observation Tool score. The baseline sedation level of each patient must reach RASS ≥2 before the administration of the study drug.

Ciprofol group: Patients would receive a loading dose of 0.1 mg/kg ciprofol intravenously within 5 min and then a maintenance dose of 0.3 mg/kg/h ciprofol via continuous pumping. The maintenance dose range of ciprofol would be 0.06–0.8 mg/kg/h. An additional dose of 0.05 mg/kg ciprofol

**TABLE 1 Measurement schedule.**

| Time points | Baseline | Before study drug | Study drug intervention | | | | | | | Day after study drug ended | Discharged from hospital |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day1 (per 4 h) | Day2 (per 4 h) | Day3 (per 4 h) | Day4 (per 4 h) | Day5 (per 4 h) | Day6 (per 4 h) | Day7 (per 4 h) | | |
| Informed consent | × | | | | | | | | | | |
| Inclusion/ Exclusion criteria | × | | | | | | | | | | |
| Demographic characteristics | × | | | | | | | | | | |
| Medical History | × | | | | | | | | | | |
| APACHE II | × | | | | | | | | | | |
| SOFA | × | | | | | | | | | | |
| Blood test | | × | | | | | | | | × | |
| Blood biochemistry | | × | | | | | | | | × | |
| Cytokines | | × | | | | | | | | × | |
| Blood coagulation | | × | | | | | | | | × | |
| Cardiac LVEF | | × | | | | | | | | × | |
| Remifentanil | | × | | | | | | | | | |
| CPOT | | × | | | | | | | | | |
| CAM-ICU | | × | | | | | | | | | |
| RASS | | × | × | × | × | × | × | × | × | | |
| Dextrmetomidine (Yes/No) | | | × | × | × | × | × | × | × | | |
| Adverse reactions | | | × | × | × | × | × | × | × | | |
| ICU-stay time | | | | | | | | | | | × |
| Ventis | | | | | | | | | | | × |
| Hospital costs | | | | | | | | | | | × |
| 28-day mortality | | | | | | | | | | | × |

would be allowed. The injection would will be 30 s to 1 min, and the administration time would be ≥2 min.

Propofol group: Patients would be given a loading dose of 0.5 mg/kg propofol intravenously for 5 min, followed by a maintenance dose of 1.5 mg/kg/h propofol via continuous pumping. The maintenance dose range of propofol would be 0.3–4 mg/kg/h. During this process, an additional dose of 0.25 mg/kg propofol would be allowed. The injection time would be 30 s to 1 min, and the administration time would be ≥2 min.

If the maximum dose of the study drug would not be sufficient for sedation, dexmedetomidine would be infused at a rate of 0.2–1.0 μg/kg/h.

## 2.7 Data collection

The following demographic information will be collected: sex, age, BMI, prior alcohol use, and underlying disease. The following clinical data will be collected: percentage of time at target sedation (defined as the time during which additional dexmedetomidine is not required within the target sedation range), incidence of adverse events, ventilator-free days within 7 days after enrollment, 28-day mortality, ICU stay time, hospital costs, and laboratory indicators (inflammatory parameters, lipid parameters, liver function, renal function, and nutritional parameters before study drug administration and the day after study drug administration) (Table 1).

## 2.8 Trial termination

The following criteria will be used to indicate trial termination:

(1) Endotracheal tube is removed.
(2) Patient leaves the ICU.
(3) Physician discontinues treatment at 24 h.
(4) Period of 7 days after enrollment is concluded.

## 2.9 Sample size evaluation

This will be a randomized, controlled, non-inferiority trial. According to previous literature, the percentage of time in the target sedation state of propofol and ciprofol are 99.38% and 98.33% (Liu et al., 2022), respectively; however, the incidence of adverse events of ciprofol is lower than that of propofol. The sedative effect of ciprofol is not inferior to that of propofol. For a non-inferiority margin ($\delta$) of 8%, set α to 0.025 (one side), test efficiency to 0.9, and the sample size of the two groups to be equal; then, the sample size of the test group and the control group is calculated by PASS 2021 software, with N1 = N2 = 50 cases. Considering that the loss to follow-up rate is 10%, 56 cases are required for both the test and control groups; thus, 112 patients will be enrolled in total to ensure the maintenance of the scientific design of the study.

## 2.10 Data management and statistical analysis

The person in charge of the study would explain how to complete the case report form. The data collector would complete the case report form according to the original medical records. A clinical supervisor will be responsible for verifying the integrity and authenticity of the data. The data administrator would be responsible for data entry.

SPSS software will be used for the statistical analyses. For continuous variables, Student's *t*-test or the Mann–Whitney *U* test will be used based on the distribution. Examples of the mean, standard deviation, median, minimum, and maximum values will be listed. For categorical variables, the $\chi^2$ test will be used, and its frequency and percentage will be described.

## 2.11 Primary outcome

The primary outcome is the percentage of time in the target sedation state without other sedation drugs. When the lower limit of the 95% confidence interval of the mean difference between the two groups is lower than the negative limit value (−8%), then the study drug ciprofol would not be inferior to the control drug propofol.

## 2.12 Secondary outcome

Secondary outcomes will include the dosage of the study drug, number of cases with added dextrometropine, incidence of systolic blood pressure <80 or >180 mmHg, incidence of diastolic blood pressure <50 or >100 mmHg, incidence of heart rate <50 or >120 bpm, inflammatory indicators, blood lipid levels, liver and kidney functions, nutritional indicators, ventilator-free days within 7 days, 28-day mortality, ICU stay duration, and hospitalization costs.

# 3 Discussion

Propofol has advantages that include rapid onset and strong sedation. However, it can also cause adverse reactions, such as hypotension, respiratory depression, and propofol infusion syndrome, which is the most adverse reaction (Sahinovic et al., 2018). As a new sedative, ciprofol is expected to have the same sedation efficacy as propofol for ICU patients receiving long-term mechanical ventilation, with a lower incidence of adverse reactions caused by hypotension and drug accumulation than that of propofol. In a clinical trial, ciprofol was shown to be safe at a dose of 0.4–0.9 mg/kg, and it had similar onset and maintenance times as well as 4 to 5 times higher efficacy relative to propofol (Teng et al., 2021b). Due to its high efficacy, the dosage used in clinical applications can be reduced and the incidence of adverse reactions caused by drug accumulation would be lower than that of propofol. In a previous study on painless gastroscopy, the incidence of adverse effects such as hypotension and respiratory depression was lower in the propofol group than that in the control group. Further, early cognitive dysfunction was not observed after surgery (Chen X. et al., 2022). The study found that in painless gastroscopy of elderly patients, 0.2 mg/kg ciprofol can provide a sedative effect similar to that of 1 mg/kg propofol, and the induction time and recovery time did not differ significantly (Li et al., 2022). A phase 1 study of ICU patients (Teng et al., 2021b) showed that ciprofol as a 4- or 12-h infusion had good efficacy, rapid recovery, no significant accumulation, and an excellent safety profile.

In conclusion, this study will verify the efficacy and safety of ciprofol for long-term sedation in mechanically ventilated ICU patients and confirm whether it is inferior to propofol. We believe that ciprofol represents a new option for long-term sedation of ICU patients undergoing mechanical ventilation.

# Data availability statement

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

# Ethics statement

The studies involving humans were approved by the Ethics Committee of Shanghai Fourth People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

# Author contributions

XS and MZ prepared the manuscript. HZ and XF revised the manuscript. CL and GB designed the study 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



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# The efficacy and safety of condoliase for lumbar disc herniation: a systematic review and meta-analysis

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**Background:** Chemonucleolysis is a minimally invasive treatment of lumbar disc herniation (LDH). However, the low specificity of the enzyme and the existence of serious adverse events limit the application of chemonucleolysis. Clinical studies in recent years have shown that Chondroitin sulfate ABC endolyase (condoliase) is a potential therapeutic enzyme for LDH. Aim. A meta-analysis was conducted to determine the efficacy and safety of condoliase in LDH treatment.

**Methods:** We searched Web of Science, Embase, PubMed, and Cochrane Library databases. Two reviewers independently screened articles, extracted data, and assessed the risk of bias. The outcomes were the total effective rate, Oswestry Disability Index (ODI) score change, the proportion of lumbar surgery after condoliase treatment, herniated mass volume change, Pfirrmann grade change, and adverse events. Review Manager 5.3 and Stata 12.0 were used for meta-, sensitivity, and bias analysis.

**Results:** Ten studies were included. A single-arm meta-analysis showed that the total effective rate was 78% [95% confidence interval (CI) 75%–81%], the proportion of surgery was 9% (95% CI 7%–12%), the proportion of Pfirrmann grade change was 43% (95%CI 38%–47%), and the adverse events were 4% (95% CI 2%–6%) after condoliase treatment. The two-arm meta-analysis showed that the ODI score change [standardized mean difference (SMD) −2.46, 95% CI −3.30 to −1.63] and the herniated mass volume change (SMD −16.97, 95% CI −23.92 to −10.03) of the condoliase treatment group were greater than those of the placebo control group, and there was no difference in adverse events between the two groups (OR 1.52, 95% CI 0.60–3.85). The results of sensitivity and publication bias analyses showed that the results were robust.

**Conclusion:** Condoliase intradiscal injection has excellent eutherapeutic and safety for LDH, thus, has considerable potential as a treatment option besides conservative treatment and surgical intervention for LDH.

**Systematic Review Registration:** https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022375492, PROSPERO (CRD42022375492).

KEYWORDS

**condoliase, lumbar disc herniation, chemonucleolysis, nucleus pulposus, systematic review and meta-analysis**

# 1 Introduction

Lumbar disc herniation (LDH) refers to the relaxation or rupture of the annulus fibrosus (AF) due to degradation of the intervertebral disc matrix tissue, resulting in extrusion of the nucleus pulposus (NP) from the intervertebral disc (Benzakour et al., 2019). The protruding tissue may irritate or compress the nerve roots, causing symptoms such as lower back pain and/or leg pain, which severely limit the patient's activity (Samuelly-Leichtag et al., 2022). The occurrence of LDH is related to genetics, excessive loading, and aging (Hoy et al., 2010). Conservative treatment is the primary recommendation for patients with LDH; however, surgery may be considered for patients who fail to respond to long-term conservative treatment. Surgery has advantages over prolonged conservative treatment; nevertheless, it comes with surgery-related risks (Rogerson et al., 2019). New treatment strategies need to be developed to provide options other than conservative treatment and surgical intervention for LDH. Chemonucleolysis involves injecting enzymes into the disc to digest part of the intervertebral disc tissue, reducing the size of the disc herniation and relieving pressure on nerve roots, thereby reducing symptoms (Gentry et al., 1985; Watters et al., 1988). Chemonucleolysis is an intermediate approach between conservative and surgical treatment, and is much less physically and emotionally burdensome than surgery. In 1982, the United States Food and Drug Administration approved chymopapain as a chemonucleolytic drug; however, chymopapain was discontinued in 1999 due to its low substrate specificity, disturbing nerve roots, and anaphylactic reactions (Nordby et al., 1993).

The chondroitin sulfate ABC endolyase (condoliase) is a mucopolysaccharide enzyme. It is highly substrate-specific for chondroitin sulfate and hyaluronic acid (Fan et al., 2022). Therefore, condoliase can specifically degrade proteoglycan-rich NP tissues, whereas the surrounding tissue remains largely unaffected (Ishibashi et al., 2019). The drug regulatory authority in Japan approved condoliase for the treatment of LDH in 2018, and multiple clinical trials have shown its safety and efficacy (Chiba et al., 2018; Matsuyama et al., 2018; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022). Intradiscal injection of condoliase may help patients to return to society sooner. However, some studies have suggested that condoliase has limited clinical efficacy in treating LDH (Ishibashi et al., 2020). Currently, there are no systematic reviews of condoliase for the treatment of LDH, which leaves clinicians with little reference when making decisions. Therefore, we conducted a meta-analysis of the efficacy and safety of condoliase in LDH treatment.

# 2 Materials and methods

The systematic review was registered in PROSPERO (CRD42022375492) https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022375492.

## 2.1 Search strategy

Two reviewers (ZH and BX) conducted an independent literature search. Electronic database search was conducted in PubMed, Web of Science, Embase, and Cochrane Library until October 2022. Keywords used for the search were as follows: "chondroitin ABC lyase", "condoliase", "chondroitin sulfate ABC endolyase", "chondroitinase ABC", "intradiscal", "back pain", "lumbar disc herniation", and "discogenic". Using PubMed as an example, the search strategy is as follows:

(1) "chondroitin ABC lyase" [ti, ab] OR "condoliase" [ti, ab] OR "chondroitin sulfate ABC endolyase" [ti, ab] OR "cchondroitinase ABC" [ti, ab]
(2) "intradiscal" [ti, ab] OR 'back pain' [ti, ab] OR 'lumbar disc herniation' [ti, ab] OR 'discogenic' [ti, ab]
(3) (1) and (2)

## 2.2 Inclusion and exclusion criteria

### 2.2.1 Inclusion criteria

1) Participants: Patients were clearly diagnosed with LDH. 2) Intervention: Intradiscal injection of condoliase. 3) Comparison: Placebo procedure, or none. 4) Study Design: Prospective studies, retrospective studies, and Randomised controlled trials (RCT). 5) Outcomes: The primary outcome was the total effective rate (proportion of individuals with ≥50% pain improvement on the visual analogue scale or numeric rating scale). Secondary outcomes included Oswestry Disability Index (ODI) score change, proportion of lumbar surgery after intradiscal injection of condoliase, herniated mass volume change, Pfirrmann grade change, and adverse events.

### 2.2.2 Exclusion Criteria

1) Repeated publications. 2) Lack of research on available data. 3) Full-text literature was not available.

## 2.3 Literature screening and data extraction

The literature was independently screened by two reviewers (ZH and BX). The basic information, study design, outcomes, and other data were extracted by two reviewers (ZH and BX). Any inconsistencies were scrutinised by a third reviewer (YL).

## 2.4 Quality assessment of the included studies

Two reviewers (BX and YL) assessed the risk of bias in RCT using to the bias risk assessment tool recommended in the Cochrane Manual (Hopp, 2015). The improved Newcastle-Ottawa scale (NOS) was used to evaluate the quality of non-RCT studies. Based on the original NOS scale, two questions related to the selection and comparison of non-exposed patients and one question related to the evaluation results were reduced, and the question of whether there was financial sponsorship from pharmaceutical enterprises was added (Stang, 2010; Huang et al., 2022). Any inconsistencies were scrutinised by a third reviewer (XS).

## 2.5 Statistical analysis

Review Manager 5.3. was used to analyse the clinical data. For the two-arm study with a control group, count data were evaluated

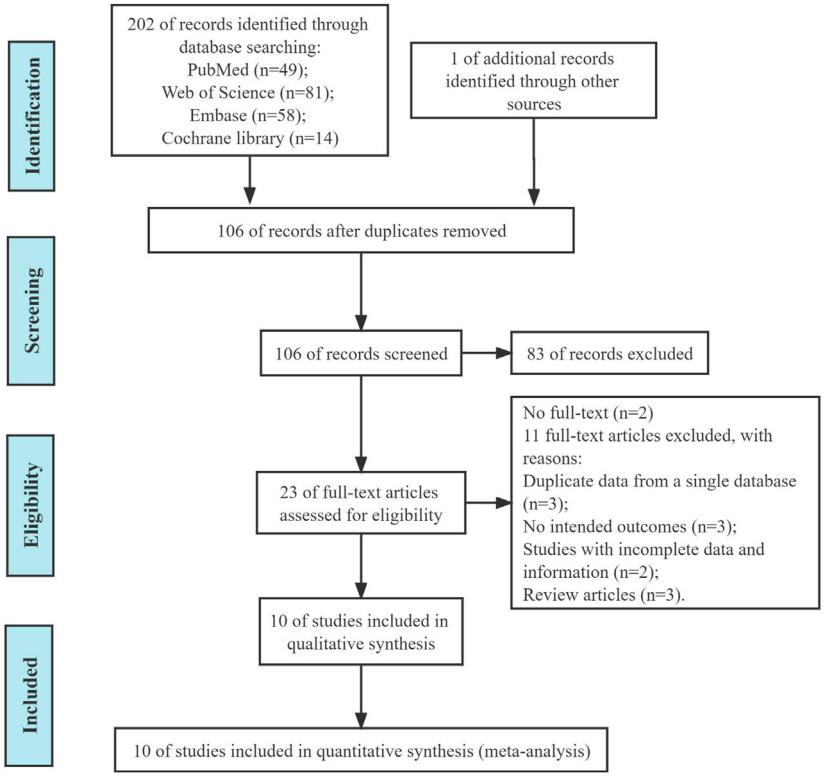


FIGURE 1
PRISMA flow diagram of the included studies.

using relative risk (RR) and 95% confidence interval (CI), and measurement data were analysed using the standardized mean difference (SMD) and 95%CI (Huang et al., 2022). For the single-arm study without a control group, the risk difference (RD, %) and 95%CI were used to analyse the event rate (Wang et al., 2021). If $I^2 < 50\%$ or $p > 0.05$, the heterogeneity among the included studies was considered small, and the fixed effect model was adopted; Otherwise, the random effects model was adopted (Cordero et al., 2021). Stata 12.0 was used for sensitivity and bias analysis to assess publication bias.

# 3 Results

## 3.1 Search results

We initially retrieved 202 (Figure 1) and deleted 96 duplicate articles. A total of 10 articles were included in this study through screening (Chiba et al., 2018; Matsuyama et al., 2018; Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022).

## 3.2 Characteristics of the included studies

The included studies included two RCT (Chiba et al., 2018; Matsuyama et al., 2018), two prospective (Inoue et al., 2021; Banno et al., 2022), and six retrospective studies (Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Okada et al., 2021; Kobayashi et al., 2022; Oshita et al., 2022). A placebo was used as a control group in both RCT studies. A total of 259 patients were enrolled in the two RCTS and the remaining eight studies were single-arm trials involving 552 patients. (Table 1).

## 3.3 Quality assessment

The methodological quality and bias risk of the included RCT and non-RCT studies are shown in Figure 2. The included 10 studies (Chiba et al., 2018; Matsuyama et al., 2018; Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022) were of good methodological quality, and none warranted exclusion in terms of methodological quality.

## 3.4 Results of meta-analysis

### 3.4.1 Total effective rate

Nine studies (Chiba et al., 2018; Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022) reported the total effective treatment rate,

**TABLE 1 Characteristics of the included studies.**

| Author, year | Study design | Sample size | Age (mean ± SD) | Gender (male/famale) | Herniation type | Intervention | Time of assessment (months) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Banno et al., 2022 | Prospective study | 60 | 44.5 ± 18.9 | 37/23 | Excluded transligamentous herniation | Condoliase, 1.25U/mL, 1mL, intradiscal injection | 12 | ①③⑤⑥ |
| Chiba et al., 2018 | RCT | 82/81 | TG: 39.5 ± 11.1 | TG: 51/31 | Excluded transligamentous herniation, or sequestration herniation | TG: Condoliase, 1.25U/mL, 1mL, intradiscal injection | 3、12 | ①②③④⑤⑥ |
| | | | CG: 39.2 ± 12.4 | CG: 51/30 | | CG: Placebo | | |
| Hirai et al., 2021 | Retrospective study | 52 | 45.0 ± 17.7 | 35/17 | Subligamentous herniation, and transligamentous herniation | Condoliase, 1.25U/mL, 1mL, intradiscal injection | 6 | ①③⑤⑥ |
| Inoue et al., 2021 | Prospective study | 84 | 44.2 ± 17.1 | 52/32 | Subligamentous herniation | Condoliase, intradiscal injection | 6 | ①③⑤⑥ |
| Kobayashi et al., 2022 | Retrospective study | 127 | 46.6 ± 17.1 | 88/39 | Subligamentous herniation, and transligamentous herniation | Condoliase, 1.25U/mL, 1mL, intradiscal injection | 3 | ①③⑤⑥ |
| Matsuyama et al., 2018 | RCT | 49/47 | TG: 41.9 ± 10.9 | TG: 38/11 | / | TG: Condoliase, 1.25U/mL, 1mL, intradiscal injection | 3、12 | ②④⑥ |
| | | | CG: 34.0 ± 10.2 | CG: 31/16 | | CG: Placebo | | |
| Nakajima et al., 2020 | Retrospective study | 42 | 46.0 ± 13.8 | 29/13 | Subligamentous herniation, and transligamentous herniation | Condoliase, 1.25U/mL, 1 mL, intradiscal injection | 3 | ①⑥ |
| Okada et al., 2021 | Retrospective study | 82 | 47.2 ± 15.5 | 55/27 | / | Condoliase, 1.25U/mL, 1 mL, intradiscal injection | 6 | ①③⑤⑥ |
| Oshita et al., 2022 | Retrospective study | 71 | / | 38/33 | Protruding, subligamentous herniation, and transligamentous herniation | Condoliase, 1.25U/mL, 1 mL, intradiscal injection | 3 | ①⑥ |
| Ishibashi et al., 2020 | Retrospective study | 34 | 32.4 ± 13.0 | 10/24 | Subligamentous herniation, and transligamentous herniation | Condoliase, 1.25U/mL, 1 mL, intradiscal injection | 3 | ①③⑥ |

Abbreviations: TG: treatment group; CG: control group; /: not mentioned; ①: total Effective Rate; ②: ODI, score change; ③: the proportion of operation after condoliase treatment; ④: erniated mass volume change; ⑤: Pfirrmann grade change; ⑥: adverse even.

including 634 patients. There was homogeneity among the studies ($p = 0.41$, $I^2 = 3\%$). The results of single-arm meta-analysis of fixed effects model showed that the total effective rate of condoliase treatment was 78% (95%CI 75%–81%). Four (Ishibashi et al., 2020; Nakajima et al., 2020; Kobayashi et al., 2022; Oshita et al., 2022), three (Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021), and two (Chiba et al., 2018; Banno et al., 2022) studies were followed up three, six, and 12 months after treatment, respectively. Subgroup analysis was performed according to the follow-up time, and all subgroups were homogeneous (all $p > 0.05$, all $I^2 < 50\%$). Subgroup analysis showed that the total effective rate at three, six, and 12 months after condoliase treatment was 74% (95%CI 69%–80%), 81% (95%CI 76%–86%), and 79% (95%CI 72%–86%), respectively (Figure 3). The results of the RCT by Chiba et al. (2018) showed a higher response rate 12 months after treatment in the condoliase (79.3%) than in the placebo control group (63%) ($p = 0.02$).

### 3.4.2 ODI score change

Two RCT (Chiba et al., 2018; Matsuyama et al., 2018) reported ODI score change in 259 patients. There was a large heterogeneity between the two groups ($p = 0.01$, $I^2 = 84\%$). The results of two-arm meta-analysis of random effects model showed that the ODI score change of the condoliase treatment group was greater than that of the placebo control group (SMD -2.46, 95%CI -3.30 to −1.63) (Figure 4).

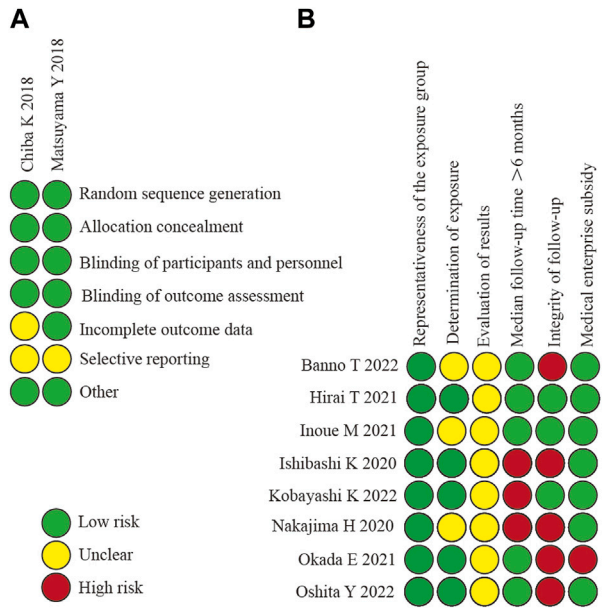


FIGURE 2
Risk of bias assessment **(A)**: the risk of bias in RCT; **(B)** the risk of bias in non-RCT).

### 3.4.3 The proportion of surgery after condoliase treatment

Seven studies (Chiba et al., 2018; Ishibashi et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022) reported the proportion of surgery performed after condoliase treatment, including 568 patients. There was homogeneity among the studies ($p$ = 0.15, $I^2$ = 37%). The results of single-arm meta-analysis of fixed effects model showed that the proportion of surgery after condoliase treatment was 9% (95%CI 7%–12%) (Figure 5).

### 3.4.4 Herniated mass volume change

Two RCT studies (Chiba et al., 2018; Matsuyama et al., 2018) reported a herniated mass volume change in 259 patients. There was a large heterogeneity between the two groups ($p$ < 0.001, $I^2$ = 95%). The results of two-arm meta-analysis of random effects model showed that the herniated mass volume change of the condoliase treatment group was greater than that of the placebo control group (SMD -16.97, 95%CI -23.92 to −10.03) (Figure 6).

### 3.4.5 Pfirrmann grade change

Six studies (Chiba et al., 2018; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022) including 449 patients reported Pfirrmann grade changes after condoliase treatment. There was homogeneity among the studies ($p$ = 0.25, $I^2$ = 25%). The results of single-arm meta-analysis of fixed effects model showed that the proportion of Pfirrmann grade change after condoliase treatment was 43% (95%CI 38%–47%) (Figure 7).

### 3.4.6 Adverse events

Ten studies (Chiba et al., 2018; Matsuyama et al., 2018; Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022) reported adverse events in 811 patients. There was

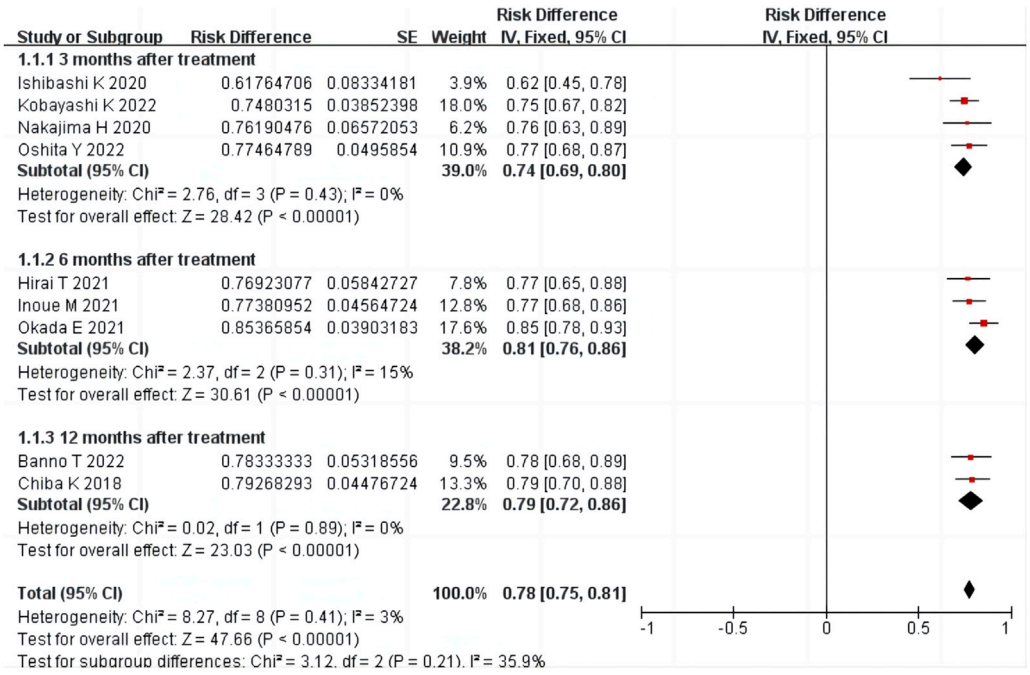


FIGURE 3
Forest plot of total effective rate.

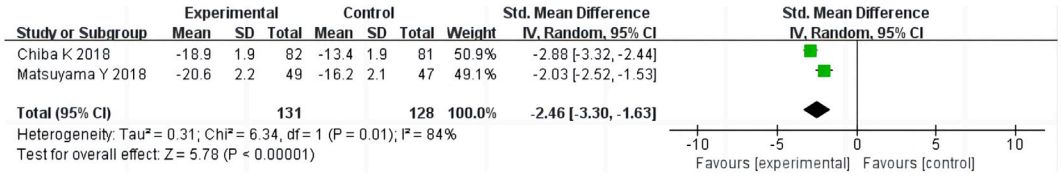


FIGURE 4
Forest plot of ODI score change.

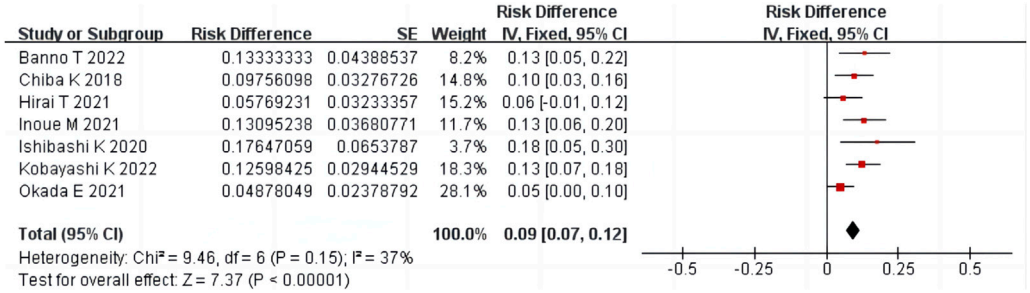


FIGURE 5
Forest plot of the proportion of surgery after condoliase treatment.

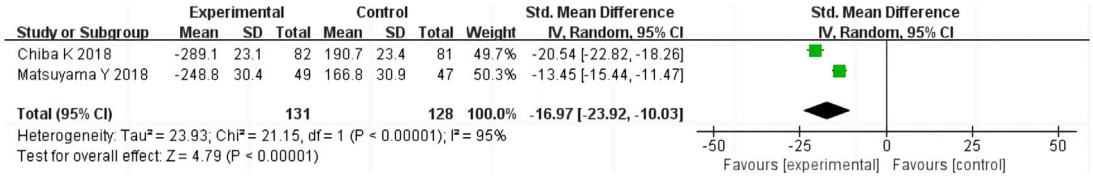


FIGURE 6
Forest plot of herniated mass volume change.

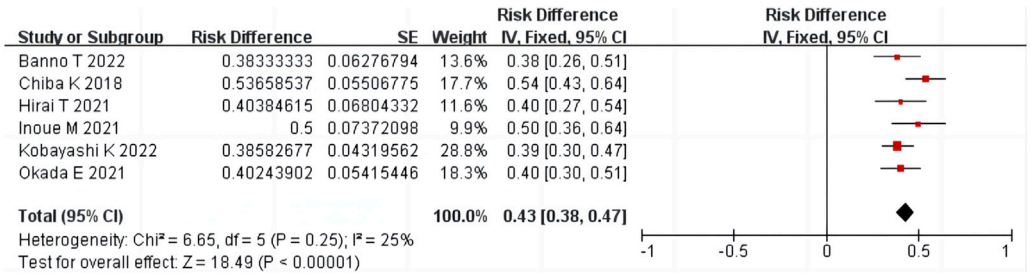


FIGURE 7
Forest plot of Pfirrmann grade change.

homogeneity among eight non-RCT studies ($p = 0.41$, $I^2 = 2\%$) (Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021; Okada et al., 2021; Banno et al., 2022; Kobayashi et al., 2022; Oshita et al., 2022). The results of single-arm meta-analysis of fixed effects model showed that the adverse events after condoliase treatment were 4% (95%CI 2%–6%) (Figure 8). There was

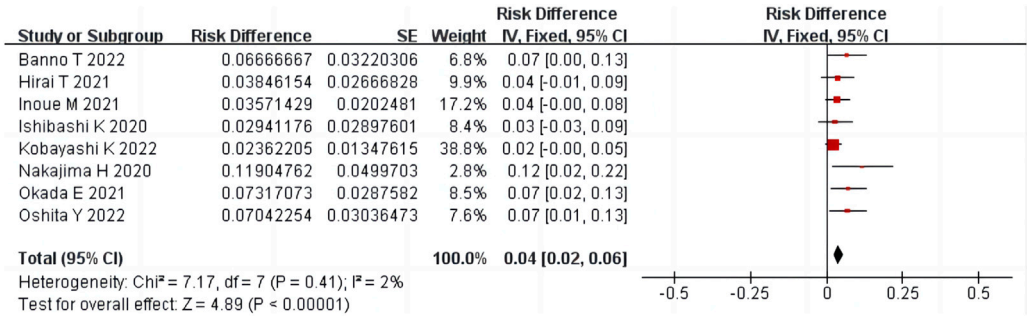


FIGURE 8
Forest plot of single-arm meta-analysis of adverse events.

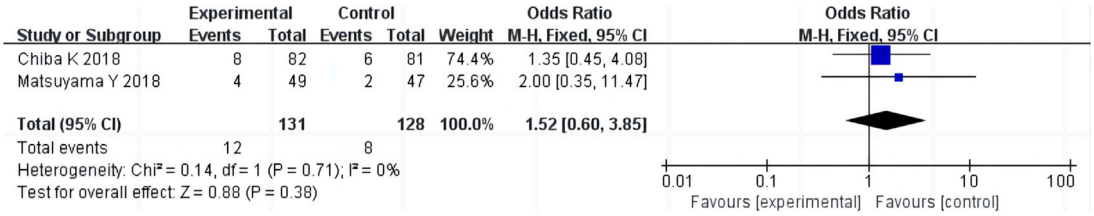


FIGURE 9
Forest plot of two-arm meta-analysis of adverse events.

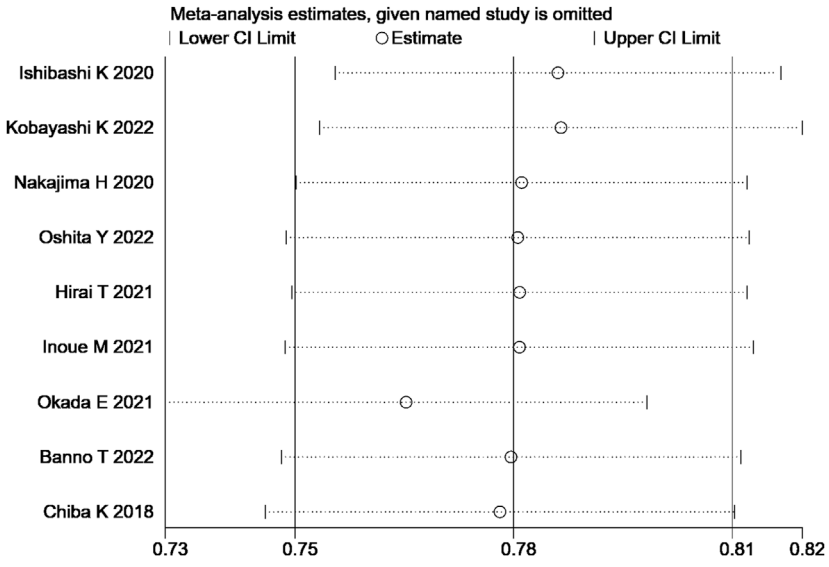


FIGURE 10
Sensitivity analysis to the total effective rate.

homogeneity among the two RCT studies ($p = 0.71$, $I^2 = 0\%$) (Chiba et al., 2018; Matsuyama et al., 2018). The results of two-arm meta-analysis of fixed effects model showed the adverse events were the same between the condoliase treatment and placebo control groups (OR 1.52, 95%CI 0.60–3.85) (Figure 9).

## 3.5 Sensitivity analysis and publication bias

The sensitivity analysis of the total effective rate suggested that the meta-analysis results were stable (Figure 10). Analysis of the funnel plot of the total effective rate showed that each study

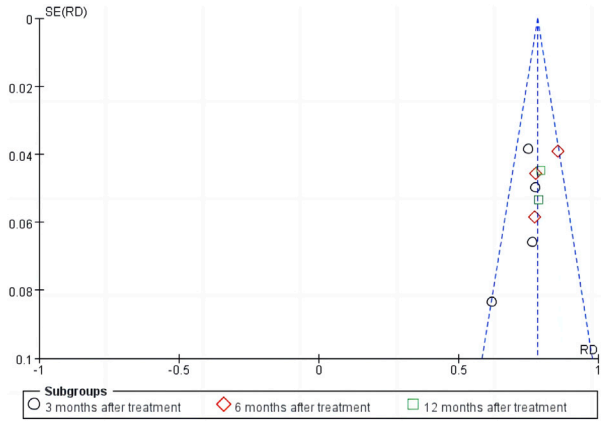


FIGURE 11
Publication bias of the funnel plot of total effective rate.

had a symmetric distribution. The *p*-value of the Egger's test was 0.052, suggesting a small possibility of publication bias (Figure 11).

# 4 Discussion

Chemonucleolysis is a minimally invasive treatment for LDH that does not require general anaesthesia, which is an important advantage over any surgical treatment (Simmons et al., 2001). More than 50 years have passed since this procedure was developed, but it has yet to become common practice. One of the main reasons for this is the low specificity for enzymes that target the NP (Brown, 1996; Nordby et al., 1996). Condoliase degrades chondroitin sulfate and hyaluronic acid chains (Takahashi, 2004). Numerous mammalian tissues contain chondroitin sulfate, including the NP, bone, and cartilage. Therefore, condoliase is a potential therapeutic enzyme for LDH (Knezevic et al., 2017; Matsuyama and Chiba, 2019). It has been verified that condoliase is significantly less harmful to the surrounding tissues, and the nervous and vascular system than chymopapain. In Japan, condoliase (HERNICORE®, Seikagaku Corporation, Tokyo, Japan) was released in 2018 for LDH treatment.

## 4.1 Effectiveness of condoliase in treating LDH

Studies show that more than 90% of LDH patients who undergo surgical treatment experience symptomatic relief within a few months (Jacobs et al., 2011). We conducted a systematic review of all available literature on the intradiscal injection of condoliase for LDH. A single-arm meta-analysis of these studies demonstrated that approximately 74%, 81%, and 79% of patients reported clinically significant pain improvement at 3, 6, and 12 months after condoliase treatment, respectively. A two-arm meta-analysis of RCT studies demonstrated that the ODI score change in the condoliase treatment group was greater than that in the placebo control group. Although there is still a gap between the efficacy of condoliase treatment and surgical treatment, approximately 78% of patients in whom conservative treatment is ineffective can achieve therapeutic effects after condoliase treatment good enough to avoid surgery. Approximately 5%–10% of patients with LDH who have undergone surgical treatment require reoperation (Sugimura et al., 1996). Our meta-analysis showed that the proportion of surgeries after condoliase treatment was 9% at the last follow-up. Therefore, chemonucleolysis with condoliase is similar to surgical treatment in preventing LDH recurrence. The pharmacological effects of condoliase involve the degradation of hyaluronic acid and dehydration of the NP, which diminishes the volume of the herniated mass; On the other hand, it may lead to further degradation of the intervertebral disc, causing signal changes in MRI and Pfirmann grading. Our two-arm meta-analysis of RCT studies demonstrated that the herniated mass volume change in the condoliase treatment group was greater than that in the placebo group. A single-arm meta-analysis showed that the proportion of patients with Pfirrmann grade change after condoliase treatment was 43% at the last follow-up. Sugimura et al. (1996); (Lønne et al., 2012) found after 28 weeks of condoliase intradiscal injection, glycosaminoglycan content recovered in monkeys, and Banno et al. (2022) found that disc degeneration caused by chemonucleolysis with condoliase could be reversed after 1 year. Thus, the effect of condoliase on the NP is only temporary, and the intervertebral disc can regenerate once enzyme activity has disappeared. The phenomenon is more prevalent in younger patients (Kobayashi et al., 2022). With the exception of the study of Banno et al. (2022), no recovery of the Pfirmann grade has been reported in any other clinical studies of condoliase; therefore, the long-term effects of condoliase require further observation.

## 4.2 Safety of condoliase in treating LDH

In an RCT study conducted by Matsuyama et al. (2018), 194 patients received condoliase intradiscal injections of 1.25, 2.5, or 5 U or a placebo intradiscal injection. The results showed that although all three doses had similar efficacy, adverse events were dose-dependent; therefore, 1.25 U of condoliase was an appropriate dose for intradiscal injections. Our meta-analysis showed that the adverse events after condoliase treatment were 4%, and the results of the two-arm meta-analysis showed no difference in adverse events between the condoliase treatment and placebo control groups. As condoliase is an exogenous protein, the risk of anaphylactic shock cannot be ignored. However, no anaphylactic shock cases were reported in the included studies. Rashes are the most common allergy-like symptoms of condoliase treatment; however, all symptoms can be resolved after standard dermatologic treatment. A small number of patients also experienced mild to moderate back pain within a week of condoliase injection, but the pain resolved or abated in most patients without treatment. No neurological deterioration or spondylitis infection was reported after condoliase intradiscal injection (Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Inoue et al., 2021).

### 4.3 Precautions

To prevent anaphylactic reactions, condoliase can be used only once in a lifetime, which makes it particularly important to identify likely responders and determine the indications for the use of condoliase. ①Herniation type: Sequestration herniation was not included in all studies. While some studies excluded transligamentous herniation (Chiba et al., 2018; Banno et al., 2022), others have shown that condoliase appears to be an effective treatment for all herniation types except sequestration herniation (Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Kobayashi et al., 2022; Oshita et al., 2022). ②Disease duration: Many reports have shown that prolonged symptom duration has an adverse impact on the prognosis of patients with LDH (Sugimura et al., 1996). Therefore, it is important to intervene at the best time rather than pursue ineffective conservative treatment. Banno et al. (2022) showed a low response rate for condoliase treatment in patients with symptoms lasting longer than 1 year. Nakajima suggested that intradiscal injection of condoliase should be performed 6 months after disease onset (Nakajima et al., 2020). ③Symptoms: The indication for condoliase intradiscal injection were symptoms of unilateral lower extremity pain with or without back pain, nerve root compression by a herniated disc confirmed using MRI, neurological signs consistent with the distribution of the compressed nerve root. LDH patients with neurological deficits such as cauda equina syndrome and severe progressive dyskinesia should not be treated with condoliase (Chiba et al., 2018; Ishibashi et al., 2018; Ishibashi et al., 2020; Nakajima et al., 2020; Hirai et al., 2021; Banno et al., 2022; Kobayashi et al., 2022). ④Age: In principle, condoliase intradiscal injection is better for young LDH patients with high water content in the NP and simple reasons for low back pain (Ishibashi et al., 2020). However, multiple clinical studies have shown that condoliase may be effective for LDH regardless of age (Hirai et al., 2021; Oshita et al., 2022). ⑤Predictive factors for better efficacy: Banno et al. (2022) and Ishibashi et al. (2020) reported that high intensity on T2-weighted MRI had a positive impact on therapeutic effects showed for chemonucleolysis. Nakajima and Ishibashi found that a larger herniated mass volume showed better efficacy for chemonucleolysis with condoliase. ⑥Risk factors: Risk factors for poor prognosis with condoliase include a history of hernia opening, presence of spondylolisthesis, or a posterior intervertebral angle of $> 5^{\circ}$ (Ishibashi et al., 2020; Hirai et al., 2021). Based on these investigations, suggestions were made for the clinical application of condoliase in treating LDH.

### 4.4 Limitations

This review and the existing literature related to condoliase have important limitations. ①This analysis only included English language studies due to language limitations. ②Though we used comprehensive search strategies in electronic databases for our study, some eligible studies may have been missed. ③Only two RCT studies on condoliase for LDH could be found, leading to only a single-arm meta-analysis for some outcomes. ④Patient characteristics such as Diabetes Mellitus, smoking, and activity levels may have an impact on the outcome of condoliase intradiscal injection, but these factors were not discussed in the included studies. ⑤Most of the included studies had short follow-up times and were inconsistent among included studies, the longer-term clinical outcomes of condoliase intradiscal injection are unknown.

## 5 Conclusion

In conclusion, our meta-analysis shows that condoliase intradiscal injection has excellent eutherapeutic and safety for LDH. Thus condoliase intradiscal injection has considerable potential as a treatment option besides conservative treatment and surgical intervention. However, the strength of this conclusion is diminished due to limitations in the quality and type of studies included in this study. In the future, large double-blinded double-arm RCT studies are still needed.

## 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

ZH, BX, and YjL contributed to the study design. ZH, YwL, and BX contributed to the data collection. Statistical analyses and interpretation of results were performed by ZH, XS, HC, and XC. ZH, BX, and YwL drafted the manuscript. YjL and XS edited the language. 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



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# Global prevalence of polypharmacy and potentially inappropriate medication in older patients with dementia: a systematic review and meta-analysis

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**Background:** Older patients with dementia always need multiple drugs due to comorbidities and cognitive impairment, further complicating drug treatment and increasing the risk of potentially inappropriate medication. The objective of our study is to estimate the global prevalence of polypharmacy and potentially inappropriate medication (PIM) and explore the factors of PIM for older patients with dementia.

**Methods:** We searched PubMed, Embase (Ovid), and Web of Science databases to identify eligible studies from inception to 16 June 2023. We conducted a meta-analysis for observational studies reporting the prevalence of potentially inappropriate medication and polypharmacy in older patients with dementia using a random-effect model. The factors associated with PIM were meta-analyzed.

**Results:** Overall, 62 eligible studies were included, of which 53 studies reported the prevalence of PIM and 28 studies reported the prevalence of polypharmacy. The pooled estimate of PIM and polypharmacy was 43% (95% CI 38–48) and 62% (95% CI 52–71), respectively. Sixteen studies referred to factors associated with PIM use, and 15 factors were further pooled. Polypharmacy (2.83, 95% CI 1.80–4.44), diabetes (1.31, 95% CI 1.04–1.65), heart failure (1.17, 95% CI 1.00–1.37), depression (1.45, 95% CI 1.14–1.88), history of cancer (1.20, 95% CI 1.09–1.32), hypertension (1.46, 95% CI 1.05–2.03), ischemic heart disease (1.55, 95% CI 0.77–3.12), any cardiovascular disease (1.11, 95% CI 1.06–1.17), vascular dementia (1.09, 95% CI 1.03–1.16), chronic obstructive pulmonary disease (1.39, 95% CI 1.13–1.72), and psychosis (1.91, 95% CI 1.04–3.53) are positively associated with PIM use.

**Conclusion:** PIM and polypharmacy were highly prevalent in older patients with dementia. Among different regions, the pooled estimate of PIM use and polypharmacy varied widely. Increasing PIM in older patients with dementia was closely associated with polypharmacy. For other comorbidities such as heart failure and diabetes, prescribing should be cautioned.

KEYWORDS

polypharmacy, potentially inappropriate medication, older, dementia, meta-analysis, factors

# 1 Introduction

The statistics of epidemiology revealed that in 2019, there were 703 million individuals aged 65 years or above living in the world, and the number was expected to reach 1.5 billion by 2050 (He and Kinsella, 2020). The global population aging would further accelerate the increase in the geriatric population, which imposed significant demands on the healthcare system. Meanwhile, increased medication use is one of the important challenges (Chiatti et al., 2012; Johnell, 2015).

Polypharmacy is defined as the concurrent use of multiple drugs, generally taking five or more drugs (Masnoon et al., 2017; Rankin et al., 2018). The older population often suffered multiple diseases, and polypharmacy was insufficient for controlling or curing diseases. A cross-sectional study performed by Chandrasekhar reported that the prevalence of polypharmacy in 210 inpatients aged 65 years or above was up to 60% and that of hyperpolypharmacy (ten or more drugs) was 35.7% (Chandrasekhar et al., 2019). Moreover, aging-related alteration in pharmacokinetics and pharmacodynamics might lead to stronger drug effects and prolongation of drug action time (Shi et al., 2008). Thus, the management of adverse effects on multiple drugs and potential drug–drug interaction among the older population was rather complicated and challenging.

Dementia, a degenerative nervous system disorder, features irreversible decline in cognitive function (Prince et al., 2013). Patients diagnosed with dementia were especially sensitive to adverse effects of central nervous system (CNS) drugs (Bell et al., 2012). Communication disorder caused by cognitive impairment and concomitant mental symptoms would lead to more complicated drug use in patients with dementia (Johnell, 2015). Furthermore, compared with non-dementia, dementia was more likely to be accompanied by other chronic diseases, such as hypertension and diabetes, exposing a higher risk of polypharmacy (Clague et al., 2017). Banta et al. indicated older patients with dementia are more likely to have five or more current prescriptions (Banta, 2017). Therefore, we should attach great importance to drug medications for older patients with dementia.

Potentially inappropriate medication (PIM) is an important concept to assess the quality of drug use. The term was first proposed by the American Panel in 1991, defined as those drugs with potential risks outweighing the benefits (Renom-Guiteras et al., 2015). A large number of studies have demonstrated PIM was associated with drug-related problems and adverse outcomes, such as increasing risk of hospitalization and death and incurring extra medical expenditure (Hagstrom et al., 2015; Hyttinen et al., 2017; Murphy et al., 2020). In order to evaluate PIM use and avoid the occurrence of adverse events, several explicit tools based on expert census were developed. A systematic review showed a total of 46 screening lists of PIM in the world that were identified, covering four continents and 13 countries (Kaufmann et al., 2014). The most frequently used criteria were Beers criteria and STOPP/START criteria (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; O'Mahony et al., 2018), including drugs that should be avoided for treating common systemic diseases in elderly patients, possible adverse reactions, drug–drug interactions, drug–disease interactions, and risky drug use based on the renal function level. PIM use among older people was prevalent, especially in frail patients with dementia who need long-term care (Kristensen et al., 2018). Due to the difference of medical habits in each country and screening tools, the prevalence of PIM in patients with dementia varied widely. In European countries, 60% of older patients with dementia had at least one PIM based on the European Union (7)-PIM list (Renom-Guiteras et al., 2018). In China, the prevalence of PIM was 39.43% evaluated using 2019 Beers criteria (Zhao et al., 2022). Thus, a pooled analysis is necessary to conduct for evaluating the PIM and polypharmacy in patients with dementia, further providing a reference for countries that have not yet carried out a relevant study about drug burden in older patients with dementia.

To date, several reviews about PIM use and polypharmacy in dementia have been published (Johnell, 2015; Disalvo et al., 2016; Redston et al., 2018; Hukins et al., 2019; Delgado et al., 2020), but limited to a specific type of dementia or specific population (such as community or inpatients), or only qualitatively described the prevalence of PIM use or polypharmacy. In the systematic review and meta-analysis, we first summarized the pooled estimate of PIM and polypharmacy in older patients with dementia (not including mild cognitive impairment) across different regions and explored the association between PIM and polypharmacy and reviewed other factors associated with PIM use.

# 2 Methods

The study protocol of this systematic review and meta-analysis was registered on PROSPERO (CRD42022368310). The study was conducted based on MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2015).

## 2.1 Search strategy

A comprehensive search of PubMed, Embase (Ovid), and Web of Science was performed from inception to 16 June 2023. The search strategy was using a combination of Medical Subject Headings (MeSH) and free text words. The specific search details in different databases are listed in Supplementary Table S1. In addition, we performed manual searching of selected published full-text reviews, identifying other potential relevant articles.

## 2.2 Selection criteria

Studies were included if they recruited older adults with dementia (≥65 years, or mean age ≥70 years), reported the prevalence of polypharmacy (five or more) or PIM in dementia,

used explicit criteria to identify PIM, and wrote the manuscript in English. The diagnosis of dementia was based on medical records, DSM criteria, ICD code, or other criteria. In addition, the study design of the included articles was observational studies (cross-sectional study or cohort study).

Studies were excluded if study subjects had mild cognitive impairment, or if those studies were conference abstracts, reviews, and comments.

## 2.3 Data extraction

Two reviewers (MN Zhao and ZY Chen) independently extracted and verified the data. We extracted information including study characteristics (first author, year of publication, and country), basic information of study subjects (age, sex, and sample size), and study design (setting, prevalence of polypharmacy or PIM, and explicit criteria to evaluate PIM). Any discrepancy between two reviewers was resolved by consultation with a third reviewer (FY, Tian).

## 2.4 Selection of studies

Two reviewers (MN Zhao and ZY Chen) independently screened the titles and abstracts of initially included literature according to the inclusion and exclusion criteria. The full text was further assessed if the eligibility of the study was not clearly determined from the abstract. Any inconsistency in the process of screening was resolved by consulting a third senior investigator (Ting Xu).

## 2.5 Quality assessment

The methodological quality of the cross-sectional study was evaluated using the Agency for Healthcare Research and Quality (AHRQ) (Rostom et al., 2004; Hu et al., 2015). A total of 11 items were listed in AHRQ, including 1) the source of data; 2) eligible criteria for study subjects; 3) time period for included population; 4) whether or not subjects were consecutive; 5) whether the outcome indicators are affected by other factors; 6) any assessments for quality assurance; 7) explanation for excluding any patients from the analysis; 8) measurements taken for controlling confounding factors; 9) description for the handing of missing data; 10) summary for patient response rate and completeness of data collection; 11) clarification of follow-up results. The highest score was 11, while the lowest score was 0. If the score was 8 or above, this study was considered high quality. If the score was 3 or below, this study was considered low quality. If the score was between 3 and 8, this study was considered medium quality. The methodological quality of the cohort study was evaluated by the Newcastle–Ottawa scale (Stang, 2010). If the NOS score ≥8, this study was considered high quality. If the NOS score ≤5, this study was considered low quality. If the NOS score was 6 or 7, this study was considered medium quality (Bedaso and Duko, 2022).

## 2.6 Statistical analysis

We applied STATA, version 16 (Stata Corporation, College Station, Texas, United States) to perform a meta-analysis for polypharmacy and PIM. The pooled prevalence estimate was reported as a proportion with 95% confidence intervals (CI). The I2 statistics was used to assess the magnitude of heterogeneity. When I2 >50%, heterogeneity among studies was considered large and the DerSimonian–Laird random-effect model was applied in analysis. In case of significant heterogeneity, subgroup analysis (e.g., regions, the proportion of females, criteria, and severity of dementia)) was performed to investigate the source of heterogeneity. We also estimated the 95% prediction interval, which further accounts for between-study heterogeneity and evaluates the uncertainty for the effect that would be expected in a new study addressing that same association (Higgins et al., 2009; Migliavaca et al., 2022). Furthermore, a pooled odds ratio was used to analyze the association between PIM and factors when two or more studies reported the same and adjusted odds ratio. Regarding the risk of publication bias, we adopted Egger's and Begg's tests for evaluation.

# 3 Results

## 3.1 Study selection

Overall, 5,642 records were initially obtained through PubMed, Embase, and Web of Science databases. After removing duplication (n = 1,302), 4,337 records were used to screen the title and abstract. Finally, 62 studies (Zuckerman et al., 2005; Raivio et al., 2006; Holmes et al., 2008; Chan et al., 2009; Lau et al., 2010; Somers et al., 2010; Tjia et al., 2010; Andersen et al., 2011; Lau et al., 2011; Bosboom et al., 2012; Colloca et al., 2012; Parsons et al., 2012; Thorpe et al., 2012; Fiss et al., 2013; Koyama et al., 2013; Montastruc et al., 2013; Toscani et al., 2013; Tjia et al., 2014; Hanlon et al., 2015; Skoldunger et al., 2015; Barry et al., 2016; Cross et al., 2016; Walsh et al., 2016; Chuang et al., 2017; Clague et al., 2017; Hyttinen et al., 2017; Kanagaratnam et al., 2017; Oesterhus et al., 2017; Ramsey et al., 2017; Wucherer et al., 2017; Kristensen et al., 2018; Nguyen et al., 2018; Renom-Guiteras et al., 2018; Bala et al., 2019; Brimelow et al., 2019; Denholm et al., 2019; Eshetie et al., 2019a; Kristensen et al., 2019; Soysal et al., 2019; Eshetie et al., 2020; Eshetie et al., 2020; Forgerini et al., 2020; Murphy et al., 2020; Rausch and Hoffmann, 2020; Ruangritchankul et al., 2020; Delgado et al., 2021; Ferreira et al., 2021; Gareri et al., 2021; Growdon et al., 2021; Jaramillo-Hidalgo et al., 2021; Kristensen et al., 2021; Thapaliya et al., 2021; Vickers et al., 2021; Buckley et al., 2022; Chao et al., 2022; Delgado et al., 2022; Rangfast et al., 2022; Riedl et al., 2022; Yoon et al., 2022; Zhao et al., 2022; Bae-Shaaw et al., 2023; Ryskina et al., 2023) were included based on the eligibility criteria after thoroughly reading the full text (n = 122). The flow diagram of literature screening is shown in Figure 1.

## 3.2 Characteristics of included studies

Of all included studies, 53 studies reported the prevalence of PIM (Zuckerman et al., 2005; Raivio et al., 2006; Holmes et al., 2008;

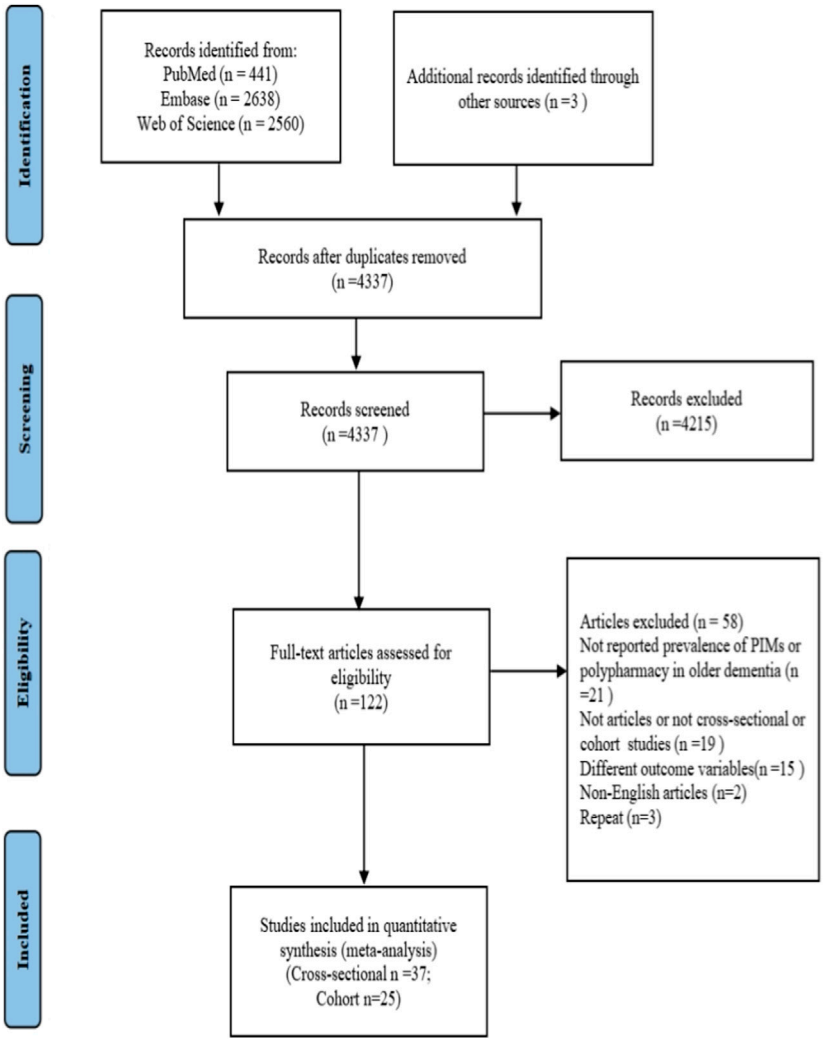


FIGURE 1
PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PIM, potentially inappropriate medication.

Chan et al., 2009; Lau et al., 2010; Somers et al., 2010; Tjia et al., 2010; Andersen et al., 2011; Lau et al., 2011; Bosboom et al., 2012; Colloca et al., 2012; Parsons et al., 2012; Thorpe et al., 2012; Fiss et al., 2013; Koyama et al., 2013; Montastruc et al., 2013; Toscani et al., 2013; Tjia et al., 2014; Hanlon et al., 2015; Skoldunger et al., 2015; Barry et al., 2016; Cross et al., 2016; Chuang et al., 2017; Hyttinen et al., 2017; Oesterhus et al., 2017; Ramsey et al., 2017; Wucherer et al., 2017; Kristensen et al., 2018; Nguyen et al., 2018; Renom-Guiteras et al., 2018; Eshetie et al., 2019a; Bala et al., 2019; Brimelow et al., 2019; Denholm et al., 2019; Eshetie et al., 2020; Eshetie et al., 2020; Forgerini et al., 2020; Murphy et al., 2020; Rausch and Hoffmann, 2020; Ruangritchankul et al., 2020; Delgado et al., 2021; Ferreira et al., 2021; Jaramillo-Hidalgo et al., 2021; Kristensen et al., 2021; Vickers et al., 2021; Buckley et al., 2022; Delgado et al., 2022; Rangfast et al., 2022; Riedl et al., 2022; Yoon et al., 2022; Zhao et al., 2022; Bae-Shaaw et al., 2023; Ryskina et al., 2023), and 28 studies reported the prevalence of polypharmacy (Lau et al., 2010; Somers et al., 2010; Lau et al., 2011; Bosboom et al., 2012; Montastruc et al., 2013; Hanlon et al., 2015; Cross et al., 2016; Walsh et al., 2016; Clague et al., 2017; Kanagaratnam et al., 2017; Oesterhus et al., 2017; Kristensen et al., 2018; Nguyen et al., 2018; Kristensen et al., 2019; Soysal et al., 2019; Forgerini et al., 2020; Rausch and Hoffmann, 2020; Ruangritchankul et al., 2020; Ferreira et al., 2021; Gareri et al., 2021; Growdon et al., 2021; Jaramillo-Hidalgo et al., 2021; Thapaliya et al., 2021; Vickers et al., 2021; Chao et al., 2022; Delgado et al., 2022; Riedl et al., 2022; Zhao et al., 2022). The sample size ranged from 34 to 259,291, comprising a total of 658,431 study subjects. Most studies (n = 30) were conducted in Europe (Raivio et al., 2006; Andersen et al., 2011; Colloca et al., 2012; Parsons et al., 2012; Fiss et al., 2013; Montastruc et al., 2013; Toscani et al., 2013; Skoldunger et al., 2015; Barry et al., 2016; Hyttinen et al., 2016; Walsh et al., 2016; Clague et al., 2017; Kanagaratnam et al., 2017; Oesterhus et al., 2017; Wucherer et al., 2017; Kristensen et al., 2018; Renom-Guiteras et al., 2018; Denholm et al., 2019; Kristensen et al., 2019; Soysal et al., 2019; Murphy et al., 2020; Rausch and Hoffmann, 2020; Delgado et al., 2021; Gareri et al., 2021; Jaramillo-Hidalgo et al., 2021; Kristensen et al., 2021; Buckley et al., 2022; Delgado et al., 2022; Rangfast et al., 2022; Riedl et al., 2022), only two studies were

**TABLE 1 Characteristics of included studies.**

| Study | Year | Setting | Country | Region | Type | Criteria | Age (mean or median) | Female (%) | Sample | PIM | PP | Identification of dementia population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Andersen et al | 2011 | Community | Norway | Europe | Cross-sectional | STOPP v1 | 80.9 (±7.1) | 60.0% | 187 | 37.00% | NR | ICD-10 |
| Bala et al | 2019 | Community | New Zealand | Oceania | Cross-sectional | 2015 Beers Criteria | NR* | NR | 2,190 | 66.90% | NR | CPS |
| Barry et al | 2016 | Community | Ireland | Europe | Cross-sectional | STOPP (36) v2 | 79.6 (±8.0) | 64.4% | 6,826 | 64.40% | NR | Anti-dementia drugs |
| Bosboom et al | 2012 | Care homes | Australia | Oceania | Cross-sectional | 2003 Beers criteria | 85.9 (±7.7) | 74.8% | 226 | 54.90% | 92.00% | Clinical diagnosis of dementia and MMSE<=24 |
| Brimelow et al | 2012 | Care homes | Australia | Oceania | Cross-sectional | 2012 Beers criteria | 86 (±8.9) a | 74.3%a | 441 | 50.40% | NR | Medical records |
| Chao et al | 2022 | Inpatient | China | Asia | Cross-sectional | - | 86 (79–90) | 37.8% | 74 | - | 79.70% | NIA—AA or DSM-5 |
| Chan et al | 2008 | Community | United States | North America | Cross-sectional | 2003 Beers criteria | 81.5 (±6.2) | 78.0% | 118 | 82.20% | NR | DSM-IV |
| Clague et al | 2017 | Community | UK | Europe | Cross-sectional | - | 82.6 (±7.4) | 70.6% | 10,528 | - | 57.11% | Standard clinical coding system in use in the UK primary care |
| Colloca et al | 2012 | Outpatient | Italy, France, Finland | Europe | Cross-sectional | Holmes criteria | 84.2 (±8.9) | 75.0% | 1,449 | 44.90% | NR | CPS |
| Cross et al | 2016 | Community | Australia | Oceania | Cross-sectional | 2012 Beers/STOPP v2 | 77.6 (±7.4) a | NA | 779 | 21.05% | 68.30% | DSM-IV |
| Ferreira et al | 2021 | Community/ care homes | Brazil | South America | Cross-sectional | 2019 Beers criteria | NR* | 65.0% | 234 | 66.70% | 45.30% | ICD-10 |
| Fiss et al | 2011 | Outpatient | Germany | Europe | Cross-sectional | PRISCUS list | 82.7 (±6.8) | 31.7% | 111 | 27.00% | NR | DemTect score |
| Forgerini et al | 2020 | Community | Brazil | South America | Cross-sectional | Modify PIM list | 81 (76–87) | 67.1% | 143 | 63.60% | 57.30% | ICD-10 |
| Gareri et al | 2020 | Community | Italy | Europe | Cross-sectional | 2019 Beers criteria | 82.4 (±8.4) | 64.8% | 972 | - | 85.20% | Medical records |
| Growdon et al | 2021 | Outpatient | United States | North America | Cross-sectional | - | 81 | 63.0% | 918 | - | 72.00% | ICD-9 and ICD-10 |
| Hanlon et al | 2015 | Care homes | United States | North America | Cross-sectional | 2012 Beer criteria | NR* | 3.0% | 1,303 | 26.90% | 26.25% | ICD-9 |
| Hidalgo et al | 2021 | Community | Spain | Europe | Cross-sectional | STOPP Frail criteria | 89 (87–93) | 76.0% | 100 | 85.00% | 81.00% | FAST |

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**TABLE 1 (*Continued*) Characteristics of included studies.**

| Study | Year | Setting | Country | Region | Type | Criteria | Age (mean or median) | Female (%) | Sample | PIM | PP | Identification of dementia population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Holmes et al | 2008 | Community/ care homes | United States | North America | Cross-sectional | Holmes criteria | 83.8 | 74.0% | 34 | 29.00% | NR | FAST |
| Kristensen et al | 2018 | Community/ care homes | Denmark | Europe | Cross-sectional | Red–yellow–green list | 83.2 (77.5–88.2) | 64.0% | 35,476 | 24.40% | 62.60% | ICD-10 |
| Kristensen et al | 2019 | Community/ care homes | Denmark | Europe | Cross-sectional | - | 83.0 (77.3–88.0) | 63.8% | 33,870 | - | 68.10% | ICD-10 |
| Kristensen et al | 2020 | Community/ care homes | Denmark | Europe | Cross-sectional | Red–yellow–green list | NR* | 63.3% | 36,031 | 43.50% | NR | ICD-10 |
| Lau et al | 2010 | Community | United States | North America | Cross-sectional | 2003 Beers criteria | 77.8 (±6.8) | 53.2% | 2,467 | 15.00% | 51.92% | CDR global score and Functional Activities Questionnaire total score |
| Montastruc et al | 2013 | Community | France | Europe | Cross-sectional | Beers criteria/Laroche list | 77.9 (±6.8) | 71.1% | 684 | Beer 25.3%<br>Laroche 46.8% | 43.70% | DSM-IV and NINCDS-ADRDA criteria |
| Oesterhus et al | 2017 | Community | Norway | Europe | Cross-sectional | NORGEP criteria | 77 (71–81) | 58.0% | 251 | 14.00% | 45.00% | DSM-IV |
| Parsons et al | 2012 | Care homes | UK | Europe | Cross-sectional | STOPP v1 (31) | 86.8 (±6.7) | 79.8% | 119 | 46.20% | NR | ICD-10 |
| Rangfast et al | 2022 | Community | Sweden | Europe | Cross-sectional | Sweden and national welfare | 82.7 (±6.6) | 61.8% | 35,212 | 21.70% | NR | ICD-10 |
| Riedl et al | 2022 | Community/ care homes | Germany | European | Cross-sectional | 2019 Beers criteria | 74.1 (±11.1) | 56.0% | 191 | 39.00% | 49.70% | ICD-9 |
| Ruangritchanku et al | 2020 | Community/ care homes | Australia | Oceania | Cross-sectional | 2019 Beers criteria | 82.3 (±7.1) | 53.8% | 416 | 56.00% | 78.00% | Medical records and CPS |
| Somers et al | 2010 | Care homes | Australia | Oceania | Cross-sectional | 2003 Beers criteria | 85.2 (±7.8) | 75.0% | 351 | 50.40% | 91.00% | Medical records |
| Thorpe et al | 2012 | Community | United States | North America | Cross-sectional | 2003 Beers criteria | 79.5 (±6.6) | 39.1% | 566 | 33.00% | NR | Medical records |
| Tjia et al | 2014 | Care homes | United States | North America | Cross-sectional | Holmes criteria | NR* | 78.4% | 5,406 | 53.90% | NR | Medical records and CPS |
| Nguyen et al | 2018 | Outpatient | Vietnam | Asia | Cross-sectional | Vietnamese PIMcog list | 71.9 (±11.0) | 51.6% | 128 | 41.40% | 14.10% | Medical records |
| Vickers et al | 2021 | Community | United States | North America | Cross-sectional | 2015 Beers Criteria | NR* | 60.1% | 73 | 33.20% | 58.10% | ICD-10 |

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**TABLE 1 (*Continued*) Characteristics of included studies.**

| Study | Year | Setting | Country | Region | Type | Criteria | Age (mean or median) | Female (%) | Sample | PIM | PP | Identification of dementia population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Walsh et al | 2016 | Outpatient | Ireland | Europe | Cross-sectional | - | 84 (79–89) | 57.7% | 147 | - | 83.70% | Medical records |
| Wucherer et al | 2017 | Community | Germany | Europe | Cross-sectional | PRISCUS list | NR* | NR | 168 | 16.10% | NR | ICD-10 |
| Yoon et al | 2020 | Outpatient | Korea | Asia | Cross-sectional | 2015 Beer criteria | 77 (73–81) | 63.1% | 2,100 | 47.00% | NR | ICD-10 |
| Zhao et al | 2022 | Outpatient | China | Asia | Cross-sectional | 2019 Beer criteria | 80.88 (±7.69) | 49.2% | 18,624 | 39.43% | 16.15% | ICD-10 |
| Bae-Shaaw et al | 2023 | Community | United States | North America | Cohort | 2019 Beers criteria | 81.4 (±8.1) | 64.5% | 259,291 | 31.63% | NA | ICD-9 or ICD-10 |
| Buckley et al | 2022 | Inpatient | Ireland | European | Cohort | 2015 Beers or STOPP criteria v2 | 78 (73–83) a | NA | 261 | 29.90% | NA | DSM-IV |
| Chuang et al | 2017 | Inpatient/ outpatient | China | Asia | Cohort | Holmes criteria | 85 (80–89) | 46.9% | 6,532 | 10.47% | NA | ICD-9 |
| Delgado et al | 2020 | Community/ nursing home | UK | European | Cohort | STOPP v2 | 84.4 (±7.4) | 65.6% | 11,175 | 73.50% | NA | Medical records |
| Delgado et al | 2022 | Primary/second care | UK | European | Cohort | STOPP v2 | 84.5 (±7.4) | 65.7% | 9,324 | 75.4 | 81.60% | Medical records |
| Denholm et al | 2019 | Primary care | UK | European | Cohort | Holmes criteria | 86.6 (±7.3) | 64.0% | 6,923 | 49.90% | NA | ICD-10 |
| Eshetie et al | 2019 | Community | Australia | Oceania | Cohort | STOPP v2 | 80 (75–85) | 60.0% | 1,176 | 85% | NA | Anti-dementia drugs |
| Eshetie et al | 2020 | Community | Australia | Oceania | Cohort | STOPP v2 | 83 (77–88) | 63.4% | 8,280 | 79.10% | NA | Anti-dementia drugs |
| Eshetie et al | 2020 | Inpatient | Australia | Oceania | Cohort | 2019 Beers criteria | 87 (81.7–91) | 51.7% | 91 | 84.60% | NA | Medical records |
| Hyttinen et al | 2016 | Community | Finland | European | Cohort | Finnish criteria | NR* | 64.7% | 50,494 | 12.20% | NA | Medical records |
| Kanagaratnam et al | 2017 | Inpatient | France | European | Cohort | - | 82 (±8) | 61.4% | 293 |  | 83.60% | DSM-IV |
| Koyama et al | 2013 | Community | United States | North America | Cohort | 2003 Beers criteria | NR* | 100.0% | 260 | 33.10% | NA | DSM-IV |
| Lau et al | 2011 | Community | United States | North America | Cohort | 2003 Beers criteria | 77.4 (±6.6) | 49.2% | 1994 | 16.20% | 48.70% | CDR |
| Murphy et al | 2020 | Community | Ireland | European | Cohort | STOPP v2 | 72.56 (±8.19) | 62.3% | 448 | 55.80% | NA | NINCDS-ADRDA criteria combined with MMSE |
| Raivio et al | 2006 | Inpatient/ nursing home | Finland | European | Cohort | 2003 Beers criteria | 86a | 85.5% | 255 | 36.90% | NA | DSM-IV |

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**TABLE 1 (*Continued*) Characteristics of included studies.**

| Study | Year | Setting | Country | Region | Type | Criteria | Age (mean or median) | Female (%) | Sample | PIM | PP | Identification of dementia population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ramsey et al | 2018 | Inpatient | United States | North America | Cohort | 2015 Beers Criteria | 80.5 (±7.8) | 51.8% | 2,448 | 63.40% | NA | Medical records |
| Rausch et al | 2020 | Nursing home | Germany | European | Cohort | Holmes criteria | 86.4 (±6.5) | 67.8% | 29,052 | 26.80% | 85.20% | ICD-10 |
| Renom-Guiteras et al | 2018 | ILTC facility/ home care | England, Estonia, Finland, France, Germany, the Netherlands, Spain, and Sweden | European | Cohort | European Union (7)-PIM list | 83 (±6.6) | 67.5% | 2,004 | 60% | NA | Standard diagnosis of dementia and MMSE |
| Ryskina et al | 2023 | Nursing home | United States | North America | Cohort | 2019 Beer criteria | NR* | 71.10% | 54,713 | 49.50% | NA | Validated algorithm based on medical information |
| Skoldunger et al | 2015 | Community/ nursing home | Norway | European | Cohort | Swedish National Board of Health and Welfare | 74.8 (±11.1) a | NA | 319 | 27% | NA | DSM-III |
| Soysal et al | 2019 | Community | UK | European | Cohort | - | 80.7 (±8.7) | 61.1% | 12,148 | - | 39% | ICD-10 |
| Thapaliya et al | 2021 | Community | Australia | Oceania | Cohort | _ | NR* | 100.0% | 970 | - | 67.42% | Medical records |
| Tjia et al | 2010 | Nursing home | United States | North America | Cohort | Holmes criteria | 85.3 (±7.5) | 85.4% | 323 | 37.50% | NA | Medical records and CPS |
| Toscani et al | 2013 | Community/ nursing home | Italy | European | Cohort | Holmes criteria | 86.0 (81–92) | 80.3% | 410 | 2% | NA | Medical records and FAST |
| Zuckerman et al | 2005 | Nursing home | United States | North America | Cohort | 1997 Beer criteria | NR* | NA | 334 | 19% | NA | Diagnostic and Statistical Manual of Mental Disorders III |

NR*: reported, but inclusion criteria limited to older population aged 65 years or above.

[a]represents the total sample; PIM, potentially inappropriate medication; pp, polypharmacy; FAST, Functional Assessment Staging Tool.

MMSE, mini-mental state examination; CPS, Cognitive Performance Scale; DSM, the diagnostic and statistical manual of mental disorders; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease; CDR, the Clinical Dementia Rating; NIA—AA, National Institute on Aging—Alzheimer's Association.



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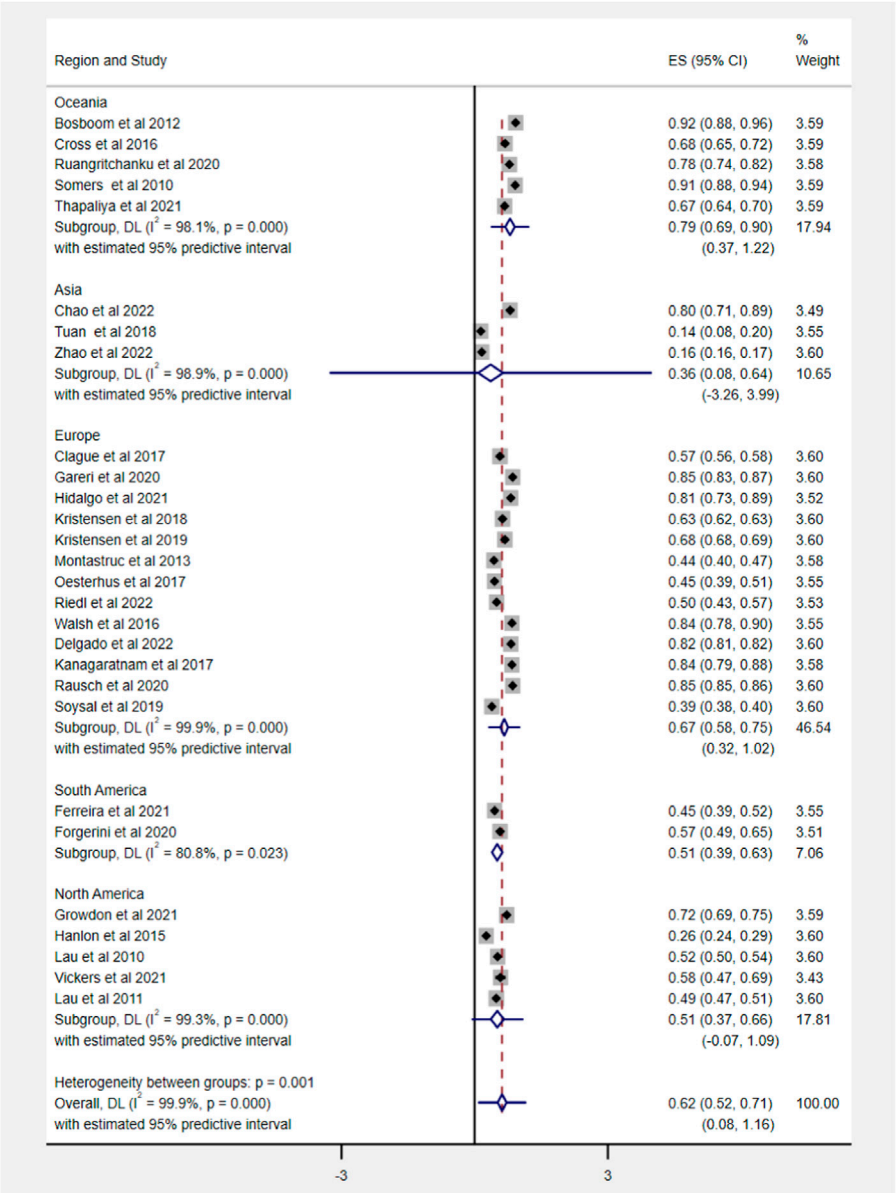


FIGURE 2
Prevalence of polypharmacy in older people with dementia across various geographic regions. Note that with <3 studies, the distribution is inestimable and hence not displayed.

conducted in South America (Forgerini et al., 2020; Ferreira et al., 2021), and the rest of the studies conducted in Oceania (Somers et al., 2010; Bosboom et al., 2012; Cross et al., 2016; Bala et al., 2019; Eshetie et al., 2019b; Brimelow et al., 2019; Eshetie et al., 2020; Eshetie et al., 2020; Ruangritchankul et al., 2020; Thapaliya et al., 2021) ($n$ = 10), North America (Zuckerman et al., 2005; Holmes et al., 2008; Chan et al., 2009; Lau et al., 2010; Tjia et al., 2010; Lau et al., 2011; Thorpe et al., 2012; Koyama et al., 2013; Tjia et al., 2014; Hanlon et al., 2015; Ramsey et al., 2017; Growdon et al., 2021; Vickers et al., 2021; Bae-Shaaw et al., 2023; Ryskina et al., 2023) ($n$ = 15), and Asia (Chuang et al., 2017; Nguyen et al., 2018; Chao et al., 2022; Yoon et al., 2022; Zhao et al., 2022) ($n$ = 5). Table 1 presents the characteristics of the included studies.

## 3.3 Quality of the included studies

The results of quality assessment are presented in Supplementary Table S2, 3. For the cross-sectional study, we found that the lowest score was 4, and the highest score was 8. Seven research articles were of high methodological quality (AHRQ score ≥8), and 30 articles were of moderate methodological quality (AHRQ score 3–8). For the cohort studies, 20 research articles were of high methodological quality (NOS score ≥8), four articles were of moderate methodological quality (NOS score 6–7), and one article was of low quality (NOS score ≤5).

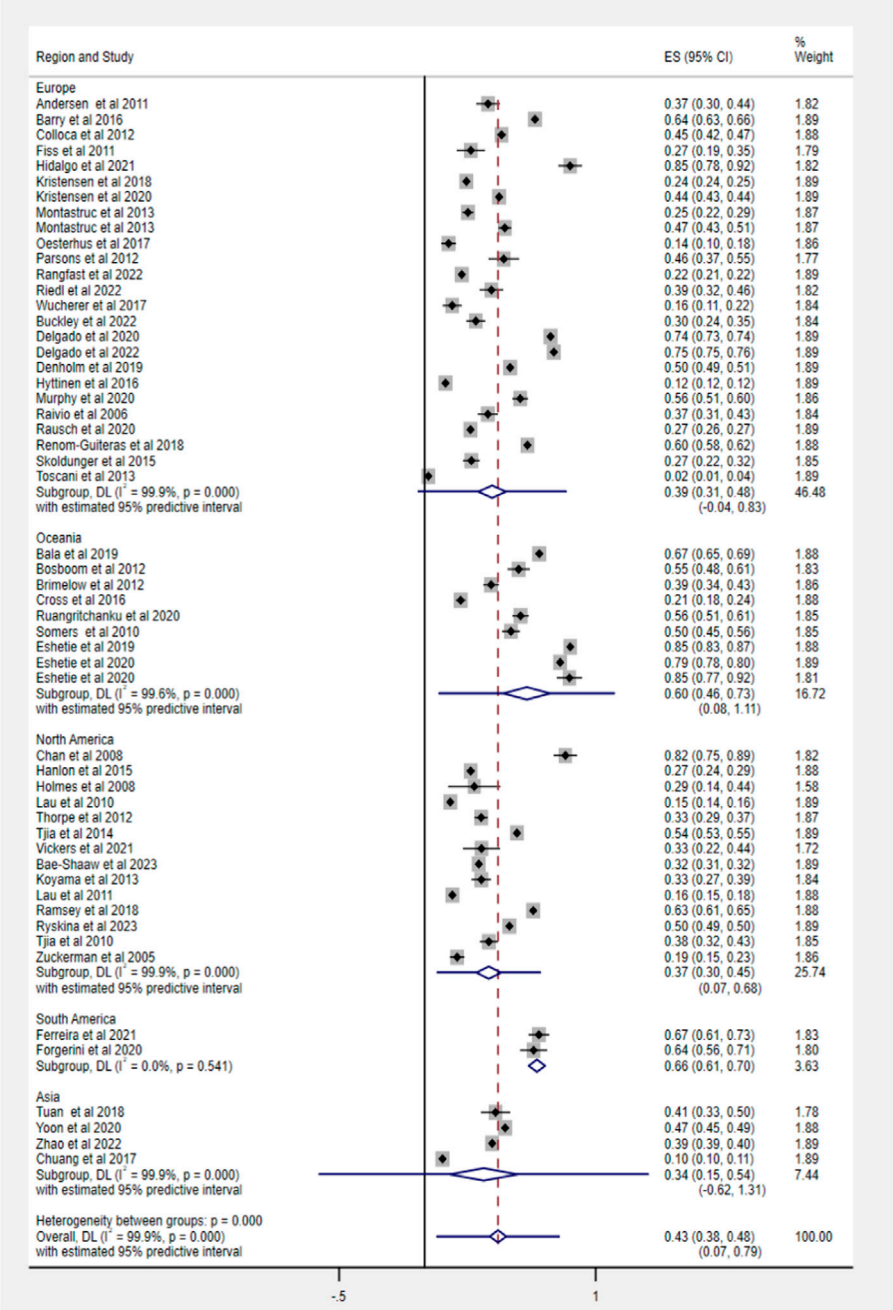


FIGURE 3
Prevalence of PIM use in older people with dementia across various geographic regions.

## 3.4 Prevalence of polypharmacy

Out of 62 included studies, 28 studies, comprising 4,813,226 older patients with dementia, reported the prevalence of polypharmacy, ranging from 14.10% to 92%. The pooled estimate of polypharmacy was 62% (95% CI 52–71). After weighing the population size by region, a significant difference among different regions was observed (df = 4, $p < 0.0001$). The pooled prevalence in Oceania was highest (79%, 95% CI 69–90) and lowest in Asia (36%, 95% CI 8–64). The detailed data about regions are shown in Figure 2.

## 3.5 Prevalence of potentially inappropriate medication

Fifty-three studies evaluated the prevalence of PIM based on different criteria, ranging from 2% to 85.1%. The pooled prevalence estimate of PIM was 43% (95% CI 38–48), as shown in Figure 3. Among regions, the prevalence of PIM showed a significant difference in statistics (Q = 59.5, df = 4, $p < 0.0001$), ranging from 34% in Asia (95% CI 15–54) to 66% in South America (95% CI 61–70).

**TABLE 2 Stratified meta-analysis of the prevalence of polypharmacy and PIM use.**

| Characteristics | Number of studies | Pooled prevalence (95% CI) | 95% PI | I2 (%) | Z | Heterogeneity between groups | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Q | df | P |
| PIM | | | | | | | | |
| Year of publication | | | | | | 5.15 | 1 | 0.023 |
| ≤2015 | 21[a] | 0.36 (0.27, 0.44) | (-0.08, 0.79) | 99.5% | 8.15 | | | |
| >2015 | 32 | 0.48 (0.42, 0.54) | (0.07,0.79) | 100% | 15.12 | | | |
| Percentage of female | | | | | | 6.98 | 1 | 0.008 |
| <50% | 6 | 0.26 (0.12, 0.40) | (-0.27, 0.78) | 99.8% | 3.57 | 9.88 | 2 | 0.007 |
| ≥50% | 40[a] | 0.47 (0.42, 0.53) | (0.11, 0.84) | 99.9% | 16.68 | | | |
| NR | 7 | 0.31 (0.13, 0.50) | (-0.38,1.00) | 99.4% | 3.28 | | | |
| Mean age | | | | | | 5.75 | 2 | 0.056 |
| ≥80 | 27 | 0.50 (0.43, 0.57) | (0.12, 0.87) | 99.9% | 14.25 | | | |
| <80 | 10[a] | 0.36 (0.22, 0.51) | (-0.14, 0.86) | 99.8% | 4.89 | | | |
| NR | 16 | 0.36 (0.25, 0.46) | (-0.22, 0.94) | 99.9% | 6.35 | | | |
| Criteria | | | | | | 98.57 | 2 | <0.0001 |
| Beers | 23 | 0.44 (0.39, 0.49) | (0.17, 0.70) | 99.8% | 16.42 | | | |
| STOPP | 9 | 0.68 (0.63, 0.73) | (0.51, 0.85) | 98.9% | 28.04 | | | |
| Other | 21[a] | 0.32 (0.26, 0.38) | (0.03, 0.61) | 99.9% | 10.87 | -- | -- | -- |
| Degree of dementia | | | | | | 79.60 | 3 | <0.0001 |
| Mild | 1 | 0.14 (0.10, 0.18) | - | - | 6.40 | | | |
| Mild–moderate | 3[a] | 0.39 (0.25, 0.52) | (-0.27, 1.04) | 98.4% | 5.62 | | | |
| Advanced | 10[a] | 0.36 (0.25, 0.45) | (-0.07, 0.80) | 99.9% | 6.29 | | | |
| NR | 40 | 0.45 (0.40, 0.50) | (0.07, 0.82) | 99.9% | 15.51 | | | |
| Type | | | | | | 0.06 | 1 | 0.8 |
| Cross-sectional | 31[a] | 0.42 (0.37, 0.48) | (0.12, 0.73) | 99.8% | 16.13 | | | |
| Cohort | 22 | 0.44 (0.35, 0.52) | (0.00, 0.79) | 100% | 10.05 | | | |
| Polypharmacy | | | | | | | | |
| Year of publication | | | | | | 0.11 | 1 | 0.74 |
| ≤2015 | 6 | 0.59 (0.40, 0.78) | (-0.13, 1.31) | 99.7% | 6.00 | | | |
| >2015 | 22 | 0.63 (0.52, 0.74) | (0.07, 1.18) | 100.0% | 11.27 | | | |
| Percentage of female | | | | | | 7.71 | 2 | 0.021 |
| <50% | 4 | 0.42 (0.23, 0.61) | (-0.49, 1.34) | 99.7% | 4.41 | | | |
| ≥50% | 23 | 0.65 (0.59, 0.71) | (0.32, 0.98) | 99.8% | 19.93 | | | |
| NR | 1 | 0.68 (0.65, 0.72) | - | - | 40.97 | | | |
| Mean age | | | | | | 15.09 | 2 | 0.001 |
| ≥80 | 17 | 0.71 (0.59, 0.84) | (0.14, 0.29) | 100% | 11.22 | | | |
| <80 | 6 | 0.42 (0.35, 0.50) | 0.15, 0.70) | 96.5% | 10.85 | | | |
| NR | 5 | 0.53 (0.32, 0.74) | 0.62 (0.08, 1.16) | 99.4% | 4.92 | | | |

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**TABLE 2 (*Continued*) Stratified meta-analysis of the prevalence of polypharmacy and PIM use.**

| Characteristics | Number of studies | Pooled prevalence (95% CI) | 95% PI | I2 (%) | Z | Heterogeneity between groups | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Q | df | P |
| Type | | | | | | 0.46 | 1 | 0.496 |
| Cross-sectional | 22 | 0.60 (0.50, 0.71) | (0.06, 1.15) | 99.9% | 11.05 | | | |
| Cohort | 6 | 0.68 (0.50, 0.86) | (0.00, 1.35) | 99.9% | 7.33 | | | |

PIM, potentially inappropriate medication; PI, prediction interval.

[a]One study reported two PIM prevalence using different PIM lists.

Note that with <3 studies, the distribution is inestimable and hence not displayed.

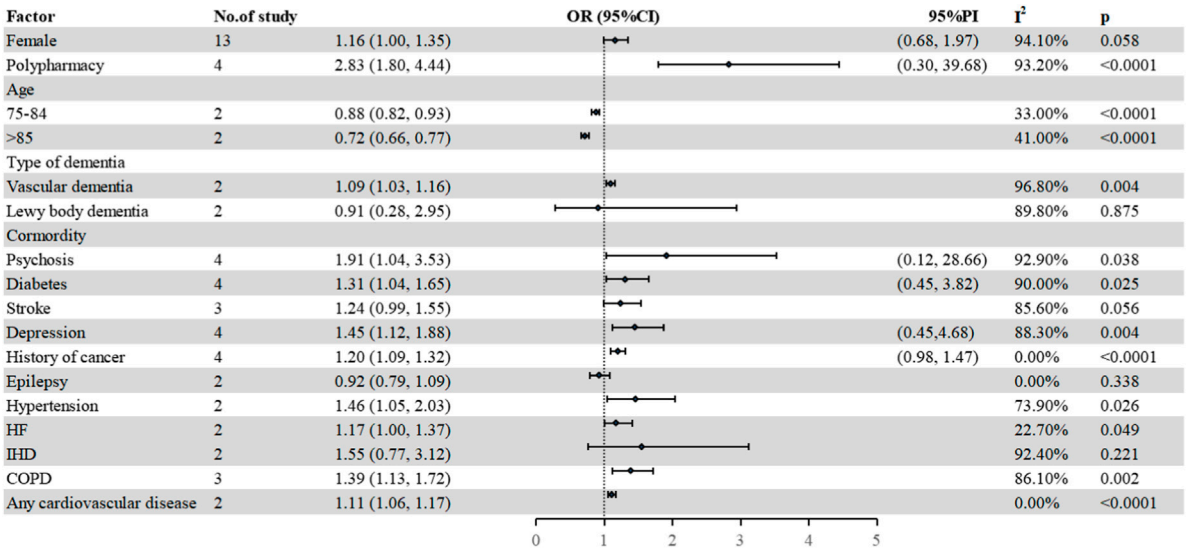


FIGURE 4
Factors associated with PIM use. HF, heart failure; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; PI, prediction interval.

## 3.6 Stratified analysis

We applied the stratified analysis for estimating the substantial heterogeneity in pooled prevalence of polypharmacy and PIM. Based on various basic characteristics, such as the proportion of females, year of publication, study design, and severity of dementia, we stratified the studies.

The subgroup analysis based on study design found no significant heterogeneity between groups in PIM use (cross-sectional: 42%, 95% CI 37–48; cohort: 44%, 95% CI 35–52). According to PIM criteria, we estimated that the pooled prevalence of PIM using the STOPP tool was highest (68%, 95% CI 63–73), following Beers criteria (44%, 95% CI 39–49) and other screening tools (32%, 95% CI 26–38). The specific data information in each subgroup for PIM use and polypharmacy is summarized in Table 2.

## 3.7 Factors associated with potentially inappropriate medications

A total of sixteen studies (Lau et al., 2010; Colloca et al., 2012; Fiss et al., 2013; Montastruc et al., 2013; Barry et al., 2016; Chuang et al., 2017; Hyttinen et al., 2017; Oesterhus et al., 2017; Renom-Guiteras et al., 2018; Murphy et al., 2020; Delgado et al., 2021; Ferreira et al., 2021; Rangfast et al., 2022; Tuan et al., 2018; Yoon et al., 2022; Zhao et al., 2022) referred to potential confounding factors with PIM in older patients with dementia. The specific details of each study reporting factors are shown in Supplementary Table S4. In the study, 15 factors, namely, age, female, polypharmacy, type of dementia, diabetes, heart failure, depression, psychosis, epilepsy, hypertension, stoke, ischemic heart disease, history of cancer, and chronic obstructive pulmonary disease or asthma were further analyzed (Figure 4).

Four studies (Montastruc et al., 2013; Ferreira et al., 2021; Yoon et al., 2022; Zhao et al., 2022) investigated the relationship between polypharmacy (five or more) and the risk of PIMs in older patients with dementia. The pooled estimate was 2.83 (95% CI 1.80–4.44), which indicated that increasing PIM risk was related with polypharmacy.

Regarding gender, a total of thirteen studies (Colloca et al., 2012; Fiss et al., 2013; Montastruc et al., 2013; Barry et al., 2016; Chuang et al., 2017; Hyttinen et al., 2017; Oesterhus et al., 2017; Nguyen et al., 2018; Murphy et al., 2020; Ferreira et al., 2021; Rangfast et al., 2022; Yoon et al., 2022; Zhao et al., 2022) were pooled to explore the

association between females and PIM in older patients with dementia, in which six studies (Fiss et al., 2013; Montastruc et al., 2013; Barry et al., 2016; Oesterhus et al., 2017; Yoon et al., 2022; Zhao et al., 2022) showed that women were positively associated with PIM use, six studies (Colloca et al., 2012; Chuang et al., 2017; Murphy et al., 2020; Ferreira et al., 2021; Tuan et al., 2018; Rangfast et al., 2022) showed no correlation in statistics, and one study showed a negative association with PIM use (Hyttinen et al., 2017). The pooled estimate was 1.16 (95% CI 1.00–1.35). Three studies (Lau et al., 2010; Rangfast et al., 2022; Tuan et al., 2018) mentioned the impact of the type of dementia on PIM use. Two studies (Rangfast et al., 2022; Tuan et al., 2018) were further pooled to explore the relationship between the type of dementia and PIM use. Compared with Alzheimer's disease (AD), patients with vascular dementia were more likely to suffer PIM, while in case of Lewy body dementia, there was no difference in statistics (vascular dementia: 1.09, 95% CI 1.03–1.16; Lewy body dementia: 0.91, 95% CI 0.28–2.95). For other potential confounding factors (age, diabetes, hypertension, psychosis, and heart failure), the details are shown in Figure 4.

### 3.8 Publication bias assessment

Egger's and Begg's tests were used to assess the publication bias in the pooled estimate of polypharmacy and PIM. The results for the pooled estimate of polypharmacy were 0.855 (Egger's test) and 0.767 (Begg's test), indicating no publication bias. Regarding PIM, no statistically significant publication bias was observed (Egger test: $p$ = 0.058; Begg's test: $p$ = 0.765).

## 4 Discussion

To our knowledge, the current study first comprehensively summarized the pooled prevalence of PIM and polypharmacy in older patients with dementia across different regions and analyzed potential confounding factors associated with PIM use. This review may provide evidence for healthcare decision-makers in avoiding adverse drug use events in elderly with dementia.

For the included studies, the prevalence of PIM varied widely, ranging from 2% to 85.1%. Several reasons could explain the phenomenon well. First, the difference in marketing drugs and medical habits and the gap in healthcare systems in different regions might significantly affect the prevalence of PIM. Based on the pooled results by region, we clearly found a vast difference in PIM prevalence. Renom-Guiteras et al. evaluated the PIM prevalence of eight European countries using the European Union (7)-PIM list and found the PIM prevalence ranging 47%–67.5% (Renom-Guiteras et al., 2018). Zhao et al. also reported differences in PIM prevalence across different cities in China, ranging from 28.48% to 44.79% (Zhao et al., 2022). Second, the screening tools were considered a factor resulting in differences in PIM. To date, many screening tools have been applied to evaluate PIM, such as Beers criteria, STOPP/START criteria, and Holmes criteria (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; O'Mahony et al., 2018; Holmes et al., 2008). In our study, a total of 13 criteria were used, of which the most frequently used was Beers criteria, accounting for nearly 50%, followed by STOPP/START criteria. Published PIM lists have important differences in terms of contents and number (e.g., 81 items in STOPP criteria, while 91 in Beers criteria), which might lead to different prevalence of PIM. Target population and clinical practice among various PIM lists might also affect PIM prevalence, such as Holmes criteria mainly focusing on advanced dementia and NORGEP criteria for ambulatory patients (Kaufmann et al., 2014). The stratified analysis based on different criteria in our study also found differences in PIM prevalence. Although the same tool was used, the proportion of patients receiving PIM still varied, which were mainly attributed to how the tools were applied and the edition of the criteria. For instance, several studies just used part of the items of Beers criteria due to the absence of diagnostic information or other laboratory indicators, underestimating PIM to some extent (Chan et al., 2009; Lau et al., 2010; Thorpe et al., 2012; Montastruc et al., 2013). Therefore, before conducting research, researchers must consider how to select appropriate tools and how to apply them based on the collected information and diagnoses. In addition to the impact of region and screening tools on PIM, severity of dementia should be considered. In the analysis, we found that advanced dementia has a lower pooled estimate of PIM than mild–moderate dementia. Despite that patients living with advanced dementia depended completely on others, suffering from a series of distressing symptoms, such as neuropsychiatric symptoms and pain (Moens et al., 2014; Hendriks et al., 2015; Sampson et al., 2018), the emphasis of therapy for those was on ensuring patient comfort and symptom management and reducing polypharmacy (Disalvo et al., 2016). A review by Parsons summarized a viewpoint of physicians about drug use for advanced dementia, recommending discontinuation of anticholinesterase inhibitors, memantine, quetiapine, and simvastatin (Parsons et al., 2010). This may lead to a lower prevalence of PIM in advanced dementia. Despite the vast difference in PIM prevalence among included studies, the pooled estimate of PIM use in our analysis was up to 43%, which was higher than the PIM estimate for older patients in worldwide as given in Tian et al. (2023). Thus, we should pay great attention on the PIM use of older patients with dementia.

The drug management of older patients living with dementia often takes place in the context of additional comorbidities, which result in a large number of prescriptions for patients with dementia (Blass et al., 2008; Callahan and Schubert, 2014; Amy et al., 2018). In the analysis, polypharmacy was found to be prevalent with an estimated overall prevalence of 62%, slightly higher than that found in the study by Janice et al., with an estimate of 59% (Toh et al., 2023). Overall, significant heterogeneity was observed in the prevalence of polypharmacy. The difference may be attributed to several factors, for example, study subjects from different settings, geographical regions, study design, and year of publication. Although heterogeneity did not decrease by subgroups, significant differences were observed between some groups. In our review, we clearly found that the prevalence of polypharmacy in Asia was lowest compared with other regions. This may be due to socioeconomic-related healthcare inequalities between developing

and developed countries in the access to healthcare. A report from the WHO declared that developed regions account for 11.6% of the worldwide burden, but account for 90.2% of health expenditure worldwide (Murray and Lopez, 1997). Different settings might affect the prevalence of polypharmacy. In this study, two out of three studies in the Asian region were outpatient studies, with a proportion of only over 10% for polypharmacy. Of note, the same definition of polypharmacy (five or more) shows a difference in measurement, which also might affect the outcome. Lau et al. declared that medications for topical applications, vitamins, and herbal medications were excluded in polypharmacy, with the prevalence of 51.92%, while Bosboom et al. considered all different medications in prescription were being counted, with the prevalence of 92% (Lau et al., 2011; Bosboom et al., 2012). In addition, the time of exposure to the medications has an impact on polypharmacy estimates. Kristensen et al. and Rausch et al. reported the prevalence of polypharmacy at 3 and 6 months as 62.6% and 85.2%, respectively (Kristensen et al., 2018; Rausch and Hoffmann, 2020). Although differences in distribution of regions, measurement, and exposure of time affect the estimate of polypharmacy, polypharmacy still cannot be ignored.

Several studies have been reported regarding potential confounding factors associated with PIM use. The association between PIM and polypharmacy for older patients with dementia was always discussed by researchers. Due to different definitions of polypharmacy and other factors, different studies concluded different results. Ferreira et al. reported polypharmacy was not related to PIM use (Ferreira et al., 2021), while Yoon et al. declared that a strong association between polypharmacy and PIM use was observed (Yoon et al., 2022). In our study, patients with polypharmacy (five or more) were exposed to a higher risk of PIM use, which was consistent with the observation of Tian et al. (2021) (reported older patients). A growing body of studies reported the impact of gender on PIM use, but a consensus has not yet been reached. According to our meta-analysis, no statistically significant difference was observed in women. Of note, we found vascular dementia was more susceptible to PIM use than Alzheimer's disease. This may be related to cardiovascular events being the main cause of vascular dementia (Leys et al., 2005). Cardiovascular diseases and well-recognized high-risk factors of cardiovascular diseases, diabetes and hypertension, were associated with PIM use. This may be due to the use of non-steroidal drugs, regular insulin, and sulfonylureas of the PIM list. Other factors, such as comorbidity, psychosis, depression, and history of cancer, were considered to increase the risk of PIM in the current study. The long-term use of antidepressants, antipsychotics, and opioids in order to control symptoms may explain the phenomenon. Although several factors associated with PIM use were identified in our study, more relevant research was still needed for further validation.

PIM and polypharmacy in older patients with dementia are common. A large number of studies have shown PIM use and polypharmacy were related to hospitalization and death (Gnjidic et al., 2012; Maher et al., 2014). Therefore, it is necessary to optimize drug management for older patients with dementia. Deprescribing is an approach to reduce PIM and polypharmacy (Wu et al., 2021). Due to the use of multiple drugs and memory loss in older patients, drug compliance was relatively poor (Dunbar-Jacob and Mortimer-Stephens, 2001; Smith et al., 2017). For older patients with dementia featuring cognitive impairment and communication disorder, the adherence of drug medication was poorer. Deprescribing could not only reduce the number of medications taken but also increase the drug compliance of elderly patients (Basheti et al., 2016; Jäge et al., 2017). Research has confirmed the advantages of deprescribing in reducing PIM and polypharmacy (Ibrahim et al., 2021). Thus, deprescribing can be applied in the clinics to solve polypharmacy and PIM.

Although the analysis quantitatively summarized the prevalence of PIM and polypharmacy and further explored potential factors with PIM use, providing a reference for the prescription of old patients with dementia, we must acknowledge some limitations of the study. First, those studies included were from all over the world, and other factors, such as culture, education level, geographical location, and social status, would affect the results of polypharmacy and PIM. Second, the included studies show substantial heterogeneity, which may be related to the study subject, sample size, and screening tools used. Third, some studies did not specify the living conditions of the study population and type of dementia, so we cannot conduct a subgroup analysis based on living conditions and type of dementia. Fourth, included studies were limited to English articles, leading to results that could either underestimate or overestimate the prevalence. In addition, only factors using multivariate regression were extracted and several factors in our study were only examined in two studies, which gave biased results. Thus, a further study regarding factors affecting PIM use will be explored.

## 5 Conclusion

The analysis revealed that PIM use and polypharmacy were highly prevalent in older patients with dementia. Among different regions, the pooled estimate of PIM use and polypharmacy varied widely. Increasing PIM was related with polypharmacy, women, and vascular dementia. These findings highlight the necessity of some measures taken to improve the prescription quality of older patients with dementia, and they also imply that more caution should be taken when prescribing for women, polypharmacy, and vascular dementia.

## 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

MZ: developing design, literature search and screening, data extraction, and manuscript writing. ZC: literature screening and analysis of results. TX: management and manuscript editing. FT: data extraction and manuscript editing. PF: management and manuscript editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1221069/full#supplementary-material

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# Problems and challenges encountered by Chinese medical institutions in implementing the national centralized drug procurement

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**Objective:** The problems and challenges encountered by Chinese medical institutions in implementing the national centralized drug procurement was investigated and analyzed in order to provide reference for the regulatory agencies to formulate policies.

**Methods:** A questionnaire survey was conducted to collect the problems encountered by 329 Chinese medical institutions in implementing the national centralized drug procurement and the corresponding suggestions provided by relevant experts. Statistical analysis was performed to identify differences in the themes and the number of collected problems, further revealing the relevance to the region in which the medical institutions is located.

**Result:** 1360 problems and suggestions were collected from 329 Chinese medical institutions that located in North (19.15%), Northeast (5.78%), East (33.43%), Central (10.03%), South (9.73%), Southwest (14.89%), and Northwest China (6.99%). There was statistically significant difference in the number of collected problems and suggestions between regions ($p < 0.001$). Furthermore, the content of gathered problems and suggestions involves in 15 themes including system construction, organizational system and work responsibilities, reasonable measurement and reporting of procurement volume et al. These themes that these medical institutions are focusing on are mainly centered on the supply guarantee (15%), reasonable measurement and reporting of procurement volume (11.40%) and guarantee measures for clinical priority use (9.48%) of drugs with national centralized procurement. Meanwhile, we found that problems regarding the supply guarantee of drugs with national centralized procurement displayed significant difference between regions ($p = 0.0096$).

**Conclusion:** Chinese medical institutions are facing great challenges in implementing the national centralized drug procurement. The scientific study and judgment of the current situation and the construction of corresponding solution require a precise classification of the problems encountered by medical institutions in the process of implementing the national centralized drug procurement policy, which is of great practical significance for deepening the reform of the medical and health system.

KEYWORDS
national centralized drug procurement, medical institutions, problems, challenge, China

# Introduction

Increasing pharmaceutical expenditures is plaguing many countries worldwide (Lopez Bastida et al., 2000; Smith.2004). Global medicine spending is projected to increase at 2–5% annually and exceed $1.1 trillion in 2024 (Institute.2020). In China, healthcare expenditures increased rapidly at a nearly 20% annual growth rate (Yuan et al., 2021). In order to reduce the pharmaceutical expenditures and standardize drug circulation, the Chinese government has implemented national centralized drug procurement (NCDP) since 2018. As of February 2022, prices of 234 medicines have been lowered through national centralized procurement, with the average rate of reduction exceeding 53%, and the cumulative savings in drug costs have exceeded 260 billion yuan (Zou et al., 2023). Moreover, national centralized drug procurement is being optimized and improved, gradually including the basic medical insurance drugs with bulk usage and procurement-volume and all types of clinical essential medicines with reliable quality (Chinese Government.2019; 2021).

Public medical institutions are required to participate in the national centralized drug procurement and prioritize the use of drugs with national centralized procurement (DNCP) in accordance with clinical demands (Gong et al., 2021). The application of NCDP has brought significant economic and social benefits and enhanced the rational use of clinical drugs, playing a positive effect on healthcare reform in China (Chen et al., 2020; Yuan et al., 2021). For instance, pharmaceutical expenditures and irrational clinical use rate were reduced comparison before and after NCDP policy (Hu et al., 2022; Wan et al., 2022; Wang et al., 2021). Meanwhile, drug utilization and substitution rate of generic drugs significantly increased after policy intervention (Xie et al., 2021; Zhao et al., 2022). However, some problems have been disclosed in practicing NCDP by medical institutions, which significantly affected the effects of NCDP implementation. For example, lacking scientific estimation system resulted in large discrepancies between procurement volume and usage volume by medical institutions (Xu.2022). Due to the difficulty of securing drug supply in primary medical institutions, some drugs with national centralized procurement are in shortage or even out of supply, thus affecting clinical use of drugs (Guo et al., 2015). In some medical institutions, non-winning drugs are completely discontinued in order to complete the contract dosage, so that the patient's drug needs are not met, thus aggravating the doctor-patient disputes (Li et al., 2022). Therefore, it is necessary and urgent to comprehensively understand the difficulties encountered by medical institutions in implementing the NCDP and provide corresponding solutions to promote the in-depth implementation of the national centralized drug procurement policy.

To further improve the standardization of NCDP policy at medical institution level, several provinces and autonomous regions have issued expert consensus or recommendations on the implementation of NCDP in Chinese medical institutions (Chen et al., 2022; Ye et al., 2021). Our group as co-leader gathered up 302 multidisciplinary experts from 128 Chinese medical institutions to write the " Consensus of Chinese expert on the precise management of national centralized drug volume-based procurement in medical institutions" in 2022 (Chinese Pharmacists Association.2023). This study aims to comprehensively reveal the problems encountered by Chinese medical institutions during implementing of NCDP policy and provide relevant recommendations given by experts, which is an important reference for the development of relevant policies.

# Methods

## Research subjects

This study conducted a targeted survey of 329 Chinese public medical institutions from 22 provinces, 5 autonomous regions and 4 municipalities directly under the Central Government (excluding Hong Kong, Macao and Taiwan). These medical institutions include provincial or university-affiliated hospitals, municipal, county and community health service centers. Meanwhile, 578 participants, which belong to multiple disciplines or departments including pharmacy department, medical department, clinical department, medical insurance department, and medical quality control department, involved in this survey.

## Questionnaire design and data collection

After considerable discussion, the outline of the questionnaire was determined by the research committee. As is shown in Supplementary Table S1, the questionnaire contains 6 primary catalogs which further subdivided into 15 secondary catalogs, involved the whole process of implementation of NCDP in medical institutions. Besides, open-ended questions included in each catalog intentionally, mainly for collection of the problems in the implementation of NCDP and corresponding suggestions. Subsequently, the questionnaires were directly conducted to 329 medical institutions. These collected questions are categorized into 15 secondary categories. Regarding the handling of open-ended questions, they will be grouped under the 15 entries mentioned above. However, in case of disputes they will be further discussed by the research committee. Ultimately, these questionnaire results were further analyzed, summarized, and organized using statistical methods.

## Statistical methods

IBM 24.0 SPSS statistical software (IBM Corp., Armonk, NY, United States) was used for analysis. Count data were expressed as cases or percentages, and the $\chi^2$ test and one-way ANOVA analysis were used for comparison between groups. $p < 0.05$ was considered a statistically significant difference.

# Results

## Characteristics of the surveyed medical institutions and respondents

To examine the status of implementing of national centralized drugs procurement in Chinese medical institutions, this study

**TABLE 1 Characteristics of the medical institutions.**

| Characteristic | Number (%) $n$ = 329 |
|---|---|
| **Regions** | |
| East China | 110 (33.43) |
| North China | 63 (19.15) |
| Southwest China | 49 (14.89) |
| Central China | 33 (10.03) |
| South China | 32 (9.73) |
| Northwest China | 23 (6.99) |
| Northeast China | 19 (5.78) |
| **Types** | |
| Provincial or university -affiliated medical institutions | 172 (52.28) |
| Municipal medical institutions | 103 (31.31) |
| Community health service center | 46 (13.98) |
| County-level medical institutions | 8 (2.43) |
| **Levels** | |
| Comprehensive medical institutions | 311 (94.53) |
| Specialized medical institutions | 18 (5.47) |

**TABLE 2 Distribution of the departments of the participants.**

| Discipline or department | Number of staff | Percentage (%) |
|---|---|---|
| Pharmacy Department | 517 | 89.45 |
| Medical Departments | 36 | 6.23 |
| Clinical Departments | 20 | 3.46 |
| Medical Insurance Department | 3 | 0.52 |
| Medical Quality Control Department | 2 | 0.35 |

conducted targeted research on 329 Chinese medical institutions. The recall rate and efficiency rate of the questionnaires were 100% and 100%, respectively, attributing to the fact that the research was conducted in a targeted manner. The regional and hierarchical distribution of medical institutions were taken into full consideration. As shown in Table 1, the regions of 329 surveyed medical institutions were located North (19.15%), Northeast (5.78%), East (33.43%), Central (10.03%), South (9.73%), Southwest (14.89%), and Northwest China (6.99%). These investigated institutions contain the provincial or university-affiliated medical institutions (52.28%), municipal medical institutions (31.31%), community health service centers (13.98%), and county-level medical institutions (2.43%). Of note, a total of 578 participants mainly distributed in department of pharmacy, medical, clinical, medical insurance, and medical treatment control, basically covering the essential departments for implementing national centralized drugs procurement. Among of these participants, pharmacy department presented largest number of personnel (89.45%) (Table 2), because they have taken on the primary task of implementing NCDP in medical institutions. Taken together, this research not only reflects the actual situation of implementing of NCDP in different regions and levels of Chinese medical institutions, but also visualizes the problems encountered by the main enforcement departments of NCDP in medical institutions.

## Characteristics of problems encountered by Chinese medical institutions in implementing of NCDP

In order to gain an in-depth understanding of the difficulties faced by Chinese medical institutions in implementation of national centralized drug procurement, the 1360 gathered problems and suggestions were further analyzed. As is shown in Table 3, the content of compiled problems and suggestions could be categorized into 15 aspects covering the whole process of implementing NCDP in medical institutions, which revealed the fact that Chinese medical institutions are facing serious challenges in the implementation of NCDP. Statistical analysis revealed significant differences in the number of relevant problems and suggestions between the 15 categories. The gathered opinions and suggestions were relatively focused on the procurement and supply, reporting of procurement volume, and clinical priority use of security measures of drugs with national centralized procurement in Chinese medical institutions, as evidenced by the number of relevant opinions and suggestions accounted for 15%, 11.40%, and 9.48%, respectively. To illustrate the problems and suggestions under the various themes, the detailed enumeration of collected problems and suggestions is displayed in Table 4; Supplementary Table S2.

## Correlation between the region of the medical institution and collected problems

In this study, questionnaires were distributed to 329 Chinese medical institutions and collected 1360 problems and suggestions. As displayed in Table 5, there was statistically significant difference in the number of problems and suggestions between regions ($p < 0.001$), indicating that the implementation of NCDP by medical institutions is closely related to the region of the medical institution. Besides, the gathered feedback regarding the procurement and supply of drugs with national centralized procurement displayed significant difference ($p = 0.0096$) between regions (Table 6). Therefore, subsequent policy development and optimization should take regional differences into account.

# Discussion

NCDP is a unique form of drug procurement in China, which playing a positive role in Chinese healthcare reform through reducing the prices of medicines and improving the rationality of clinical use of medicines. However, NCDP has gradually highlighted

**TABLE 3 Thematic content distribution of problems and suggestions.**

| Theme | Number (%) |
|---|---|
| 1. The procurement and supply of DNCP in medical institutions | 204(15.00) |
| 2. Reasonable measurement and reporting of data related to the procurement volume of DNCP in medical institutions | 155(11.40) |
| 3. Safeguards for priority clinical use of DNCP in medical institutions | 129(9.48) |
| 4. Catalog construction and management of DNCP in medical institutes | 125(9.19) |
| 5. Policy advocacy guidance and risk prevention and control of NCDP | 95(6.98) |
| 6. Rational allocation of contract usage of DNCP in medical institutes | 92(6.76) |
| 7. Progress monitoring and analysis of contract usage completion of DNCP in medical institutes | 87(6.40) |
| 8. Management of clinical rational use of alternative DNCP | 78(5.74) |
| 9. Health insurance fund balance retention incentive system of NCDP | 76(5.58) |
| 10. Clinical reasonable use assessment system of DNCP in medical institutes | 74(5.43) |
| 11. Implementation of DNCP-related system construction in medical institutes | 65(4.79) |
| 12. Information technology support system of management of DNCP in medical institutes | 53(3.91) |
| 13. The organization system and responsibilities of working group on NCDP in medical institutions | 46(3.35) |
| 14. Monitoring and management of quality and adverse event of DNCP | 41(3.03) |
| 15. Comprehensive clinical evaluation work of DNCP | 40(2.95) |
| ***p-value*** | <0.01 |

$\chi 2$ test.

a number of typical problems and contradictions over the years, which have directly led to a reduction in the efficiency of the policy (Gong et al., 2021; Zou et al., 2023). In this study, we aimed to reveal the situation of NCDP in Chinese medical institutions. The questionnaires were distributed to 329 Chinese medical institutions from North, Northeast, East, Central, South, Southwest, and Northwest China, which contains provincial, municipal, and community medical institutions. Meanwhile, this survey focused on multidisciplinary medical staff centered on pharmacy staff, which play a key role in the implementation of NCDP in medical institutions. Therefore, this study provides a more comprehensive and in-depth understanding of the current situation of NCDP in Chinese medical institutions. Furthermore, 329 valid questionnaires and 1360 problems and suggestions were collected. These problems and suggestions cover the whole process of implementation of NCDP, indicating the Chinese medical institutions is facing great challenges in the execution of NCDP.

There was statistically significant difference in the number of problems and suggestions between regions. Of these, the medical institutions coming from Southwest and Northwest regions have the highest average number of opinions and suggestions, probably due to the fact that these regions contain more remote areas, making it more difficult to implement the policy. The most suggested topics involve the clinical rational use of DNCP in medical institutions, including six aspects such as reasonable allocation of contract dosage, monitoring and analysis of completion progress, guarantee measures for clinical priority use, totaling 536 articles (39.41%). In addition, a total of 484 recommendations (35.59%) related to the procurement and supply guarantee of DNCP in medical institutions, including the reasonable measurement and reporting of data related to procurement volume, the construction and management of DNCP catalogs, and procurement and supply, which are basically consistent with those reported in the literature (Chinese Pharmacists Association.2023; Zou et al., 2023). The results demonstrated that the rational clinical use and security of supply are still the most important concerns of medical institutions in the process of implementing the NCDP policy. Among the collected opinions and suggestions, the largest number of problems and suggestions are related to DNCP procurement supply, a total of 204, accounting for 15%, focusing on the shortage of supply of the winning drugs. Some medical institutions reflected that most varieties of the winning drugs were in short supply at the beginning of national centralized drug procurement and 1 to 2 months before the end of the procurement cycle, resulting in discontinuity of clinical treatment, and even some winning drugs were in short supply for a long time, such as acarbose tablets, celecoxib capsules and tenofovir disoproxil fumarate tablets (Xu.2022). Remote areas such as Tibet and Xinjiang lack drug manufacturers, and the vast majority of drugs are transported from the mainland (Li, Yan, Bai, Li and Shao.2022). In addition, icy roads in winter make drugs not available in time, which can further cause local drug shortages and stock-outs. At the same time, some drugs are used in remote areas in small quantities and cannot reach the minimum delivery quantity of the manufacturer, which can also lead to abnormal drug supply. These results are mainly the result of three reasons. First of all, there are problems with the production capacity of manufacturers for winning drugs. Some of winning drug manufacturers failed to fully anticipate the inaccuracy of the medical institutions to report the volume or exceed the agreed procurement volume, resulting in an oversupply (Liu.2023; Sun et al., 2023). Secondly, there are problems with distribution enterprises in the transportation of winning drugs (Yang et al., 2023). According to

**TABLE 4 The model sample of collected problems and suggestions in major themes.**

| |
|---|
| **1. Purchasing supply of DNCP** |
| ***P:*** The shortage of supply for winning drugs. |
| ***S:*** The higher authorities, distribution companies and medical institutions are optimally managed in three stages: before, during and after the event. |
| **2. Rational measurement and reporting of data related to procurement volume** |
| ***P:*** (1) The long procurement cycle and time gap between the reporting of purchase volume and execution resulting in contract usage not being completed as expected. |
| (2) Clinical use of antimicrobial drugs is affected by several factors, making it more difficult to complete the agreed procurement volume. (3) Specialized hospitals hard to complete the agreed procurement volume of non-specialized drugs. |
| ***S:*** (1) Timely sorting the clinically relevant guidelines, establishing a channel for reporting complaints in the implementation process. (2) Special management drugs allowed to report volume according to actual situation, rather than enforcing the contracted volume. (3) Fully consideration of the special demands for specialized hospitals. |
| **3. Safeguard measures of clinical priority use for DNCP** |
| ***P:*** DNCP, national essential drugs (NED) and provincial centralized procurement drugs have the control requirements of indicators, which will affect each other during clinical use. |
| ***S:*** (1) Centralized procurement of drugs only carried out by the state. (2) The varieties of drugs centralized procurement at the national and provincial levels should be separated. (3) More NED should be implemented for national centralized procurement, while more DNCP should be included in the catalog of NED. (4) Medical insurance, healthcare and other related departments to strengthen coordination and develop a unified assessment index. |
| **4. Construction and management of catalog of DNCP in medical institutions** |
| ***P:*** The increase in the number of batches and the different starting times of each batch increase the difficulty of managing the catalog of DNCP in medical institutions. |
| ***S:*** Extend the renewal cycle appropriately and try to align the timing of renewal batches. |
| **5. Policy advocacy guidance and risk control of DNCP in medical institutions** |
| ***P:*** (1) Some patients and medical professionals refuse to drug replacement for lack confidence in the efficacy and quality of the winning drugs, resulting from the insufficiency of the publicity and guidance on DCNP. (2) The inability of continuously supply for winning drugs has seriously affected the publicity effect. |
| ***S:*** (1) Experts from authoritative departments were invited to popularize and promote science for the public and medical personnel through mainstream newspapers, magazines and new media. (2) National drug supervision and management departments strictly control the quality of DNCP, increase the frequency of DNCP quality sampling and real-time publication of the results. (3) The provincial health insurance bureaus and other relevant departments establish emergency reserves of manufacturers, inventory and discontinuation of production reporting system, for the inability to protect the behavior of drugs to take measures such as compensation, discipline, withdrawal, alternative and emergency security. |

Note. ***P***, problems. ***S***, suggestions.

**TABLE 5 Regional distribution of collected problems and suggestions.**

| Regions | Medical institutions | Problems and suggestions | |
|---|---|---|---|
| | Number | Number | Mean |
| | *n* = 329 | *n* = 1360 | — |
| Southwest China | 49 | 416 | 8.490 |
| East China | 110 | 346 | 3.145 |
| Northwest China | 23 | 191 | 8.304 |
| Central China | 33 | 175 | 5.303 |
| South China | 32 | 103 | 3.219 |
| North China | 63 | 96 | 1.524 |
| Northeast China | 19 | 33 | 1.737 |
| *p-value* | — | — | <0.001 |

One-way ANOVA, analysis.

the relevant documents, only one distribution enterprise is allowed for the winning drugs, but some of the distribution enterprises are small in scale with narrow distribution network, which affects the stability of the drug supply. Third, drug manufacturers control the sale of drugs in quantity and distribution. Some of the selected drug manufacturers who have completed the quantitative procurement of the winning drugs have controlled the distribution of drugs, resulting in tight supply or even shortage of drugs.

In order to avoid the above problems, experts from the participating medical institutions suggest optimizing the management involved in the

**TABLE 6 Regional distribution of problems in the supply of DNCP.**

| Regions | Problems and suggestions |
|---|---|
| — | $n$ = 204 |
| Southwest China | 66 |
| East China | 49 |
| Northwest China | 23 |
| Central China | 41 |
| South China | 15 |
| North China | 7 |
| Northeast China | 3 |
| $p$-value | 0.0096 |

One-way ANOVA analysis.

pre, in and post process. For the pre-event phase, the competent authorities in the tender to fully assess the supply capacity of drug manufacturers. The winning drugs have at least two distribution enterprises for medical institutions to choose. By increasing the supervision of drug distribution enterprises to achieve a smooth interface between the drug manufacturer and the distributor (Tan et al., 2020). Because primary medical institutions in remote areas have less demand for drug use, which inevitably reduces the motivation of enterprises to distribute, the distribution rate of drugs in remote areas can be included as part of the qualification audit of distribution enterprises. In addition, medical institutions can make appropriate reserves of non-winning drugs before the start of a new batch of centralized procurement, leaving a buffer period of 1–2 months between procurement cycles. For the in-event phase, the competent departments regularly supervise drug manufacturers and distribution enterprises. Medical institutions establish contingency plans for shortages of DNCP, and report the production and distribution of the selected enterprises and distribution enterprises to the management. Collective drug procurement platform records the selected drug shortage information and vouchers, while the temporary procurement quantity is combined into the agreed procurement volume. For the post-event phase, the regulatory authorities can strengthen the monitoring and evaluation of the selected production enterprises, and include their production capacity, ability to guarantee supply and integrity into the assessment system. At the same time, it is recommended that specific penalty regulations be formulated at the national level to punish the consequences of default such as malicious bidding or inability to complete the procurement schedule after winning a bid, and failure to guarantee product quality after winning a bid. Increasing penalties at the national level can guide enterprises to bid wisely and strengthen the contractual spirit.

## Conclusion

The problems collected in this research cover the whole process of implementing NCDP by medical institutions, and some relatively concentrated problems cannot be solved by medical institutions on their own, which suggests that only continuous summary experience, comparative research and based on national conditions can consolidate and expand the results of NCDP. The deep-seated conflicts in the procurement process should be directly confronted and corresponding solutions proposed in order to achieve meeting the clinical demand for drugs, promoting rational drug management, optimizing hospital management, and forming a market-based price formation mechanism. Only by formulating scientific and reasonable policies, combining and forming synergy from medical insurance, medical treatment, medicine, and patients, can we break through the existing blind spots and blockages, ensure that drug procurement policies are gradually moving on a good and correct track, and realize the reform of the medical and health system to benefit the general public.

## 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

Writing—WZ and QX; Research and data collection—JP, XZ, and LC; Data analysis—YW and KY; Conceptualization and supervision—JL and XL. 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.2023.1233491/full#supplementary-material

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# Impact of early heparin therapy on outcomes in patients with solid malignancy associated sepsis: a marginal structural model causal analyse

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**Background:** Previous studies documented that heparin can inhibit the invasion and metastasis of tumors, but its role on outcomes in patients with solid malignancy complicated sepsis remains unclear.

**Methods:** A retrospective cohort study was conducted in critically ill patients with solid malignancy associated sepsis from the Medical Information Mart for Intensive Care (MIMIC)-IV database. The primary endpoint was intensive care unit (ICU) mortality, secondary outcomes were thrombosis and hospital mortality. Propensity score matching (PSM), marginal structural Cox model (MSCM), cox proportional hazards model, stratification analysis and E-value were used to account for baseline differences, time-varying confounding and unmeasured variables.

**Results:** A total of 1,512 patients with solid malignancy complicated sepsis were enrolled, of which 683 in the heparin group with intensive care unit mortality, thrombosis rate and hospital mortality were 9.7%, 5.4%, 16.1%, and 829 in the non-heparin group with ICU mortality, thrombosis rate and hospital mortality were 14.6%, 12.5%, 22.6%. Similar results were observed on outcomes for patients with PSM (ICU mortality hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.41–0.92), thrombosis rate (HR 0.42, 95% confidence interval 0.26–0.68); hospital mortality HR 0.70, 95% CI 0.50–0.99). marginal structural Cox model further reinforced the efficacy of heparin in reducing ICU mortality (HR 0.48, 95% CI 0.34–0.68). Logistic regression and Cox regression model showed heparin use also markedly reduced thrombosis (HR 0.42; 95% CI 0.26–0.68; $p < 0.001$) and hospital mortality (HR 0.70; 95% CI 0.50–0.99; $p = 0.043$). Stratification analysis with the MSCM showed an effect only those with digestive system cancer (HR 0.33, 95% CI 0.16–0.69).

**Conclusion:** Early heparin therapy improved outcomes in critically ill patients with solid malignancy complicated sepsis. These results are evident especially in those with digestive system cancer. A prospective randomized controlled study should be designed to further assess the relevant findings.

KEYWORDS

**sepsis, heparin, mortality, thrombosis, solid malignancy**

# Introduction

Over the past decades, although clinical research on tumor therapy has improved rapidly, but cancer is the leading cause of deaths in all over the world (Bray et al., 2021; Sung et al., 2021). Targeted antitumor therapy mainly affects tumor formation and regulation, the tumor microenvironment, specific tumor markers, immune modulators, and targeted tumor stem cells (Danai et al., 2006; Vincent et al., 2009; Schünemann et al., 2020; Khan et al., 2021). Antitumor therapy readily releases damage-associated molecules in patients with solid malignancies, exacerbating undesirable inflammatory responses (Yuan et al., 2020). Many tumor-targeting drugs may affect angiogenesis, damage endothelial cells, and lead to cancer-associated coagulopathy, which increases the risk of thrombosis. It has been demonstrated that patients with cancer are more likely to develop venous thromboembolism (VTE) than those without cancer (Schünemann et al., 2020).

Patients with cancer exhibit an increased risk of sepsis owing to immune dysfunction. It is reported that, among cancer cases, the sepsis incidence increases by approximately 10 times than that of non-cancer cases (Vincent et al., 2009). A recent study showed that malignant tumors can be detected in 1/6 of intensive care unit (ICUs) inpatients experiencing sepsis (Danai et al., 2006), and if solid tumors patients suffer sepsis shock, the 28-day mortality rate was 69.4% (Cuenca et al., 2022). With the development of social economy and the improvement of clinical treatment, patients with cancer are always admitted to the ICU because of secondary sepsis and sepsis-induced coagulopathy (SIC). SIC and cancer-associated coagulopathy intensify VTE incidence among patients with solid malignancies concomitant sepsis.

As an anticoagulation agent, heparin has been widely used for prophylaxis VTE for several decades. Previous studies documented that heparin inhibited the invasion and metastasis of tumors (Wei et al., 2023), but limited data exists on whether heparin administration provide a survival advantage in patients with solid malignancies concomitant sepsis. Therefore, we conducted a retrospective cohort study adopted data based on the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to assess whether anticoagulation with heparin used in solid malignancy concomitant sepsis cases hospitalized in the ICU offered survival benefits, including advantages in ICU mortality, hospital mortality, and thrombosis, and estimated heparin application timing as well as dosing.

# Materials and methods

## Data source and study design

We performed a retrospective cohort study using data from MIMIC-IV (version 1.0). It included two in-hospital database systems, namely, ICU-specific clinical data and the custom hospital-wide electronic health record (EHR), which covered anonymous, integrated clinical information of cases at ICUs in Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019. Individuals finishing a collaborative institutional training initiative examination (certification number 38995627 for author Huang) were allowed to enter this database.

## Participants

Altogether 382,278 individuals with 51,150 patients were admitted to the ICUs during our research. Patient selection criteria were as follows: 1) those aged over 18 years, 2) those meeting Sepsis 3.0 criteria (namely, a rapid elevation of Sequential Organ Failure Assessment (SOFA) score ≥2 in combination with suspicious infection (Singer et al., 2016), and 3) those diagnosed with malignant cancer.

Patients conforming to the following conditions were excluded: 1) those admitted to the ICU several times; 2) those aged <18 years or stayed in the ICU for <24 h; 3) those who used heparin in treatment or dialysis, but not in prophylactic application, or those who received warfarin or low-molecular-weight heparin (LMWH) in ICU stay; 4) pregnant women; 5) those with previous heparin-caused thrombocytopenia; 6) those with liver failure; 7) those with stage 5 chronic kidney disease (CKD); and 8) those with hematological malignancies.

## Research procedures and definitions

The study collected information based on the MIMIC-IV database by Structured Query Language. Approaches described previously were adopted to search the above database (sepsis) and analyze the patient information collected (Zou et al., 2022). For patients who were hospitalized repeatedly, initial hospitalizations were collected. Basic features, together with laboratory findings on day one upon ICU admission, were extracted, which included age upon admission to the hospital, gender, weight, laboratory examinations (hemoglobin levels, white blood cell [WBC] count, platelet count, international normalized ratio [INR], prothrombin time [PT], partial thromboplastin time [PTT]), vital signs (heart rate, temperature, respiratory rate, mean arterial pressure [MAP], partial pressure of oxygen [$PO_2$]), concurrent diseases (diabetes, hypertension, chronic lung disease, chronic heart disease (CHD)), urine output, mechanical ventilation, vasopressor use, acute kidney injury (AKI) stage, and renal replacement therapy (RRT). This study further collected the results of clinical severity scales, such as the

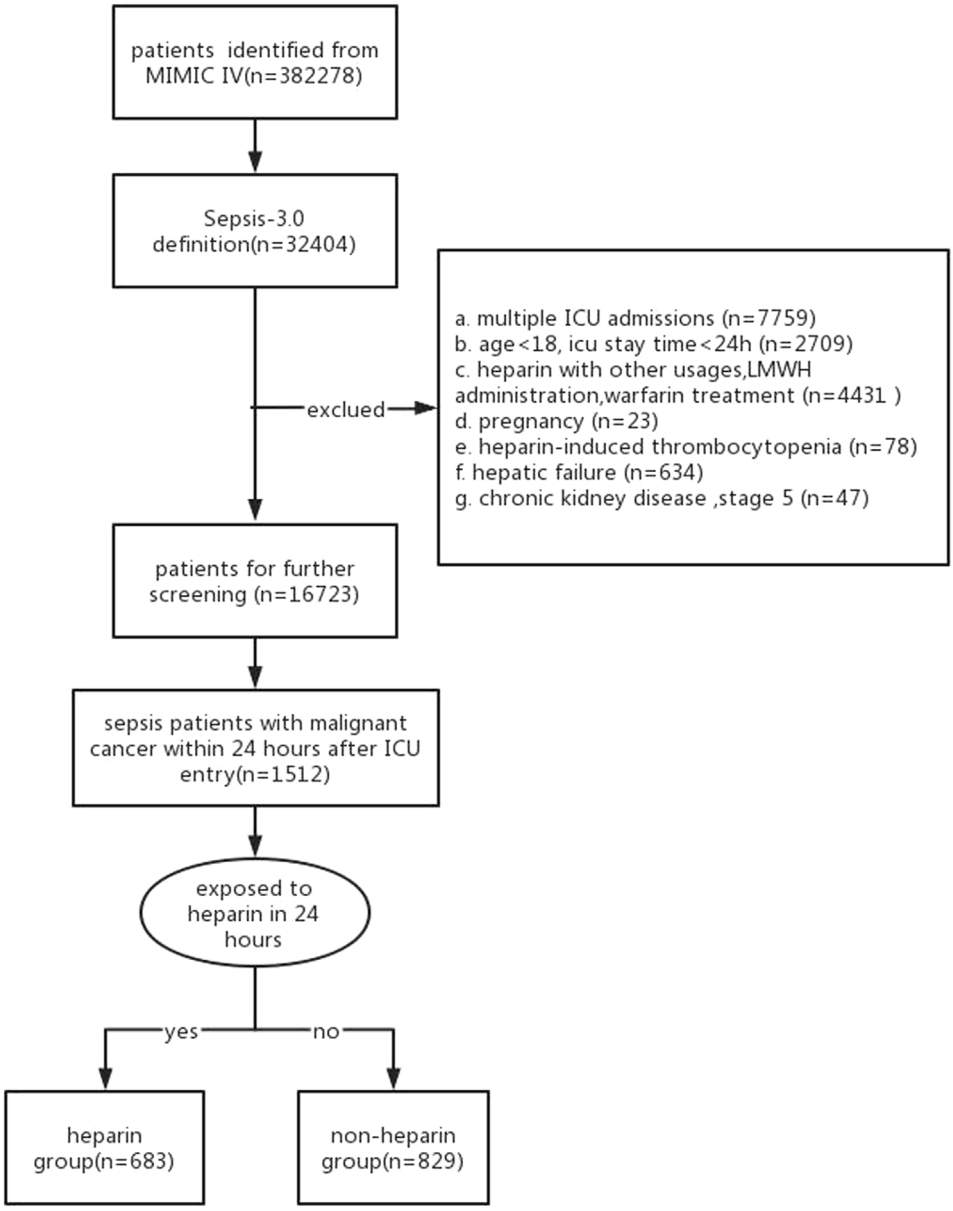


FIGURE 1
Flowchart of participants selection by the Sepsis-3 definition.

SOFA score or Simplified Acute Physiology Score II (SAPS II). Typically, the SOFA score was determined in the initial 24-h after post-admission to the ICU. AKI diagnosis was based on the Kidney Disease: Improving Global Outcomes (KDIGO) standards (Ostermann et al., 2020). AKI stages were determined based on creatinine and urine output levels within the initial 24-h after post-admission to the ICU.

The laboratory variable activated partial thromboplastin time (APTT) was extracted throughout all ICU stay. In addition, the present work obtained the physiological values and measurement chart time based on a database. If the cases were measured repeatedly, only the highest daily APTT was included in the analyses. These screening variables had <15% missing values (Supplementary Table S1) and were later subjected to single imputation.

## Exposure and outcomes

Participants were divided into two groups: a heparin group that enrolled patients receiving subcutaneous heparin 24 h after post-admission into the ICU at preventive doses and a control group that included patients not receiving heparin on day one. Our primary outcome was ICU mortality, which was deemed to be patient survival upon discharge from the ICU. The secondary outcomes included in-hospital mortality and thrombosis.

**TABLE 1 Baseline characteristics of critically ill patients with solid malignancy associated sepsis before and after propensity score matching.**

| | Propensity score matching | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Before | | | | After | | | |
| Patients characteristics | No heparin (n = 829) | Heparin (n = 683) | *p*-value | SMD | No heparin (n = 528) | Heparin (n = 528) | *p*-value | SMD |
| **Demographics** | | | | | | | | |
| Gender, male (%) | 539 (65.0) | 414 (60.6) | 0.087 | 0.091 | 329 (62.3) | 337 (63.8) | 0.655 | 0.031 |
| Age (yr) | 68.97 (12.97) | 68.89 (12.70) | 0.909 | 0.006 | 68.77 (13.41) | 68.71 (12.98) | 0.948 | 0.004 |
| Ethnicity (%) | | | 0.305 | 0.136 | | | 0.946 | 0.08 |
| White | 567 (68.4) | 472 (69.1) | | | 366 (69.3) | 366 (69.3) | | |
| Asian | 43 (5.2) | 41 (6.0) | | | 32 (6.1) | 34 (6.4) | | |
| Black | 89 (10.7) | 65 (9.5) | | | 42 (8.0) | 49 (9.3) | | |
| Other | 130 (15.7) | 105 (15.4) | | | 88 (16.6) | 79 (15.0) | | |
| Weight (kg) | 78.08 (19.95) | 78.14 (21.21) | 0.953 | 0.003 | 77.41 (20.24) | 77.89 (21.21) | 0.706 | 0.023 |
| Heart rate (bpm) | 89.37 (16.98) | 89.13 (16.04) | 0.775 | 0.015 | 89.32 (17.18) | 89.79 (16.35) | 0.648 | 0.028 |
| MAP (mmHg) | 76.22 (10.08) | 75.48 (10.05) | 0.157 | 0.073 | 75.85 (9.62) | 75.80 (10.28) | 0.938 | 0.005 |
| Respiratory rate (bpm) | 19.79 (4.22) | 19.77 (4.14) | 0.956 | 0.003 | 19.55 (4.31) | 19.87 (4.25) | 0.23 | 0.074 |
| Temperature (°C) | 36.84 (0.46) | 36.89 (0.49) | 0.031 | 0.111 | 36.86 (0.47) | 36.86 (0.48) | 0.891 | 0.008 |
| Spo2 (%) | 90.79 (7.64) | 91.27 (5.68) | 0.174 | 0.071 | 91.38 (7.20) | 90.93 (6.09) | 0.27 | 0.068 |
| **Laboratory findings** | | | | | | | | |
| Hemoglobin (g/L) | 9.18 (2.13) | 9.84 (1.89) | <0.001 | 0.328 | 9.72 (2.08) | 9.68 (1.88) | 0.736 | 0.021 |
| Minimum platelet ($10^3$/μl) | 173 (116) | 212 (114) | <0.001 | 0.339 | 201 (118) | 197 (109) | 0.506 | 0.041 |
| WBC ($10^3$/μl) | 15.32 (12.10) | 15.25 (9.96) | 0.897 | 0.007 | 15.05 (10.00) | 15.33 (10.36) | 0.651 | 0.028 |
| Maximum INR | 1.73 (1.13) | 1.47 (0.46) | <0.001 | 0.302 | 1.48 (0.49) | 1.50 (0.48) | 0.508 | 0.041 |
| PT(s) | 18.67 (11.55) | 16.09 (4.81) | <0.001 | 0.291 | 16.17 (5.16) | 16.39 (5.03) | 0.47 | 0.044 |
| APTT(s) | 37.01 (19.44) | 37.47 (16.71) | 0.628 | 0.025 | 36.94 (21.37) | 38.20 (17.25) | 0.293 | 0.065 |
| **Complication** | | | | | | | | |
| Hepertension,n (%) | 337 (40.7) | 309 (45.2) | 0.081 | 0.093 | 228 (43.2) | 222 (42.0) | 0.756 | 0.023 |
| Diabetes,n (%) | 109 (13.1) | 177 (25.9) | <0.001 | 0.326 | 97 (18.4) | 108 (20.5) | 0.437 | 0.053 |
| Chronic heart disease,n (%) | 85 (10.3) | 100 (14.6) | 0.012 | 0.133 | 62 (11.7) | 66 (12.5) | 0.777 | 0.023 |
| Chronic pulmonary disease,n (%) | 221 (26.7) | 187 (27.4) | 0.798 | 0.016 | 134 (25.4) | 137 (25.9) | 0.888 | 0.013 |
| Urine output (mL) | 1,679 (1,231) | 1,617 (1,046) | 0.299 | 0.054 | 1,641 (1,214) | 1,644 (1,060) | 0.960 | 0.003 |
| AKI stage,n (%) | | | 0.023 | 0.159 | | | 0.983 | 0.025 |
| 0 | 420 (50.7) | 303 (44.4) | | | 246 (46.6) | 246 (46.6) | | |
| 1 | 121 (14.6) | 97 (14.2) | | | 78 (14.8) | 76 (14.4) | | |
| 2 | 186 (22.4) | 198 (29.0) | | | 142 (26.9) | 140 (26.5) | | |
| 3 | 102 (12.3) | 85 (12.4) | | | 62 (11.7) | 66 (12.5) | | |
| RRT,n (%) | 17 (2.1) | 11 (1.6) | 0.66 | 0.033 | 6 (1.1) | 8 (1.5) | 0.788 | 0.033 |
| Vasopressor,n (%) | 344 (41.5) | 252 (36.9) | 0.077 | 0.094 | 217 (41.1) | 212 (40.2) | 0.802 | 0.019 |
| Ventilation,n (%) | 275 (33.2) | 266 (38.9) | 0.023 | 0.12 | 207 (39.2) | 193 (36.6) | 0.41 | 0.055 |

(Continued on following page)

**TABLE 1 (*Continued*) Baseline characteristics of critically ill patients with solid malignancy associated sepsis before and after propensity score matching.**

| Patients characteristics | Propensity score matching | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Before | | | | After | | | |
| | No heparin (n = 829) | Heparin (n = 683) | *p*-value | SMD | No heparin (n = 528) | Heparin (n = 528) | *p*-value | SMD |
| SOFA score, median (IQR) | 6 [4.8] | 5 [3.8] | 0.001 | 0.166 | 5 [4.8] | 5 [3.75.8] | 0.873 | 0.01 |
| SAPS II score, median (IQR) | 42 [32.57] | 40 [32.50] | 0.099 | 0.085 | 41 [33.50] | 41 [32.50] | 0.834 | 0.013 |

Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; SAPS II, simplified acute; physiology score II., Values are shown as the mean (SD) unless otherwise indicated. n, IQR,interquartile range.

**TABLE 2 Association between heparin use and clinic outcomes in critically ill patients with solid malignancy associated sepsis.**

| Outcomes n (%) | Propensity score matching cohort (n = 1,056) | | | | | All eligible for propensity score (n = 1,512) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All patients n = 1,056 | Non-heparin n = 528 | Heparin n = 528 | HR (95%) | *p*-value | All patients n = 1,512 | Non-heparin n = 829 | Heparin n = 683 | HR (95%CI) | *p*-Value |
| Primary | | | | | | | | | | |
| ICU mortality | 131 (12.4) | 77 (14.6) | 54 (10.2) | 0.61 (0.41.0.92) | 0.019 | 187 (12.4) | 121 (14.6) | 66 (9.7) | 0.67 (0.46.0.97) | 0.033 |
| Secondary | | | | | | | | | | |
| Thrombosis | 87 (8.2) | 60 (11.4) | 27 (5.1) | 0.42 (0.26.0.68) | <0.001 | 141 (9.3) | 104 (12.5) | 37 (5.4) | 0.44 (0.30.0.66) | <0.001 |
| Hospital mortality | 206 (19.5) | 115 (21.8) | 91 (17.2) | 0.70 (0.50.0.99) | 0.043 | 297 (19.6) | 187 (22.6) | 110 (16.1) | 0.66 (0.49.0.90) | 0.008 |

Abbreviations: HR, hazard ratio; ICU, intensive care unit.

## Statistical analysis

Categorical variables were presented in the form of numbers and percentages. They were compared between the heparin and nonheparin groups using Fisher's exact test and chi-square test, whereas continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range [IQR]) as appropriate.

The present study adopted propensity score matching (PSM) to interpret the basic differences in whether the patient received heparin treatment (Huang et al., 2023). During PSM analysis, prophylactic heparin was administered to the heparin group 24 h post-ICU admission. The treatment group was then matched to the control group through nearest-neighbor matching. Besides, this work also determined standardized mean difference (SMD) was calculated to examine whether PSM reduced the differences between two groups. Finally, a Cox proportional hazards model was used to adjust for residual imbalance by including parameters with $p$ values < 0.05 and potential confounding factors judged by clinical expertise.

In this study, we determined heparin administration during the ICU stay to be the time-dependent variable for the marginal structural Cox model (MSCM). The possible basic confounders, including age, gender, mechanical ventilation, vasopressor, RRT, SOFA, and SAPS II scores, were acquired on the first day after ICM entry. The APTT in the entire ICU stay period was a time-varying confounder and was incorporated into the above model. In addition, MSCM parameters were predicted based on inverse probability weighting (IPW) (IPW) to correct selection bias or confounders, such as informative censoring (Shinozaki and Suzuki, 2020). IPW was adopted to weigh all cases, which helped to create two pseudopopulations close in terms of basic and time-dependent confounders, whereas they were distinct with regard to heparin exposure. IPWs were estimated using the IPW package (Grafféo et al., 2019).

To explore the differences in heparin use and ICU mortality among diverse subgroups stratified according to gender, race, AKI stage, vasopressor medication, mechanical ventilation use, and malignant cancer, a stratification analysis was performed. The Cox model, with adjustments for every variable in basic patient characteristics, was adopted for the subgroup analysis. E-values were determined to analyze the probability of non-measured confounders of heparin with ICU mortality (Haneuse et al., 2019). E-values could be used to quantify the necessary magnitude of the non-methylated confounder to negate the detected relationship of heparin with ICU mortality. Additionally, a pre-specified subgroup analysis was carried out using MSCM. $p$ < 0.05 (two-tailed) stood for statistical difference. R software (version 4.1.1) was used for the analysis.

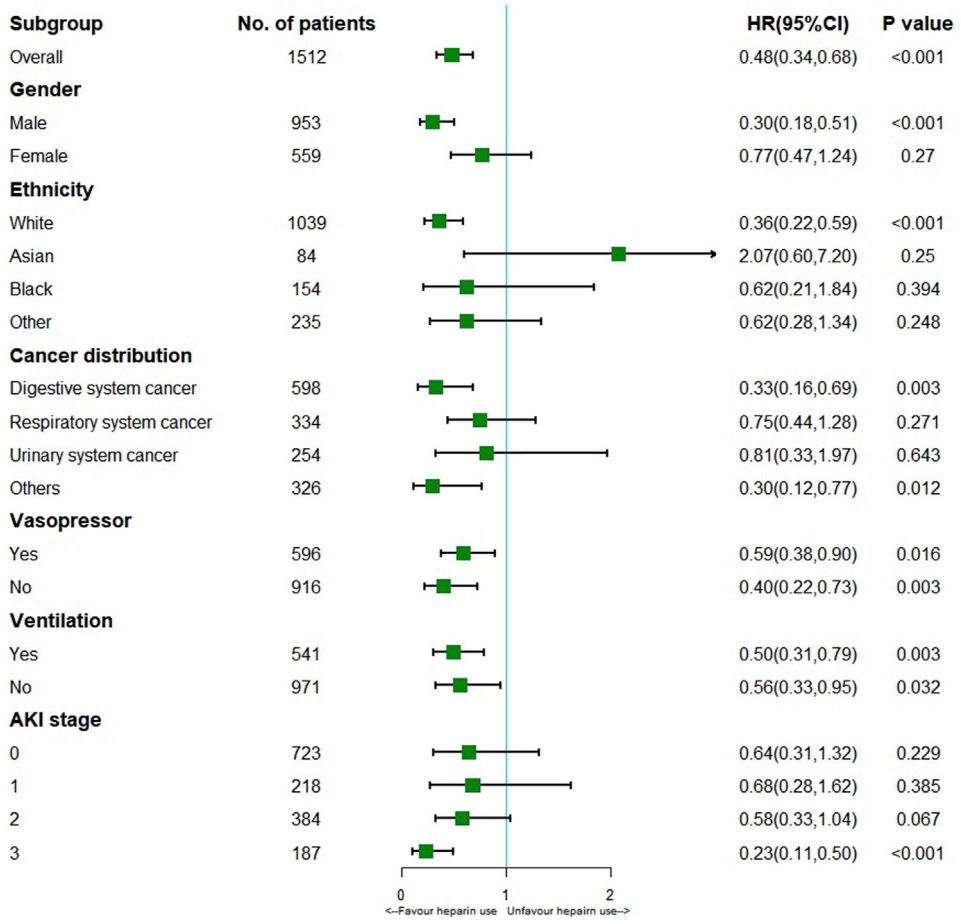


FIGURE 2
Results of ICU mortality in overall population with MSCM and stratification analysis Abbreviations: AKI, acute kidney injury; HR, hazard ratio.

**TABLE 3 Dose-response relationship between heparin and ICU mortality in critically ill patients with solid malignancy associated sepsis.**

| Daily heparin usage (non-heparin group as References) | No. Of patients[a] | HR (95%CI) | *p*-Value |
|---|---|---|---|
| $0U < x \leq 5000U$ | 174 | 1.33 (0.65.2.75) | 0.433 |
| $5000U < x \leq 7500U$ | 217 | 0.61 (0.28.1.32) | 0.210 |
| $7500U < x \leq 10000U$ | 266 | 0.47 (0.27.0.82) | 0.008 |
| $10000U < x \leq 12500U$ | 121 | 0.25 (0.12.0.53) | <0.001 |
| $12500U < x \leq 15000U$ | 90 | 0.55 (0.22.1.39) | 0.204 |

[a]Number of patients receiving prophylactic heparin.

# Results

## Patient characteristics

Upon a preliminary search, 382,278 ICU entries were found in the MIMIC-IV database. There were 32,404 cases satisfying the definition, while 1,512 septic patients had complicated malignant cancer 24 h after admission into the ICU. Of those study cases, 683 received heparin treatment within the initial 24 h post-admission to the ICU, whereas the remaining 829 did not administer heparin (Figure 1).

As shown in Table 1, temperature, hemoglobin levels, platelet levels, INR, PT, presence of diabetes, presence of chronic heart disease, AKI stage, ventilation, and SOFA score were significantly different between the two groups. Notably, the non-heparin group had a higher number of critical cases than the heparin group (SOFA score, 6 [4.8] vs. 5 [3.8], $p < 0.001$). Moreover, the heparin group displayed an increased requirement for

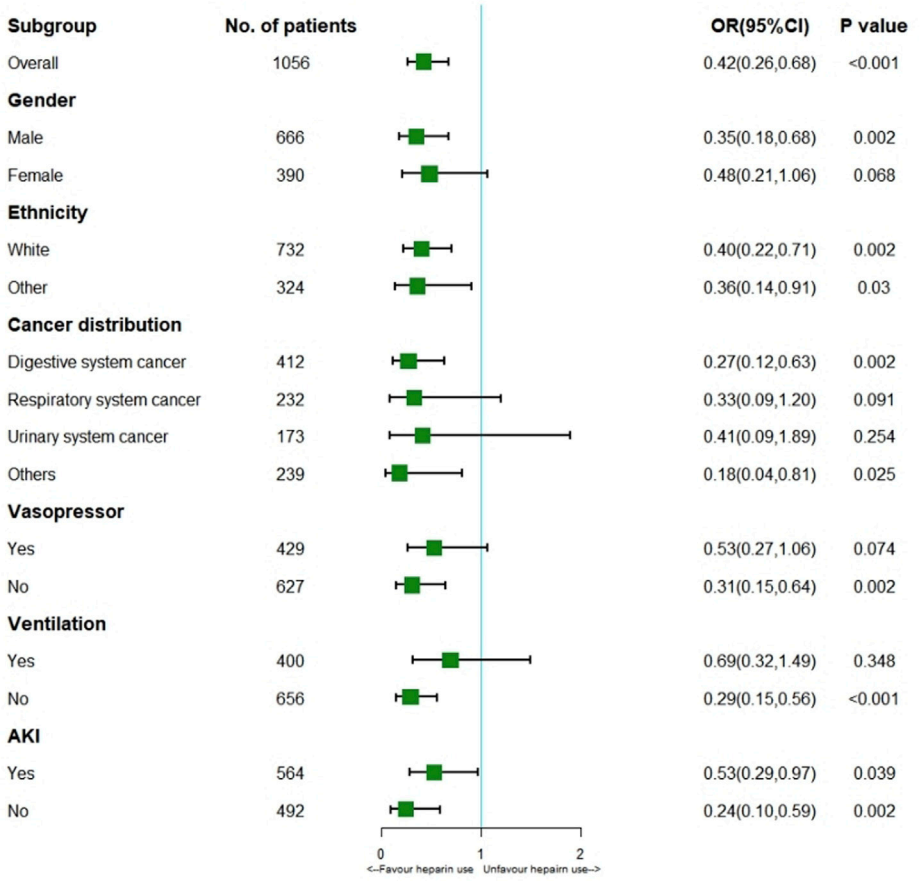


FIGURE 3
Results of thrombosis in overall population with logistic regression model and stratification analysis. Abbreviations: AKI, acute kidney injury; OR, odds ratio.

mechanical ventilation (38.9% vs. 33.2%, $p = 0.023$) compared to the non-heparin group.

# Outcomes

## Propensity score analysis

A total of 1,512 solid malignancy patients with sepsis were enrolled in the study, of which 683 in the heparin group had ICU mortality, thrombosis rate, and hospital mortality of 9.7%, 5.4%, 16.1%, and 829 in the non-heparin group, and ICU mortality, thrombosis rate, and hospital mortality were 14.6%, 12.5%, and 22.6%, respectively (Table 2). PSM was then conducted to match 528 cases receiving heparin with 528 patients not receiving heparin, which markedly decreased the imbalances between both groups (Supplementary Figure S1, Table 1). Owing to the presence of residual imbalances between both groups, this study utilized the Cox proportional hazards model. As a result, heparin use led to decreased mortality for the entire cohort (ICU mortality: hazard ratio [HR],0.61; 95% CI 0.41–0.92; $p = 0.019$). Secondary outcomes were similar (hospital mortality: HR, 0.70; 95% CI 0.50–0.99; $p = 0.043$, thrombosis: HR:0.42; 95% CI 0.26–0.68; $p < 0.001$) (Table 2).

## Marginal structural cox model and stratification analysis

This study incorporated heparin use and time-varying confounders into MSCM. As a result, heparin use reduced ICU mortality (HR 0.48; 95% CI 0.34–0.68; $p < 0.001$) for the entire cohort. According to the stratification analysis results, heparin use decreased the incidence of ICU mortality among patients with solid malignancies concomitant sepsis among males (HR 0.30; 95% CI 0.18–0.51; $p < 0.001$) and those of white ethnicity (HR 0.36; 95% CI 0.22–0.59; $p < 0.001$), stage 3 AKI (HR 0.23; 95% CI 0.11–0.50; $p < 0.001$), and digestive system cancer (HR 0.33; 95% CI 0.16–0.69; $p = 0.003$) (Figure 2). It was observed that, in patients with solid malignancy concomitant sepsis, treatment with 7,500–12500 IU heparin daily was associated with a lower risk of ICU mortality than no heparin treatment (Table 3).

## Logistic regression, cox regression model and stratification analysis

Logistic regression model showed heparin use markedly reduced thrombosis (HR 0.42; 95% CI 0.26–0.68; $p < 0.001$)

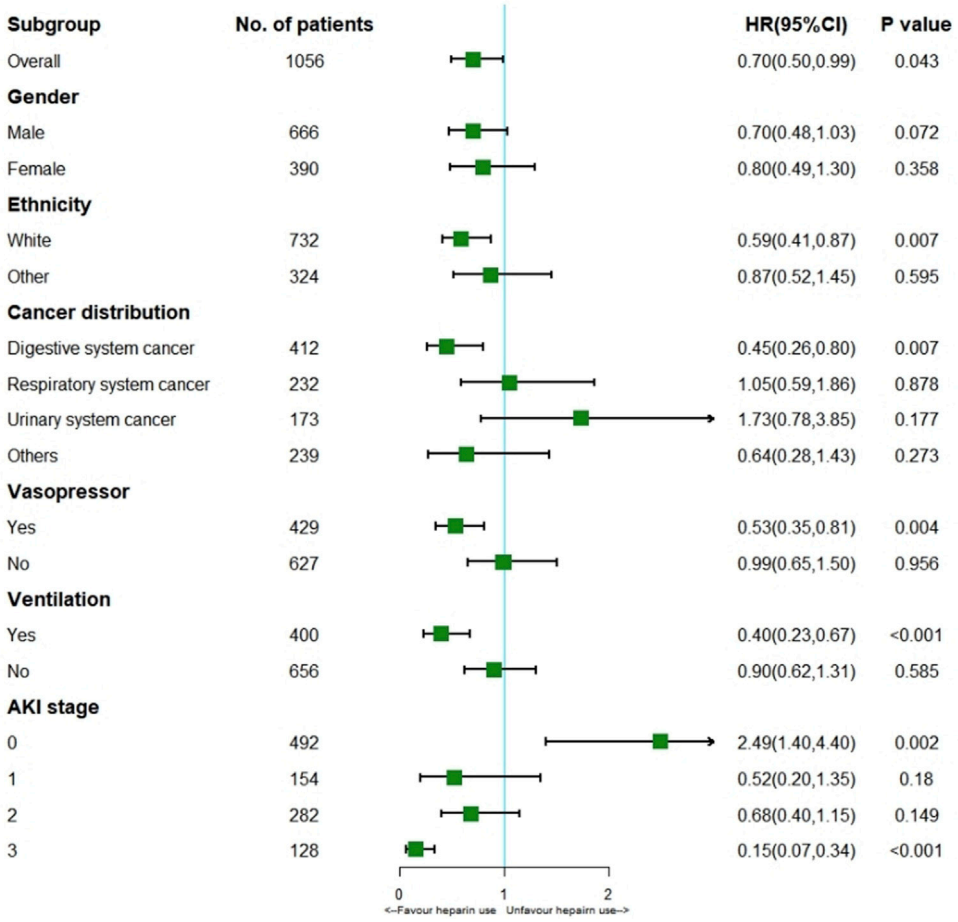


FIGURE 4
Results of hospital mortality in overall population with cox regression model and stratification analysis.

for the entire cohort. According to the stratification analysis results, heparin use decreased the incidence of thrombosis in patients with solid malignancies concomitant sepsis among males (HR 0.35; 95% CI 0.18–0.68; $p$ = 0.002) and those of white ethnicity (HR 0.40; 95% CI 0.22–0.71; $p$ = 0.002) or other ethnicity (HR 0.36; 95% CI 0.14–0.91; $p$ = 0.03), digestive system cancer (HR 0.27; 95% CI 0.12–0.63; $p$ = 0.002), non-Vasopressor use (HR 0.31; 95% CI 0.15–0.64; $p$ = 0.002), non-Ventilation (HR 0.29; 95% CI 0.15–0.56; $p$ < 0.001) and AKI (HR 0.53; 95% CI 0.29–0.97; $p$ = 0.039). (Figure 3).

Cox regression model showed heparin use markedly reduced hospital mortality (HR 0.70; 95% CI 0.50–0.99; $p$ = 0.043) for the all cohort. According to the stratification analysis results, heparin use decreased the incidence of hospital mortality in patients with solid malignancies concomitant sepsis among those of white ethnicity (HR 0.59; 95% CI 0.41–0.87; $p$ = 0.007), digestive system cancer (HR 0.45; 95% CI 0.26–0.80; $p$ = 0.007), Vasopressor use (HR 0.53; 95% CI 0.35–0.81; $p$ = 0.004), Ventilation (HR 0.40; 95% CI 0.23–0.67; $p$ < 0.001) and stage 3 AKI (HR 0.15; 95% CI 0.07–0.34; $p$ < 0.001). (Figure 4).

## Sensitivity analysis

Distinct measured and known ICU mortality-related risk factors identified in the multivariable Cox proportional hazards model following PSM were SAPS II (HR, 1.02; 95% CI, 1.01–1.04), AKI 2 (HR, 1.91; 95% CI, 1.10–3.32), chronic pulmonary disease (HR, 2.27 (1.51.3.41); 95% CI, 1.51–3.41), and diabetes (HR, 1.74; 95% CI, 1.09–2.79) (Table 4).

E-values were analyzed to assess the sensitivity to non-measured confounders (https://www.evalue-calculator.com/evalue/). Reliable preliminary results were obtained, only if non-measured confounders existed, the ICU mortality risk was relatively low and the HR was over 2.66 (upper limit of 4.05), suggesting the capability of residual confounders of explaining the detected connection when one non-measured covariate with the relative risk association with prophylactic heparin use and ICU mortality of >2.66 existed. Therefore, unknown and non-measured confounders might not significantly affect ICU mortality (relative risk >2.66) compared with known risk factors.

**TABLE 4 Multivariable cox regression model after propensity score matching in critically ill patients with solid malignancy associated sepsis.**

| Variables | HR (95%CI) | *p* |
|---|---|---|
| Gender | | |
| Famale | References | |
| Male | 0.96 (0.62.1.47) | 0.850 |
| Age | 1.00 (0.98.1.01) | 0.670 |
| Weight | 0.99 (0.98.1.00) | 0.212 |
| $SPO_2$ | 0.96 (0.94.0.98) | <0.001 |
| PT | 0.84 (0.67.1.05) | 0.122 |
| SOFA | 1.05 (0.96.1.13) | 0.276 |
| SAPS II | 1.02 (1.01.1.04) | 0.008 |
| AKI stage | | |
| 0 | References | |
| 1 | 1.60 (0.84.3.02) | 0.151 |
| 2 | 1.91 (1.10.3.32) | 0.022 |
| 3 | 1.62 (0.76.3.47) | 0.209 |
| Vasopressor use | | |
| No | References | |
| Yes | 0.87 (0.54.1.40) | 0.560 |
| Ventilation use | | |
| No | References | |
| Yes | 0.55 (0.34.0.89) | 0.016 |
| Chronic heart disease | | |
| No | References | |
| Yes | 1.09 (0.57.2.07) | 0.800 |
| Chronic pulmonary disease | | |
| No | References | |
| Yes | 2.27 (1.51.3.41) | <0.001 |
| Diabetes | | |
| No | References | |
| Yes | 1.74 (1.09.2.79) | 0.021 |
| Hypertension | | |
| No | References | |
| Yes | 0.85 (0.58.1.24) | 0.386 |

Abbreviations: PT, prothrombin time; AKI, acute kidney injury; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II.

## Discussion

Due to the immunosuppression observed in cancer patients, sepsis may develop. Although animal studies have demonstrated that heparin can combine with lipopolysaccharide (LPS) to reduce the mortality resulting from Gram-negative bacterial infection (Tang et al., 2021; Yuan et al., 2021), and we found that early administration heparin provide a survival advantage in critically ill patients with sepsis (Zou et al., 2022), unfortunately, cancer patients were excluded from our previous studies. Thus, this conclusion may not be suitable for patients with cancer complicated with sepsis. Notably, minimal data exist on anticoagulation with heparin on outcomes in critically ill patients with solid malignancy associated sepsis as far. Whether administration heparin would provide a

survival advantage in critically ill patients with solid malignancies concomitant sepsis remains unknown. Therefore, we designed another study on effectiveness of heparin therapy to patients with solid malignancies, and the results from the MIMIC-IV data demonstrate that heparin administration is associated with improved ICU mortality, thrombosis and hospital mortality in patients with solid malignancy concomitant sepsis.

As administration heparin is time-dependence variable, so we employed MSCM model to adjust additional time-dependent interventions (de Keyser et al., 2014; Karim et al., 2014; Huang et al., 2023). The MSCM further reinforces the efficacy of heparin in reducing ICU mortality. For the unmeasured confounding variables, we used risk factor analysis with a multivariable Cox proportional hazards model and E-value analysis to perform a combined analysis of the data. The result indicates that it is unlikely that an unmeasured confounder would have a substantially greater effect on ICU mortality than these known risk factors. E-value analysis suggested robustness to unmeasured confounding variables (Haneuse et al., 2019). Therefore, heparin therapy did demonstrate a benefit in patients not only in general populations but also in those with solid malignancies. Interestingly, stratification analysis with MSCM further indicated that administration heparin at 7,500–12500 IU a day decreased ICU mortality only among male patients and those with white ethnicity, stage 3 AKI, digestive system cancer and did not benefit those with respiratory system cancer. The underlying mechanism may involve the patient's ethnicity and race, endocrine metabolism status, tumor type and targeted therapy. The findings presented in this report provide an insight role of heparin in patients with solid malignancies concomitant sepsis.

During targeted therapy for patients with solid malignancies, injury-related molecules are readily released and trigger inflammatory reactions and coagulation disorders (Wu et al., 2021), leading to an increased risk of thrombosis. Patients with cancer are significantly more likely to develop venous thromboembolism (VTE) than people without cancer (Heit, 2015; Schünemann et al., 2020). Cancer-associated thrombosis is the second leading cause of death in cancer patients after disease progression (Farge et al., 2022), furthermore, the incidence of cancer-associated thrombosis is increasing worldwide (Schünemann et al., 2020). The prevalence of cancer-associated thrombosis is increasing because of multiple factors, including longer patient survival, the use of anticancer therapies, increased detection of incidental VTE during surveillance imaging and wider use of central venous catheters (Mulder et al., 2021). The annual risk of a venous thromboembolic event in patients with solid cancer is 4%–5% overall, with wide variation between patients with different cancer types (Akl et al., 2017). A systematic review identified the greatest benefit from heparin treatment for VTE in patients with lung cancer (RR 0.59, 95% CI 0.42–0.81) (Cuenca et al., 2022). The result is similar to our results that heparin treatment has a benefit on reducing the risk of thrombosis (HR 0.42, 95% CI 0.26–0.68, $p < 0.001$). Therefore, the international clinical practice guidelines included the recommendation of LMWHs for the initial (first 10 days) treatment and maintenance treatment of cancer-associated thrombosis (Farge et al., 2022), but it does not improve survival (Cuenca et al., 2022).

Although previous studies have documented that heparin can inhibit tumor invasion and metastasis (Wei et al., 2023), heparin therapy has not been used as a conventional antitumor method in clinical practice. Recently, in the United States, an observational cohort study based on over 1 million sepsis hospitalizations showed that in-hospital mortality in cancer-related sepsis patients was 27.9% vs. 19.5% in patients without cancer-related sepsis, and cancer-related sepsis was associated with an adjusted absolute increase in in-hospital mortality that ranged from 2.2% to 15.2% of that associated with noncancer-related sepsis (Hensley et al., 2019). There are many plausible explanations for the differential outcomes between cancer-related and noncancer-related sepsis, including the cancer itself, cancer treatment and the resulting immune suppression, critical care provider bias and the differing goals of care (Hensley et al., 2019). Research shows that approximately 70% of cancer patients in the ICU have solid malignancies, and there is no recommendation in the international sepsis guidelines on whether they need anticoagulation treatment (Evans et al., 2021). The results of this study will provide a new therapeutic insight for the treatment of solid malignancies associated sepsis. The mechanism of effectiveness of heparin therapy to patients with solid malignancies concomitant sepsis, apart from anticoagulation effect, anti-inflammatory effects, anticomplement activity, and protease regulation on heparin (Li et al., 2013; Li et al., 2014), the underlying mechanism still needs further to investigate.

However, certain limitations of the present study should be noted. First, this study was carried out based on an EHR using clinically derived data. Therefore, the process adopted in cohort screening may not be identical to guideline-defined sepsis. However, sepsis cases were identified based on guidelines identical to the third definition of sepsis (such as infection combined with rapid alteration of total SOFA score ≥2 points). Second, confounders might have affected our results because of the retrospective nature of the present work. As a result, MSCM and PSM were adopted for balancing critical confounders, both of which verified our result creditability. Finally, certain patient variables were not obtained from the database, which might have led to bias or confounders. E-values were calculated in the sensitivity analysis to quantify possible results caused by those non-extracted confounders; according to our results, the non-extracted confounders might not interpret the whole therapeutic effect.

## Conclusion

According to our results, early heparin application for patients with solid malignancy associated sepsis may improve survival, including ICU mortality, hospital mortality, and thrombosis, particularly for males and those with white ethnicity, stage 3 AKI, and digestive system cancer. In addition, patients with solid malignancy associated sepsis who received 7,500–12500 IU per day had lower ICU mortality than non-heparin cases. Consequently, more prospective randomized controlled trials are warranted to verify timing, dosage, and indications of heparin use for solid tumor cases.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by the Committee of Shenzhen Second People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because using data from MIMIC-IV (version 1.0).

## Author contributions

JH: Writing–original draft, Data curation, Formal Analysis. Investigation. ZZ: Investigation. YL: Data curation, Formal ZY: Investigation. DL: Investigation, YC: Investigation. YL: original draft, Supervision. YY: Supervision, Conceptualization, Writing–review and editing. MW: Conceptualization, Supervision, Writing–review and editing, Funding acquisition.

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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.2023.1281235/full#supplementary-material

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# Price increase negotiations to address drug shortages in South Korea's national health insurance

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South Korea has adopted a unique approach to address drug shortages by increasing reimbursement prices within its National Health Insurance Service. This study aims to analyze the characteristics, increase rates, affecting factors, and budget impacts of products that have increased price through the negotiation system. Between 2007 and 2022, there were price increase negotiations over 244 items. Of these, price increase negotiations were successful for 217 items, resulting in an agreement rate of 89%. The average rate of price increase for the agreed-upon products was 37.8%, and the overall budget increase for drugs with price increases ($n$ = 217) was approximately 24.5%. Budget impact of each variable of the negotiated agreements showed that the number of negotiated agreement items was smaller after 2015 than before 2015, but each total budget impact (initial budget, increased budget, and final budget) and the average budget impact were higher. Although domestic companies accounted for a larger overall budget, the average budget per item was larger for multinational companies. The correlation analysis of the ratio of price increase and budget impact variables showed that the ratio of price increase was positively and significantly correlated with the increased budget, while it was negatively but not significantly correlated with the initial and final budgets. The South Korean model of increasing reimbursement prices in public insurance for drugs at risk of shortages serves as an exemplary case for not only securing patient access but also considering budget management.

KEYWORDS

**drug shortage, price negotiation, health insurance, budget impact, essential drug**

## 1 Introduction

Pharmaceuticals are public goods essential for preventing and treating diseases, necessitating a national system for appropriate supply according to demand (Phuong et al., 2019). When supply falls short of demand, resulting in a drug shortage, patients may experience exacerbated conditions and be exposed to side effects due to inappropriate substitute medications (Tucker et al., 2020). Furthermore, societal costs arise from the additional time and effort expended by healthcare providers searching for alternative drugs or treatments, elevating drug shortage from a purely medical problem to a broader societal concern (Pauwels et al., 2014; Postma et al., 2023).

Drug shortages occur globally, irrespective of a nation's income level (Shukar et al., 2021). Such shortages can be attributed to not only manufacturing and quality issues but also monopolistic market behaviors and difficulties in procuring raw material (Alevizakos et al., 2016; Fox and Tyler, 2017). The globalization of supply chains has also led to transnational propagation of drug shortages (Iyengar et al., 2016). The United States recognized the severity of this issue and enacted the Food and Drug Administration Safety

and Innovation Act in 2012 (Chen et al., 2016). This legislation mandates companies to report anticipated drug shortages to the Food and Drug Administration and legally delineates the responsibilities of corporations and the government. Moreover, as countries worldwide experience global crises such as COVID-19, policies to prioritize supplying essential public goods to citizens have been further strengthened, and major pharmaceutical-producing countries have reduced export volumes to prioritize domestic demand (Badreldin and Atallah, 2021). For instance, a global shortage of acetaminophen by the end of 2022 led to competitive procurement efforts among nations. While early reporting of supply disruptions by pharmaceutical companies is crucial, strengthening domestic access to pharmaceuticals through policy support is also essential. A previous study discussed price and reimbursement policies related to drug shortages (Musazzi et al., 2020). Representative examples from Japan and Australia include postponing or exempting drugs with high clinical need from applying the drug price reduction system for a certain period to prevent a drug shortage due to problems with reimbursement prices in public insurance. According to a 2019 survey by the European Association of Hospital Pharmacists, medical professionals have identified price as a significant cause of drug shortages (Miljković et al., 2020). Furthermore, research has shown that if a shortage of specific prescription drugs persists, the risk of drug prices rising along with the disruption of patient care increases (Dave et al., 2018), and the risk of drug shortages increases even when domestic drug prices are significantly lower than those in foreign countries (Alowairdhi et al., 2023).

In this context, raising reimbursement prices within public insurance schemes can be considered a strategy to combat drug shortages. For countries such as South Korea, which operates a single-payer system through the National Health Insurance Service (NHIS), prices and drug shortages are even more closely related. However, no public insurance systems have addressed price increases to alleviate drug shortages. South Korea has been operating a price increase negotiation system for drug shortages since 2007, providing globally relevant insights into tackling drug shortages.

This study aims to analyze the characteristics, rate of price increases, contributing factors, and budget impacts of products that have experienced price hikes through South Korea's "Price Increase Negotiation System for Drug Shortages."

When South Korea's health insurance system was introduced in 2007, the eligibility criteria for price increase negotiations included only clinically essential and irreplaceable drugs. However, owing to growing concerns about drug shortages amid the COVID-19 pandemic, the criteria were expanded in 2020 to include low-cost products for which no alternative with the same active ingredient existed.

Regarding submission documents and procedures for price increase negotiation, pharmaceutical companies must submit a price-increase application along with evidence supporting the need for such an increase, such as production or import costs, to the Ministry of Health and Welfare. Subsequently, the Ministry of Health and Welfare commissions the Health Insurance Review and Assessment Service to review the documents and evaluate the drug's clinical necessity and utility. If the Health Insurance Review and Assessment Service confirms the need for a price increase, negotiations between the pharmaceutical company and the NHIS determine the final adjusted price (Figure 1).

In other words, South Korea operates a positive list system that selectively covers only drugs that have proven clinical utility and cost-effectiveness. Therefore, even if a drug has a high medical need, the payer does not accept the price increase requested by pharmaceutical companies but adjust the price increase considering the budget impact and supply sustainability. Through this system, South Korea has been able to maintain the cost of pharmaceuticals at a stable level of approximately 24% compared to the total health insurance medical expenses every year (as of 2022, total medical expenses amount to 105.9 trillion won, and pharmaceutical expenses amount to 23.4 trillion won).

# 2 Materials and methods

## 2.1 Data sources

The dataset was constructed by extracting a list of pharmaceutical products that had undergone price increases through the drug price negotiation system introduced in South Korea between January 2007 and December 2022. The data sources included the Health Insurance Drug Benefit List announced by the Ministry of Health and Welfare (HIRA, 2023a), the Drug Payment Adequacy Evaluation Report announced by the Health Insurance Review and Assessment Service (HIRA, 2023b), and the Drug Negotiation Results announced by the NHIS (NHIS, 2023b). Drug-specific indications were verified through the online site, EZDRUG, by the Korea Ministry of Food and Drug Safety (MFDS, 2023). The detailed characteristics of the analyzed drugs subject to analysis were categorized according to the Essential Medicines List provided by the World Health Organization (WHO, 2023b) and the Anatomical Therapeutic Chemical (ATC) Classification System code list (WHO, 2023a). The characteristics of pharmaceutical companies were verified through the websites of various pharmaceutical associations (KPBMA, 2023; KRPIA, 2023), and the financial impact of the price increases was gathered from the HIPDAC review results (MOHW, 2023).

## 2.2 Analysis

We analysed the characteristics of the drugs for which price increases were requested by pharmaceutical companies, accepted by the government, and negotiated. The type of drug supply was categorized into foreign imports and domestic production, so we identified the company type, and the nature of the disease and the degree of patient need were identified by ATC code, such as essential drugs, orphan drugs. We examined variables on the initial price, as the percentage increase in the final price from the initial price is an important measure of budget impact. In consideration of these, we defined the variables as follows:

1. Dependent variable: ratio of price increase = (final price−initial price)/initial price ×100

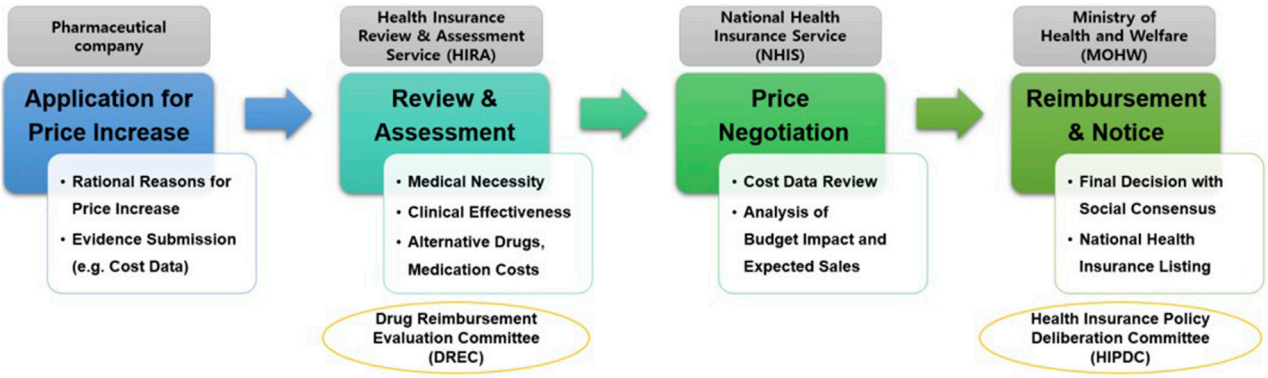


FIGURE 1
Price increase negotiation process to overcome drug shortages.

2. Independent variables: Results: agreement or non-agreement between the pharmaceutical company and the NHIS Structured
   - Company type: domestic or multinational
   - Essential drugs (EDs): designated as ED or non-ED by the World Health Organization
   - Orphan drugs (ODs): designated as OD or non-OD by the Korea Ministry of Food and Drug Safety
   - ATC code: World Health Organization's 1st ATC level (top five codes based on the number of products and the remaining codes)
   - Budget: initial budget (expenditure before price increase), final budget (expenditure after price increase), and increased budget (increased expenditure due to price increase). The budget in this study is of the National Health Insurance Service (NHIS).
   - Period: 2007–2014 or 2015–2022 (enhancing patient access to drugs for unmet needs began in 2015, including introducing the Managed Entry Agreement system) (Efthymiadou and Kanavos, 2022; NHIS, 2023a)

Descriptive statistics were used for the annual agreement ratio in drug price negotiations, increased price ratio, and budget impact analysis. The Mann-Whitney and Kruskal–Wallis tests were used in independent groups, with comparisons between 2007–2014 and 2015–2022. The analyzed variables were increased price ratios and budget impacts. However, because of the large number of subgroups and small sample sizes in each, an overall test for differences was performed instead of *post hoc* tests for variables with three or more subgroups (e.g., ATC code). Pearson's correlation analysis was used to examine the relationship between increased price ratios and budget impacts. Multiple linear regression was performed to identify the variables affecting the increased price ratio. The regression analysis was based on the 217 drugs for which NHIS negotiations were agreed upon, and there were no missing values for these 217 drugs. Multiple linear regression analysis was performed and VIF values were calculated for each independent variable to ensure that there were no multicollinearity issues.

Descriptive statistics and statistical significance tests were performed using IBM SPSS version 27.0. All *p*-values were two-tailed, and $p < 0.05$ was considered statistically significant.

## 3 Results

Between 2007 and 2022, there were price increase negotiations over 244 drugs. Of these, price increase negotiations were successful for 217 drugs, resulting in an agreement rate of 89%. The average rate of price increase for the agreed-upon products was 37.8%. During the early years of the system implementation (2009 and 2010), 27 and 53 drugs, respectively, experienced price increases. Notably, in 2022, a significant price surge in 41 drugs was observed, including multiple products containing acetaminophen, affected by COVID-induced supply shortages (Table 1).

According to the characteristics of the 217 drugs with negotiated price increases, 196 were from domestic companies and 21 were from multinational companies. EDs accounted for 92 drugs, while non-EDs accounted for 125 drugs. Only 19 of these were ODs. According to the ATC code classifications, radioactive diagnostic agents (V) had the highest count of 88, while anti-infectives (J) had the lowest count of 9. Analysis of the rate of price increase according to these variables showed a significant difference after the year 2015 ($p = 0.001$). The rates of price increase were significantly different between ODs and non-ODs ($p = 0.023$). The difference in the rates of price increase for drugs according to the ATC code classification was also statistically significant ($p = 0.011$), and the result of the *post hoc* analysis for each ATC code showed that the difference between blood products (B) and nerve agents (N) was statistically significant ($p = 0.014$; significance values were adjusted by the Bonferroni correction for multiple tests). However, the difference in the rates of price increase for drugs was not statistically significant for two variables: company type ($p = 0.534$) and EDs ($p = 0.092$) (Table 2).

The analysis results of the budget impact of each variable of the negotiated agreements showed that the number of negotiated agreement items was smaller after 2015 than before 2015, but both the total budget amount (initial budget, increased budget, and final budget) and the average budget impact of for each item were higher.

And the average budget impact was significantly different ($p = 0.002$, 0.001, and 0.001, respectively). Although domestic companies accounted for a larger overall budget, the average budget per item was larger for multinational companies ($p = 0.001$, 0.087, and 0.001). Additionally, non-EDs had larger overall and per-item budgets, except in the case of increased budgets, in which EDs were higher

**TABLE 1 The ratios of annual agreement and price increase during price negotiations.**

| Year | Products with price increase (N) | | Agreement ratio (%) | Ratio of price increase | | | |
|---|---|---|---|---|---|---|---|
| | Applied | Increased | | Mean (%) | SD (%) | Max (%) | Min (%) |
| 2008 | 8 | 7 | 87.5 | 106.7 | 0.0 | 106.7 | 106.7 |
| 2009 | 32 | 27 | 84.4 | 144.9 | 24.6 | 177.0 | 100.0 |
| 2010 | 59 | 53 | 89.8 | 130.2 | 22.5 | 174.0 | 100.0 |
| 2011 | 15 | 14 | 93.3 | 113.1 | 8.7 | 132.8 | 100.0 |
| 2012 | 17 | 15 | 88.2 | 139.4 | 18.6 | 204.6 | 118.2 |
| 2013 | 13 | 12 | 92.3 | 115.5 | 8.3 | 135.8 | 110.3 |
| 2014 | 6 | 6 | 100 | 124.4 | 22.1 | 165.8 | 106.7 |
| 2015 | 5 | 5 | 100 | 133.0 | 25.0 | 176.7 | 100.0 |
| 2016 | 18 | 18 | 100 | 142.8 | 44.5 | 319.9 | 100.0 |
| 2017 | 2 | 2 | 100 | 305.8 | 0.0 | 305.8 | 305.8 |
| 2018 | 1 | 1 | 100 | 361.5 | 0.0 | 361.5 | 361.5 |
| 2019 | 5 | 5 | 100 | 139.8 | 36.3 | 208.9 | 103.8 |
| 2020 | 9 | 9 | 100 | 182.9 | 43.3 | 220.6 | 100.4 |
| 2021 | 2 | 2 | 100 | 241.7 | 43.4 | 285.1 | 198.2 |
| 2022 | 52 | 41 | 78.8 | 134.3 | 22.4 | 176.5 | 100.0 |
| Total | 244 | 217 | 88.9 | 137.8 | 38.0 | 361.5 | 100.0 |

Note: The values of ratios are expressed in percentage units.

($p$ = 0.025, 0.003, and 0.028). Although not statistically significant ($p$ = 0.130, 0.059, and 0.184), non-ODs had larger initial budgets and increased budgets than ODs, and ODs had larger final budgets than non-ODs. Overall, the differences in the ATC codes were significant ($p$ < 0.001, 0.001, and 0.004). The total financial amount was largest for radioactive diagnostic agents (V), and the average financial size per item was largest for anti-infectives (J). The result of the *post hoc* analysis of each ATC code showed that the difference between radioactive diagnostic agents (V) and digestive metabolites (A) was significant ($p$ = 0.006, 0.018) in the case of the initial budget, and the differences between radioactive diagnostic agents (V) and digestive metabolites (A) and between radioactive diagnostic agents (V) and anti-infectives (J) were significant ($p$ = 0.018, 0.041) in the case of the final budget. However, no ATC code combination with a significant difference was identified in the case of increased budget (Table 3).

The correlation analysis of the ratio of price increase and budget impact variables showed that the ratio of price increase was positively and significantly correlated with the increased budget ($p$ = 0.005), while it was negatively but not significantly correlated with the initial and final budgets (Table 4). Although not statistically significant, drugs at risk of running out tended to have a lower ratio of price increase when their initial budget was higher.

Using multiple linear regression with the ratio of price increase as the dependent variable, the full model indicated that the period (pre- and post-2015), company type, and initial budget were significant predictors. To assess the goodness of fit of the regression model, we conducted an ANOVA analysis to test the significance of the F-value and presented the explanatory power of each model using the adjusted $R^2$ value. The model's F(p) value was 3.871, and the adjusted $R^2$ was 0.117. The variables of period, initial budget, and company type were sequentially selected in the stepwise model, and ATC V code was added to Model 4. The F(p) value was 17.644, and the adjusted $R^2$ was 0.072 (Table 5). As a result, the rate of price increase for drugs at risk of shortage was higher after 2015 (post-2015) and for multinational companies and drugs with ATC V code indications than for domestic companies and other ATC code indications. However, a higher initial budget was correlated with a lower rate of price increase.

## 4 Discussion

This study examined the South Korean case in which the government increased drug reimbursement prices in public insurance as an institutional solution to pharmaceutical shortages. This study identified which drugs were subject to this regulatory change and the resulting rates of price increase negotiated between pharmaceutical companies and payers. Budget impacts and factors affecting these price increases were also evaluated.

From 2007 to 2022, the average rate of agreement in price increase negotiations for drugs was 89%. This high rate indicates a consensus among stakeholders regarding the need and utility of a price negotiation mechanism to resolve drug shortages. In South Korea, there are 25,000 drugs that are covered by health insurance as of 2022, but the number of drugs for which price increase applications have been accepted and negotiated ($n$ = 244) is very small. This is because the government agency strictly evaluates the

**TABLE 2 Categorization of variables and ratio of price increase.**

| Variables | | N | Ratio of price increase | | *p*-value |
|---|---|---|---|---|---|
| | | | Mean (%) | SD (%) | |
| Period | Before 2015 | 134 | 29.6 | 23.0 | 0.001 |
| | After 2015 | 83 | 51.1 | 51.4 | |
| Company type | DM | 196 | 36.3 | 31.4 | 0.534 |
| | MN | 21 | 52.4 | 74.3 | |
| Essential drug | Non-ED | 125 | 37.2 | 41.7 | 0.092 |
| | ED | 92 | 38.6 | 32.4 | |
| Orphan drug | Non-OD | 198 | 39.1 | 38.6 | 0.023 |
| | OD | 19 | 24.6 | 29.1 | |
| ATC code | The rest | 21 | 45.0 | 57.4 | 0.011 |
| | J | 9 | 27.9 | 10.2 | |
| | N | 19 | 48.0 | 20.4 | |
| | A | 24 | 26.7 | 21.6 | |
| | B | 56 | 27.5 | 21.8 | |
| | V | 88 | 44.5 | 45.4 | |
| Total | | 217 | 37.8 | 38.0 | |

DM, domestic company; MN, multinational company; ED, essential drug; OD, orphan drug.
ATC, code: A, alimentary tract and metabolism; B, blood and blood forming organs. J, antiinfectives for systemic use; N, nervous system; V, various.

appropriateness of the price increase as well as the need for supply, and most of the drugs that passed HIRA's evaluation ($n = 244$) were agreed upon in negotiations with NHIS ($n = 217$). Some failed negotiations ($n = 27$) were primarily due to the policy's early years (2008–2013), and recently, in 2022, price negotiations were conducted for several mild disease (e.g., anti-inflammatory) drugs that are expected to be out of stock due to the impact of COVID-19.

Domestic companies had a higher number of items subject to price increase than multinational ones. This is likely due to the higher number of domestic companies than multinational ones. South Korea's pharmaceutical market is one of the largest in Asian countries after China and Japan, but it still relies heavily on multinational pharmaceutical companies for innovative new drugs or treatments for serious diseases. As the business model of domestic pharmaceutical companies is mainly in the generics sector, there are many cases where the original developer of the drug or the supply route in South Korea is a multinational pharmaceutical company, which raises patient access issues due to supply shortages. In order to stabilize the supply of drugs, it is necessary to improve the production infrastructure of essential drugs by domestic pharmaceutical companies in the medium to long term.

When categorized by disease characteristics, non-EDs and non-ODs were more prevalent. While previous studies have emphasized the importance of drug shortages in acute, severe, and rare diseases (Jarosławski et al., 2017), the findings of this study confirm that South Korea is addressing shortages for less severe and rare diseases through public measures. Furthermore, the application of the system and rate of price increase differed according to the therapeutic class (ATC code). According to previous studies, there is a shortage of anti-infectives (J) in the United States, and in Europe, anti-infectives (J) and nerve agents (N) are highly out of stock (Griffith et al., 2012; Turbucz et al., 2022). In other words, the pattern of drug shortage may differ depending on the country. This study showed that the risk of shortage due to the low prices of radioactive diagnostic agents (V) and blood products (B) was highest in South Korea. Previous research in Canada suggested that shortage management is necessary for drugs in the ATC classification system, including sensory drugs, which have a high patient demand and risk of being out of stock (Zhang et al., 2020). These findings imply that each country should assess its situation and apply realistic solutions, such as price increases. While our literature review identified out-of-stocks for conditions with relatively high prevalence in the U.S., Canada, and Europe, such as neurological and respiratory, we also identified out-of-stocks for specialty ATC codes such as radiopharmaceuticals and blood products. These differences may be due to the fact that price increases are driven by the availability of clinically substitutable drugs in the same class or family of drugs, not simply by a shortage of a particular drug.

From the payer's perspective, increasing drug prices to address shortages results in additional financial burden. Analysis of the budget impacts indicates that various conditions affect price negotiation outcomes. Both the total expenditure scale and expected prices have increased since 2015, implying that shortages of high-expenditure drugs are becoming more prevalent. Although the total expenditure was higher for domestic companies, the average scale per drug was higher for multinational companies. This finding suggests that if the price of drugs from multinational companies increases more frequently, the total expenditure scale could increase more quickly. Although the total expenditure scale may be smaller, the average scale may be similar or even higher for EDs and ODs listed by the World Health Organization, thus, requiring careful consideration of the fiscal impact and patient safety when resolving drug shortages. This study confirmed that drugs for diseases in the ATC classification system had a significant impact on the total budget impact and the average value per drug, suggesting the need to proactively monitor and respond to price increases to resolve drug shortages in diseases with a relatively large budget impact. The factor that ultimately showed the most significant causal relationship among the various independent variables included in the multiple regression analysis was summarized as the introduction of the government's coverage-enhancing policy variable (period), the type of pharmaceutical supplier (company type), and the distribution of therapeutic agents for specific conditions (ATC code). Regression analysis confirmed that the rate of price increase was positively correlated with the price increase negotiations for drugs by multinational companies after 2015 and was particularly high for radioactive diagnostic agents (V) compared to other ATC codes. Conversely, this study found a negative relationship between the initial expenditure scale and rate of price increase, indicating that South Korea's price increase negotiation system for drugs is trying to prevent stockouts and reduce the impact on insurance finances.

Unlike administrative dispositions based on laws and regulations, negotiations involve a variety of decision-making factors, including the purchasing power of the parties, which are difficult to quantify with objective indicators. In the case of drug price negotiations, additional explanatory variables may include the foreign listing

**TABLE 3 Budget impact according to the variables.**

| Variables | | N | Initial budget | | | p | Increased budget | | | p | Final budget | | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sum | Mean | SD | | Sum | Mean | SD | | Sum | Mean | SD | |
| Period | Before 2015 | 134 | 187,199 | 1,248 | 4,214 | 0.002 | 42,826 | 320 | 615 | 0.001 | 230,025 | 1,717 | 4,839 | 0.001 |
| | After 2015 | 83 | 222,586 | 2,368 | 5,750 | | 57,489 | 693 | 1,391 | | 280,075 | 3,374 | 7,176 | |
| Company type | DM | 196 | 347,195 | 1,607 | 4,991 | 0.001 | 86,421 | 441 | 1,001 | 0.087 | 433,616 | 2,212 | 5,977 | 0.001 |
| | MN | 21 | 62,590 | 2,235 | 4,028 | | 13,894 | 662 | 1,002 | | 76,484 | 3,642 | 4,941 | |
| Essential drug | Non-ED | 125 | 256,319 | 1,792 | 4,992 | 0.025 | 54,496 | 436 | 846 | 0.003 | 310,815 | 2,487 | 5,778 | 0.028 |
| | ED | 92 | 153,465 | 1,519 | 4,747 | | 45,820 | 498 | 1,184 | | 199,285 | 2,166 | 6,056 | |
| Orphan drug | Non-OD | 198 | 363,959 | 1,701 | 5,061 | 0.130 | 95,867 | 484 | 1,040 | 0.059 | 459,826 | 2,322 | 6,041 | 0.184 |
| | OD | 19 | 45,826 | 1,528 | 3,475 | | 4,448 | 234 | 422 | | 50,274 | 2,646 | 4,143 | |
| ATC code | The rest | 21 | 92,196 | 3,842 | 7,257 | <0.001 | 10,120 | 482 | 763 | 0.001 | 102,316 | 4,872 | 8,142 | 0.004 |
| | J | 9 | 60,264 | 5,479 | 12,772 | | 14,361 | 1,596 | 3,055 | | 74,625 | 8,292 | 16,879 | |
| | N | 19 | 21,464 | 1,073 | 1,322 | | 13,670 | 719 | 995 | | 35,134 | 1,849 | 2,322 | |
| | A | 24 | 44,384 | 1,775 | 2,492 | | 10,343 | 431 | 473 | | 54,727 | 2,280 | 2,902 | |
| | B | 56 | 86,813 | 1,336 | 5,210 | | 11,297 | 202 | 476 | | 98,110 | 1,752 | 5,959 | |
| | V | 88 | 104,663 | 1,057 | 2,262 | | 40,524 | 461 | 884 | | 145,187 | 1,650 | 2,985 | |
| Total | | 217 | 409,785 | 1,679 | 4,894 | | 100,315 | 462 | 1,003 | | 510,100 | 2,351 | 5,900 | |

Note: The value of the budget variable was calculated in million KRW (US$ 1,200 = 1 mil. KRW).

**TABLE 4 Correlation analysis of ratio of price increase and budget impact.**

| Variables | Increased price ratio | Initial budget | Increased budget | Final budget |
|---|---|---|---|---|
| Ratio of price increase | 1 | | | |
| Initial budget | −0.129 | 1 | | |
| Increased budget | .196** | .703*** | 1 | |
| Final budget | −0.079 | .993*** | .784** | 1 |

*$p < .05$, **$p < 0.005$, ***$p < 0.001$.

status of the drug, the listed price, and the cost level (profit margin) that caused the shortage in Korea. However, since these variables cannot be accurately identified except by the pharmaceutical company that owns the product or the negotiating party, it is necessary for government agencies to conduct further public research from the perspective of system improvement.

It should be noted that drug shortages are also related to supply environment and economic factors. In terms of supply environment, shortages are more likely to occur in markets with a single generic manufacturer, so health authorities need to regularly monitor ingredients that are lacking in late entrants and motivate pharmaceutical companies to participate in generic development (Zhang et al., 2020). In addition, economic factors such as low margins, small market size, and rising costs of raw materials are also factors that lead to drug shortages (Shukar S et al., 2021). In particular, for drugs with low sales revenue, there is a threshold where pharmaceutical companies cannot be forced to supply, so the Korean price increase system discussed in this study has the potential to be a realistic alternative to resolve drug shortages. Despite these findings and interpretations, this study has several limitations. A comparative analysis of countries operating similar or identical systems can provide more generalizable findings. However, this study only deals with the South Korean system and its outcomes, necessitating further research with international comparisons. Furthermore, the regression model employed in this study, which uses the rate of price increase as the dependent variable, has limited explanatory power. This limitation likely arises owing to various factors affecting price negotiations between pharmaceutical companies and governments. Future research should incorporate more factors and cases to improve the explanatory power of this model. Finally, this study used estimated drug costs at the price increase negotiation phase as the final budget, which may differ from actual consumption and, thus, may have some error. Future research should provide more insights into patient accessibility and financial sustainability if the drug price increase negotiation system can further confirm the extent to which the actual drug costs match the initially expected drug costs.

As countries have different healthcare systems for drugs prone to shortages, it is essential to operate a suitable system in a timely

**TABLE 5 Multiple linear regression analysis of the ratio of price increase.**

| Variables | Full model | | | Stepwise model | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
| | β | t | VIF | β | t | β | t | β | t | β | t |
| (Constant) | | 12.553 *** | | | 40.820 *** | | 40.934 *** | | 39.658 *** | | 32.022 *** |
| Period = After 2015 | 0.245 | 3.287 ** | 1.362 | 0.275 | 4.200 *** | 0.295 | 4.527 *** | 0.297 | 4.585 *** | 0.286 | 4.438 *** |
| Company = MN | 0.177 | 2.621 ** | 1.111 | | | | | 0.138 | 2.143 * | 0.167 | 2.557 * |
| ED = ED | 0.125 | 1.412 | 1.913 | | | | | | | | |
| OD = OD | −0.027 | −0.344 | 1.561 | | | | | | | | |
| ATC = J | −0.055 | −0.709 | 1.453 | | | | | | | | |
| ATC = N | −0.027 | −0.300 | 1.978 | | | | | | | | |
| ATC = A | −0.089 | −0.950 | 2.159 | | | | | | | | |
| ATC = B | −0.105 | −0.902 | 3.318 | | | | | | | | |
| ATC = V | 0.122 | 0.956 | 3.981 | | | | | | | 0.144 | 2.189 * |
| Initial budget | −0.146 | −2.180* | 1.104 | | | −0.164 | −2.520 * | −0.174 | −2.685 * | −0.159 | −2.454 * |
| F(p) | 3.871*** | | | 17.644*** | | 12.218*** | | 9.812*** | | 8.688*** | |
| Adj. R2 | 0.117 | | | 0.072 | | 0.094 | | 0.109 | | 0.125 | |
| Durbin-Watson | 1.016 | | | 0.969 | | | | | | | |

*$p < .05$, **$p < 0.005$, ***$p < 0.001$.
Note: Dependent variable: ratio of price increase.
Reference group: Period*before 2015, Company*DM, ED*non-ED, OD*non-OD, ATC*the rest.

manner. International cooperation is crucial in addressing global drug shortages. The South Korean model of increasing reimbursement prices in public insurance for drugs at risk of shortages serves as an exemplary case for not only securing patient access but also considering budget management. Sharing these results can provide critical insights into proactive responses to international drug shortages. Ongoing research is warranted to explore various options for addressing drug shortages worldwide.

## Data availability statement

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

## Author contributions

SY: Writing–original draft, Writing–review and editing. JL: Writing–original draft, Writing–review and editing.

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# Xanthine oxidase inhibitors treatment or discontinuation effects on mortality: evidence of xanthine oxidase inhibitors withdrawal syndrome

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**Objectives:** This study investigates the impact of xanthine oxidase inhibitors (XOI) on mortality in patients with cardiovascular diseases. XOI withdrawal has been reported to increased mortality risk due to rapid adenosine triphosphate (ATP) deficiency. This study aims to determine whether XOI treatment reduces mortality and whether XOI withdrawal increases mortality.

**Methods:** This is a real-world database study using the Japanese Registry of All Cardiac and Vascular Diseases (J-ROAD). We analyzed 1,648,891 hospitalized patients aged 20–90 with acute coronary syndrome or heart failure. In the first study, mortality rates were compared between patients without urate-lowering agents (n = 1,292,486) and those with XOI agents (n = 315,388, excluding 41,017 on other urate-lowering agents). In the second study, mortality rates were compared between the XOI continuous medication group (n = 226,261) and the XOI withdrawal group (n = 89,127).

**Results:** After multiple adjustments, XOI treatment group showed significantly lower mortality compared with that without any urate-lowering agent (odds ratio (OR), 0.576, 95% confidence interval (CI), 0.567–0.587, $p < .001$). In the sub-analysis, the group with allopurinol (OR, 0.578; 95% CI, 0.557–0.600), febuxostat (OR, 0.610; 95% CI, 0.599–0.622), and topiroxostat (HR, 0.545; 95% CI, 0.473–0.628) showed lower OR of mortality compared with that without any urate-lowering agent. XOI withdrawal group led to significantly higher death rates compared to XOI continuous group (19.8% vs. 0.03%; $p < .001$).

**Conclusion:** XOI treatment for patients with cardiovascular diseases is associated with reduced mortality. Conversely, XOI withdrawal is linked to elevated mortality risk. This emphasizes the importance of both prescribing and discontinuing XOI carefully to optimize patient outcomes.

KEYWORDS

**xanthine oxidase, xanthine oxidase inhibitors, mortality, withdrawal syndrome, epidemiology, uric acid, hyperuricemia**

# Introduction

Uric acid, the end product of adenosine triphosphate (ATP) metabolism in humans, is influenced by xanthine oxidase (XO). XO inhibitors (XOI) suppress the production of uric acid and potentially store ATP (Kuwabara et al., 2023). XOI discontinuation has shown a XOI withdrawal syndrome with ATP depletion and increased mortality (Johnson et al., 2019; Ghang et al., 2020). Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial showed that febuxostat use is associated with increased cardiovascular-related death compared to allopurinol (White et al., 2018). However, the CARES showed that nearly 85% of deaths occurred while subjects were off of therapy (Bubb, 2019). The CARES sub-analysis found increased major adverse cardiovascular events (MACE) and cardiovascular death verse events were increased in the initial stage after discontinuation of febuxostat or allopurinol (Ghang et al., 2022). The FDA showed black-box warnings for febuxostat (Abeles and Pillinger, 2019), yet the febuxostat versus allopurinol streamlined trial (FAST), which had a low dropout rate, found no group differences in cardiovascular outcomes or death between the two groups (Mackenzie et al., 2020). These results suggest that the primary causes of MACE or death are associated with the withdrawal of XOI regardless of the type of XOI used. We hypothesize that the main cause of death is from XOI withdrawal by removing beneficial effects of XOI like reducing uric acid, reducing reactive oxygen species (ROS) and inflammation, or storing ATP (Feig et al., 2008; Johnson et al., 2019).

This study tests our hypothesis that oral XOI administration improves mortality, but discontinuation leads to excess deaths. This study analyzes inpatient data of acute coronary syndrome (ACS) or heart failure patients, a high-risk population, to compare mortality with and without XOI and XOI continuation and discontinuation. This investigation aims to shed light on the potential benefits of XOI administration and the risks associated with discontinuation in this vulnerable population.

# Materials and methods

## Study design and study subjects

This study retrospectively analyzed the Japanese Registry of All Cardiac and Vascular Diseases (J-ROAD) database, which is a nationwide registry collected by the Japanese Circulation Society (JCS). The database consists of all participating (associated) training hospitals in the JCS (Yasuda et al., 2016; Yasuda et al., 2018). The main diagnoses or comorbidities of each patient were coded using the International Classification of Disease and Related Health Problems 10th revision (ICD-10) codes. As no information specifying individuals was included, the requirement for informed consent was waived. This study complied with the principles of the Declaration of Helsinki regarding investigations in human subjects and was approved by the Toranomon Hospital Institutional Research Ethics Review Board (Approved number 2208).

We collected and analyzed the J-ROAD data from April 2014 to March 2020. The study consists of two studies. As the first study, we compared all-cause mortality in inpatient with ACS or heart failure at admission between with XOI and without any urate-lowering medication. In the sub-analysis of the first study, we checked each XOI (allopurinol, febuxostat, and topiroxostat) affects mortality. As the second study, we compared rate of death between XOI continuous group and withdrawal group.

## Patient involvement

No patients were involved in setting the research question or outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

## Inclusion and exclusion criteria

The J-ROAD database had 9,825,635 inpatients data from April 2014 to March 2020. We included inpatients aged between 20 and 90 years with ACS or heart failure at admission.

which ICD-10 code was I200, I21, I22, and I50. We showed the flow diagram of the study (Figures 1, 2).

## Statistical analysis

The statistically significant level was set at probability ($p$) < 0.05 (two sided). Data are expressed as mean ± standard deviation or as percent frequency unless otherwise specified. Comparisons between two groups were performed with student *t*-tests for normally distributed variables, and $\chi^2$ analyses for categorical data.

In the first study, we compared all-cause mortality between patients with XOI and without any urate-lowering agents. To analyze the factors associated with mortality, a multilevel mixed-effect logistic regression analysis using institution as a random intercept was performed. The factors associated with mortality were evaluated both by crude models (non-adjusted) and by adjusted multivariable models with age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, cancer, and XOI.

In the second study, we checked mortality by four group categories: 1) those who were on XOI at admission and continued XOI at discharge, 2) those who were on XOI at admission and discontinued XOI at discharge, 3) those who were not on XOI at admission (XOI was given during hospitalization) and continued XOI at discharge, and 4) those were not on XOI at admission (XOI was given during hospitalization) and discontinued XOI at discharge. We compared continuous XOI group including 1) and 3) and withdrawal group including 2) and 4) by $\chi^2$ analyses and calculate odds ratio.

Statistical analyses were performed using the SPSS Statistics software version 25 for Windows (IBM SPSS Statistics; IBM, New York, USA) and the Stata version 14.2 for Windows (StataCorp, College Station, TX, United States).

## Ethical considerations

We adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all subjects by a

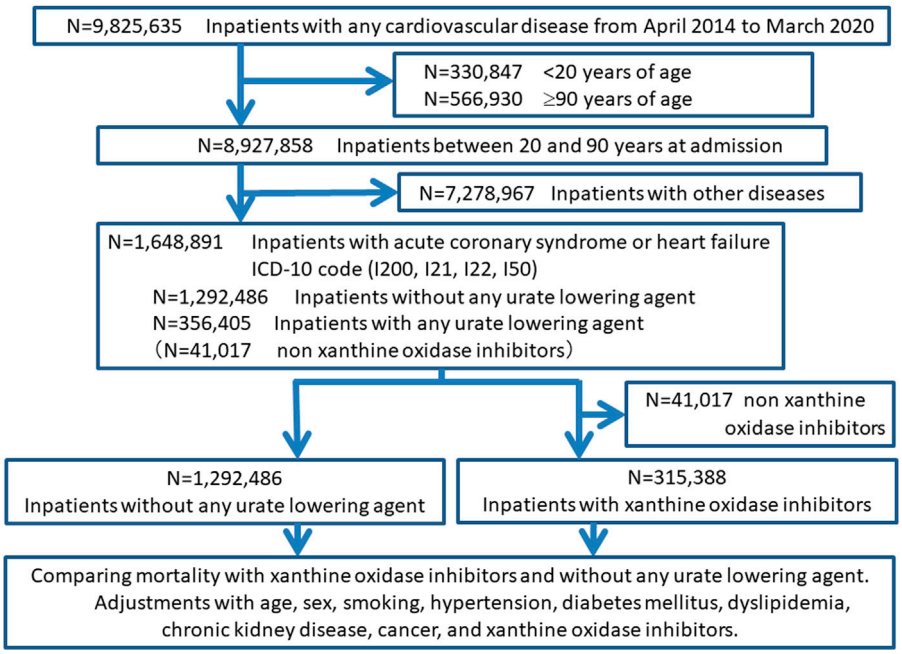


FIGURE 1
Flow diagram of the first study: xanthine oxidase inhibitors treatment and mortality.

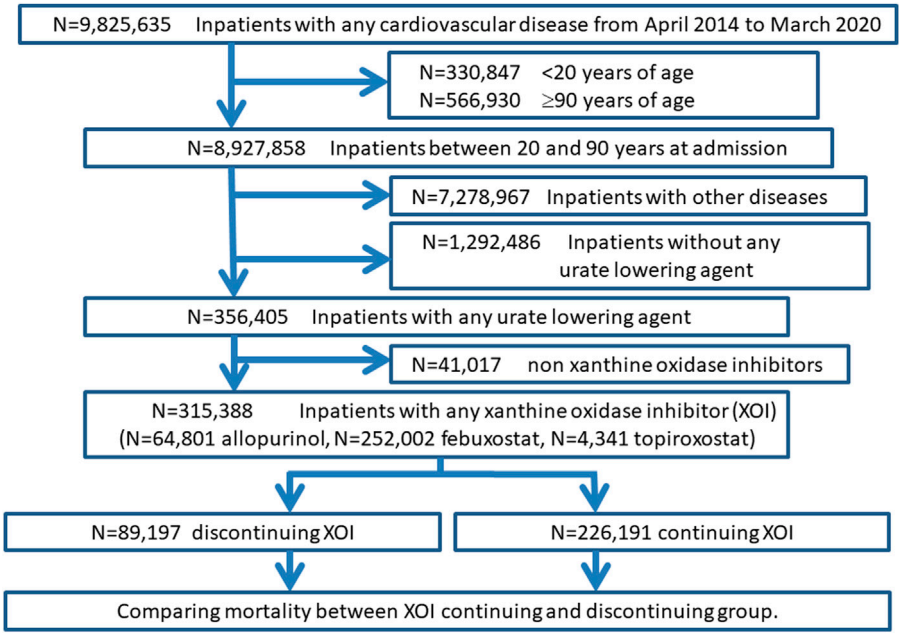


FIGURE 2
Flow diagram of the second study: xanthine oxidase inhibitors discontinuation and mortality.

comprehensive agreement method provided by St. Luke's International Hospital. All data were collected and compiled in a protected computer database. Individual data were anonymous without identifiable personal information. St. Luke's International Hospital Ethics Committee approved the protocol for this study.

# Results

## Demographics of this study subjects

Of 9,825,635 inpatients data in J-ROAD from April 2014 to March 2020, we included 8,927,858 inpatients out of excluding

**TABLE 1 Backgrounds of the study subjects.**

| | Total | Women | Men |
|---|---|---|---|
| Number of subjects | 1,648,891 | 587,229 | 1,061,662 |
| Age (years old) | 73.1 ± 11.9 | 77.2 ± 10.4 | 70.9 ± 12.2 |
| Smoking | 49.4% | 20.9% | 65.2% |
| Hypertension | 56.3% | 55.1% | 56.9% |
| Diabetes mellitus | 7.7% | 7.0% | 8.0% |
| Dyslipidemia | 37.0% | 31.6% | 40.0% |
| Hyperuricemia | 8.1% | 5.9% | 9.5% |
| Chronic kidney disease | 13.6% | 12.7% | 14.1% |
| Cancer | 5.1% | 4.4% | 5.4% |

330,847 inpatients younger than 20 years and 566,930 inpatients older than 90 years. Of those, we included 1,648,891 inpatients with ACS or heart failure. The backgrounds of the study subjects were shown in Table 1. We divided the inpatients into with urate-lowering agent (N = 356,405) and without any urate-lowering agent (N = 1,292,486). Finally, we compared mortality between 1,292,486 without urate-lowering agent and 315,388 with XOI agent after excluding 41,017 subjects with urate-lowering agent other than XOI.

## Xanthine oxidase inhibitors treatment and mortality

The number of patients with each XOI prescription was following: 64,801 allopurinol, 252,002 febuxostat, and 4,341 topiroxostat. The mortality of the whole patients of this study was 7.6%. The mortality of the study inpatient with allopurinol, febuxostat, and topiroxostat were 5.0%, 5.6%, and 4.8%, respectively, which were significantly lower than that without any urate-lowering agent.

After multivariable adjustments with age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and cancer, the group with XOI showed significantly lower odds ratio (OR) of mortality compared with that without any urate-lowering agent (OR, 0.576; 95% CI, 0.567–0.587; $p < .001$). In the sub-analysis, the group with allopurinol (OR, 0.578; 95% CI, 0.557–0.600; $p < .001$), febuxostat (OR, 0.610; 95% CI, 0.599–0.622; $p < .001$), and

**TABLE 2 Impact of xanthine oxidase inhibitors on prognosis.**

| | | Crude | | | Adjusted[a] | | |
|---|---|---|---|---|---|---|---|
| | | Odds ratio | 95% CI | p | Odds ratio | 95% CI | p |
| Age | Per 1 year increased | 1.048 | 1.047–1.049 | <0.001 | 1.043 | 1.042–1.042 | <0.001 |
| Women | Versus men | 1.211 | 1.197–1.226 | <0.001 | 1.027 | 1.021–1.041 | <0.001 |
| Smoking | Positive versus negative | 1.001 | 0.989–1.013 | 0.888 | 1.307 | 1.289–1.326 | <0.001 |
| Hypertension | Positive versus negative | 0.225 | 0.222–0.228 | <0.001 | 0.286 | 0.282–0.290 | <0.001 |
| Diabetes mellitus | Positive versus negative | 0.739 | 0.721–0.757 | <0.001 | 0.772 | 0.753–0.792 | <0.001 |
| Dyslipidemia | Positive versus negative | 0.173 | 0.170–0.176 | <0.001 | 0.266 | 0.261–0.272 | <0.001 |
| Chronic kidney disease | Positive versus negative | 1.413 | 1.391–1.435 | <0.001 | 1.263 | 1.242–1.284 | <0.001 |
| Cancer | Positive versus negative | 1.752 | 1.715–1.791 | <0.001 | 1.216 | 1.189–1.244 | <0.001 |
| XO inhibitors | Positive versus negative | 0.661 | 0.650–0.672 | <0.001 | 0.576 | 0.567–0.587 | <0.001 |
| Allopurinol[b] | Positive versus negative | 0.631 | 0.609–0.654 | <0.001 | 0.578 | 0.557–0.600 | <0.001 |
| Febuxostat[b] | Positive versus negative | 0.695 | 0.683–0.708 | <0.001 | 0.610 | 0.599–0.622 | <0.001 |
| Topiroxostat[b] | Positive versus negative | 0.582 | 0.507–0.669 | <0.001 | 0.545 | 0.473–0.628 | <0.001 |

XO, xanthine oxidase.

[a]Data adjusted for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, cancer, and XO, inhibitors.

[b]In the additional analysis, allopurinol, febuxostat, and topiroxostat were included in the analysis instead of XO, inhibitors.

topiroxostat (HR, 0.545; 95% CI, 0.473–0.628; $p < .001$) showed lower OR of mortality compared with that without any urate-lowering agent (Table 2).

## Xanthine oxidase withdrawal syndrome

Of 356,405 inpatients with any urate-lowering agent, 315,388 were on XOI (41,017 were on other urate-lowering agent). The XOI adherents were divided into the following four groups, and the number of deaths and mortality rates for each were identified as follows;

(1) those who were on XOI at admission and continued XOI at discharge: 219,020 patients, of which 59 deaths (0.03%), (2) those who were on XOI at admission and discontinued XOI at discharge: 89,035 patients, of which 17,663 deaths (19.84%), (3) those who were not on XOI at admission (XOI was given during hospitalization) and continued XOI at discharge: 7,241 patients, of which 11 deaths (0.15%), (4) those were not on XOI at admission (XOI was given during hospitalization) and discontinued XOI at discharge: 92 patients, of which 11 deaths (11.96%).

We compared rate of death between continuous medication group including (1) and (3) and withdrawal group including (2) and (4). The rate of death in XOI withdrawal group was 620 times higher than XOI continuous group (19.8% versus 0.03%; $p < .001$).

# Discussion

This study aimed to assess the prognostic impact of oral administration and discontinuation of XOI in patients hospitalized for ACS or heart failure. The findings revealed that hospitalized patients receiving XOI associated a 42% lower mortality rate compared to those without any urate-lowering agent. This trend was consistent across individual XOIs—allopurinol, febuxostat, and topiroxostat. The results suggest that XOI could reduce mortality regardless of the type of XOI used. Conversely, discontinuation of XOI was associated with a staggering 620-fold increase in mortality when compared to the group that continued XOI therapy. These results substantiate our hypothesis that XOI has intrinsic beneficial effects, while withdrawal negates these effects (Johnson et al., 2019). These results are compatible with some previous studies including the analyses of Medicare data or the United Kingdom Clinical Research Practice Datalink which indicated beneficial effects of allopurinol including reduced mortality in long-term studies (MacIsaac et al., 2016; Singh et al., 2017).

The suggested mechanisms underlying XOI's cardiovascular benefits encompass the mitigation of negative effects from ROS or hyperuricemia, as well as the positive effects of ATP augmentation (Feig et al., 2008; Kuwabara et al., 2018). The production of uric acid via XO generates ROS like superoxide or hydroxyl radical, which can be harmful to various cells and tissues. Therefore, inhibiting its generation with XOI could alleviate the consequences of ROS production. While uric acid possesses antioxidant properties in serum, it acts as a prooxidant molecule intracellularly. It activates a specific catalytic subunit of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, NOX4 (Lanaspa et al., 2012). In the endothelium, uric acid reduces the availability of nitric oxide, a vasodilator, leading to vascular endothelial damage and dysfunction, which contributes to the development of cardiovascular diseases (Kuwabara et al., 2018). While the ROS mechanisms require longer durations to manifest, Noman et al. demonstrated the prompt benefits of allopurinol over a mere 6-week period in stable chronic angina patients (Noman et al., 2010). This implies that XOI's positive impact becomes evident rapidly, and withdrawal promptly reverses these effects. ATP directly affects many organs including heart and its effects are rapid. Upon XOI cessation, the avoided deaths reappear by the lack of ATP particularly impacting the heart, leading to increased death in at-risk individuals. The notion of a "XOI withdrawal syndrome" is similar to withdrawal effects observed with cardiovascular risk-reducing medications like beta-blockers (Prins et al., 2015), a cornerstone in treatment for heart failure with reduced ejection fraction (McDonagh et al., 2021; Tsutsui et al., 2021; Heidenreich et al., 2022).

Although this study assessed all-cause mortality, detailed cause-specific mortality data were constrained by data limitations. Notably, dementia is a major contributor to poor mortality (Wolfson et al., 2001; Mitchell, 2015). Recent studies indicated a potential association between gout or hyperuricemia and dementia, suggesting higher uric acid levels was associate with lower prevalence of dementia (Scheepers et al., 2019; Min et al., 2021). Conversely, a meta-analysis unveiled a negative relationship between allopurinol exposure and dementia risk (Lai et al., 2022), implying allopurinol's protective effects. To delve into this, we undertook additional analyses to investigate XOI's potential link to dementia. The results demonstrated that the XOI group exhibited a significantly lower OR of dementia compared to the group without any urate-lowering agent, even after accounting for various factors (OR, 0.893; 95% CI, 0.874–0.912; $p < 0.001$) (Table 3). In the subgroup analysis, allopurinol and febuxostat demonstrated a similar trend, whereas topiroxostat did not attain statistical significance. Our results align with recent studies indicating that allopurinol and febuxostat were associated with a reduced risk of developing Alzheimer's disease or dementia (Singh and Cleveland, 2018; Fang et al., 2022). These findings lend support to our hypothesis suggesting that XOI might potentially contribute to dementia reduction through ATP storage (Figure 3).

Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART) study showed that treatment with allopurinol did not affect the risk of cardiovascular outcomes (Mackenzie et al., 2022). In the ALL-HEART study, the serum uric acid level in the allopurinol group was 0.34 mmol/L (5.7 mg/dL) at baseline and decreased to 0.18 mmol/L (3.0 mg/dL) after treatment. However, this study did not specifically assess the effects of hyperuricemia treatment due to its design. Additionally, the study experienced a high dropout rate, with 57.4% of participants in the allopurinol group withdrawing from the randomized treatment. The CARES trials showed that all-cause mortality and cardiovascular death was higher in febuxostat group compared with allopurinol group, (White et al., 2018), but a *post hoc* analysis revealed most deaths in the drug discontinuation group (Johnson et al., 2019). Given the results of our study, it raises

**TABLE 3 Impact of xanthine oxidase inhibitors on dementia.**

| | | Crude | | | Adjusted[a] | | |
|---|---|---|---|---|---|---|---|
| | | Odds ratio | 95% CI | p | Odds ratio | 95% CI | p |
| Age | Per 1 year increased | 1.149 | 1.148–1.151 | <0.001 | 1.136 | 1.134–1.138 | <0.001 |
| Women | Versus men | 2.516 | 2.475–2.558 | <0.001 | 1.462 | 1.440–1.496 | <0.001 |
| Smoking | Positive versus negative | 0.472 | 0.463–0.480 | <0.001 | 0.910 | 0.892–0.929 | <0.001 |
| Hypertension | Positive versus negative | 0.733 | 0.721–0.746 | <0.001 | 0.83 | 0.813–0.842 | <0.001 |
| Diabetes mellitus | Positive versus negative | 0.661 | 0.639–0.685 | <0.001 | 0.878 | 0.895–0.962 | <0.001 |
| Dyslipidemia | Positive versus negative | 0.407 | 0.399–0.416 | <0.001 | 0.624 | 0.607–0.635 | <0.001 |
| Chronic kidney disease | Positive versus negative | 1.021 | 0.998–1.045 | <0.001 | 0.92 | 0.896–0.941 | <0.001 |
| Cancer | Positive versus negative | 0.942 | 0.908–0.978 | <0.001 | 0.748 | 0.722–0.779 | <0.001 |
| XO inhibitors | Positive versus negative | 0.988 | 0.968–1.009 | <0.001 | 0.895 | 0.874–0.912 | <0.001 |
| Allopurinol | Positive versus negative | 0.82 | 0.784–0.858 | <0.001 | 0.789 | 0.754–0.826 | <0.001 |
| Febuxostat | Positive versus negative | 1.037 | 1.014–1.060 | <0.001 | 0.931 | 0.909–0.953 | <0.001 |
| Topiroxostat | Positive versus negative | 1.163 | 1.009–1.342 | 0.038 | 1.134 | 0.980–1.314 | 0.092 |

XO, xanthine oxidase.
[a]Data adjusted for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, cancer, and XO, inhibitors.
[b]In the additional analysis, allopurinol, febuxostat, and topiroxostat were included in the analysis instead of XO, inhibitors.

the possibility that there were more cardiovascular events in the group that withdrew allopurinol and fewer cardiovascular events in the group that continued allopurinol in the ALL-HEART study. Further analyses comparing the outcomes between the groups that continued and those that withdrew from the treatment are necessary. We hypothesize that in the ALL-HEART study, the group that continued medication may have experienced a reduction in events, while the discontinuation group saw an increase, leading to an overall non-significant difference in outcomes.

Our study has several limitations. First, we could not assess uric acid levels and a history of gouts from this database. Recently, a study showed that gout flares are associated with a transient increase in cardiovascular events especially within 120 days after gout flares (Cipolletta et al., 2022). The rate of gout in patients with XOI should be higher than those without any urate-lowering agent, and these groups were higher risk of cardiovascular disease. However, the better prognosis in the XOI group is a noteworthy result. Second, some of the deaths in the XOI discontinuation group were due to the fact that other medications were also discontinued, which indicates it is impossible to determine a direct causal relationship between XOI withdrawal and death. In addition, it is influenced by the fact that some patients tend to stop taking their medications prior to death. Therefore, we may overestimate the effects of XOI withdrawal syndrome. However, there are similar reports about XOI withdrawal syndrome, (Bubb, 2019; Johnson et al., 2019; Ghang et al., 2020; Ghang et al., 2022), and we should take care of discontinuing XOI. Third, we did not assess the impact of other medications, including those for ACS and heart failure. These medications can influence mortality, representing a limitation of this study. However, XOI has minimal confounding effects with other medicines, and we believe that our results remain reasonably acceptable. Fourth, our study has shown favorable outcomes in patients with hypertension, diabetes, and dyslipidemia, which may appear unreasonable. However, considering that the study specifically focused on patients hospitalized for cardiovascular diseases, these positive prognostic results could be attributed to the proper treatment provided to these patients. Fifth, due to the nature of this being a retrospective database study, we have been unable to obtain detailed information on the reasons for the initiation or discontinuation of medications and specific information on cardiovascular deaths. Previous studies have shown that XOI is often prescribed for asymptomatic hyperuricemia rather than for gout in Japan (Hakoda and Kasagi, 2019). Therefore, we assume that in this study, XOI was frequently used for treating asymptomatic hyperuricemia. Although detailed information on cardiovascular deaths would have been more informative, the available data on all-cause mortality still provide valuable insights into the XOI

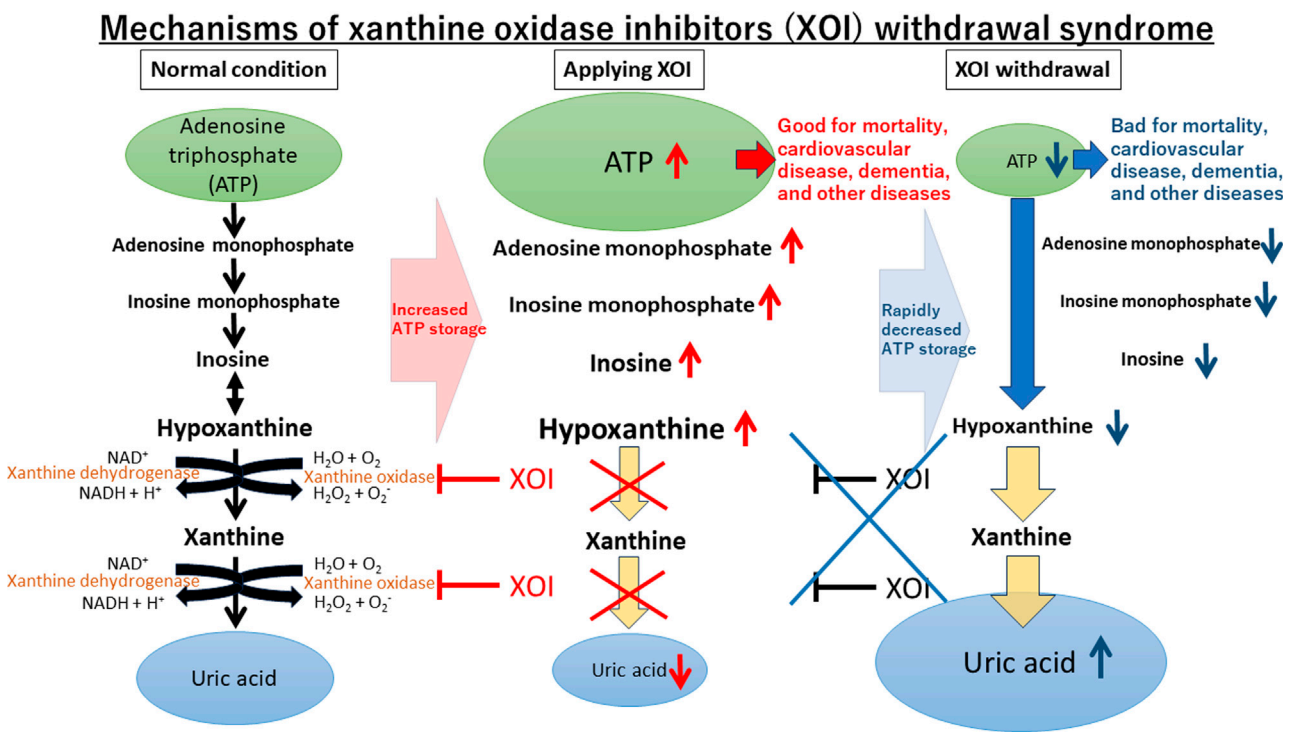


FIGURE 3
Mechanisms of xanthine oxidase inhibitors (XOI) withdrawal syndrome.

withdrawal syndrome observed in this study. Sixth, this study included patients admitted with ACS or heart failure, recognizing that many cases were complex and involved multiple conditions. Although a sub-analysis for each disease would be valuable, the complexity and overlapping nature of these diseases often make isolated analysis difficult in this database. Further research focused on individual diseases is needed. Finally, it is important to acknowledge that our study is limited in its scope, as it exclusively evaluated Japanese population. To assess generalizability, similar studies should be conducted with other populations. In Japan, insurance covers urate-lowering drugs for hyperuricemia, and the concept of treatment for hyperuricemia may differ from that in other countries.

In conclusion, our study found that inpatients with ACS or heart failure receiving XOI treatment exhibited favorable mortality outcomes. On the other hand, XOI withdrawal was associated with a significantly higher risk of death, indicating the presence of XOI withdrawal syndrome. These findings emphasize the importance of not only prescribing XOI medication but also carefully considering the withdrawal process to optimize patient outcomes.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The data underlying this article were provided by the Japanese Circulation Society by permission. Data will be shared on request to the corresponding author with permission of the Japanese Circulation Society. Requests to access these datasets should be directed to J-ROAD Secretariat, dpc-jroad@ml.ncvc.go.jp.

## Ethics statement

The studies involving humans were approved by the Toranomon Hospital Institutional Research Ethics Review Board (Approved number 2208). The studies were conducted in accordance with the local legislation and institutional requirements. The requirement for written informed consent from participants or their legal guardians/next of kin was waived, as this study utilizes an anonymized database.

## Author contributions

MK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. MN: Data curation, Formal Analysis, Methodology, Software, Supervision, Validation, Writing–review and editing. YS: Data curation, Methodology, Software, Writing–review and editing. YI: Data curation, Methodology, Software, Writing–review and editing. RA: Investigation, Project administration, Supervision, Writing–review and editing. TK: Investigation, Supervision, Writing–review and editing. IH: Investigation, Methodology, Project administration, Supervision, Writing–review and editing.

NK: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing–review and editing.

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## Conflict of interest

Author NK works as the Chairman of StaGen Co., Ltd.

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

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## Publisher's note



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# Impact of early heparin therapy on mortality in critically ill patients with sepsis associated acute kidney injury: a retrospective study from the MIMIC-IV database

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**Background:** Inflammatory-coagulation dysfunction plays an increasingly important role in sepsis associated acute kidney injury (SAKI). This study aimed to investigate whether early heparin therapy improves survival in patients with SAKI.

**Methods:** Patients with SAKI were identified from the Medical Information Mart for Intensive Care-IV database. The patients were divided into two groups: those who received heparin subcutaneously within 48 h after intensive care unit (ICU) admission and the control group, who received no heparin. The primary endpoint was ICU mortality, the secondary outcomes were 7-day, 14-day, 28-day, and hospital mortality. Propensity score matching (PSM), marginal structural Cox model (MSCM), and E-value analyses were performed.

**Results:** The study included 5623 individuals with SAKI, 2410 of whom received heparin and 3213 of whom did not. There were significant effects on ICU and 28-day mortality in the overall population with PSM. MSCM further reinforces the efficacy of heparin administration reduces ICU mortality in the general population. Stratification analysis with MSCM showed that heparin administration was associated with decreased ICU mortality at various AKI stages. Heparin use was also associated with reduced 28-day mortality in patients with only female, age >60 years, and AKI stage 3, with HRs of 0.79, 0.77, and 0.60, respectively ($p < 0.05$). E-value analysis suggests robustness to unmeasured confounding.

**Conclusion:** Early heparin therapy for patients with SAKI decreased ICU mortality. Further analysis demonstrated that heparin therapy was associated with reduced 28-day mortality rate in patients only among female, age > 60 years and AKI stage 3.

KEYWORDS

**heparin, sepsis-associated acute kidney injury, outcome, mortality, marginal structural Cox model**

# Introduction

Sepsis is a life-threatening syndrome characterized by organ dysfunction, including acute kidney injury (AKI), caused by dysregulation of a patient's response to infection (Koyner, 2021). Studies have shown that the incidence of sepsis associated acute kidney injury (SAKI) ranges from 11% to 64% (Parmar et al., 2009). In a study involving 1177 patients with sepsis in 198 intensive care units in 24 European countries, the incidence of AKI was 51% and the mortality rate was 41% (Vincent et al., 2006). In a retrospective analysis of 146,148 patients in China, the incidence of SAKI was 47.1% (Xu et al., 2015). Other studies have reported a mortality rate of 67%–70.2% in patients with SAKI (Bagshaw et al., 2007; Oppert et al., 2008). SAKI is associated with poor outcomes compared with non-SAKI (Romanovsky et al., 2014), including a significant increase in in-hospital mortality and prolonged intensive care unit (ICU) and hospital length of stay (Bagshaw et al., 2007). The development of AKI predicts a higher mortality rate and consumes a large amount of medical resources, causing great pressure on human and social healthcare.

The inflammatory reaction in the early stage of sepsis can activate the coagulation system, initiate the coagulation cascade reaction, and cause extensive microthrombosis in blood vessels, microvascular disorders, tissue hypoxia, and ischemia, leading to multiple organ dysfunction syndrome (MODS). Heparin is a sulfated polysaccharide polymer that can affect both endogenous and exogenous coagulation pathways. The purpose of anticoagulation therapy in sepsis is to restore the balance between inflammation and coagulation without interfering with the immune defense ability of the body against infection (Semeraro et al., 2015). Many studies have confirmed the therapeutic effects of heparin in sepsis, including the regulation of inflammatory reactions by antagonizing histones (Wildhagen et al., 2014), inhibiting the generation of inflammatory factors (Harada et al., 2006), immune regulation, and vascular protection (Eggimann et al., 2003). Study by Huang and colleagues revealed that heparin administration was also associated with decreased ICU mortality in patients with an SIC score of 4 (HR 0.63, 95% CI 0.45-0.89) (Huang et al., 2023). Whether heparin therapy is associated with reduced mortality in SAKI patients remains controversial. In this retrospective cohort study, we used the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to assess the effectiveness of early heparin in patients with SAKI after ICU admission and to estimate the timing and dosing of heparin.

# Materials and methods

## Data source and study design

We performed a retrospective cohort study using data from the MIMIC-IV (version 1.0), which includes two in-hospital database systems: a custom hospital-wide electronic health record (EHR) and ICU-specific clinical information including de-identified, comprehensive clinical data of patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019. An individual who has completed the Collaborative Institutional Training Initiative examination (Certification number: 39057014 for author Zhi-peng Zhou) can access the database.

## Participants

There were 382278 patients from the MIMIC-IV database.The inclusion criteria met the definition of Sepsis 3.0 criteria, which was defined as a suspected infection combined with an acute increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 (Singer et al., 2016) and AKI, which was stipulated in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Ostermann et al., 2020) and MIMIC-IV database to define AKI stages. The exclusion criteria were as follows: age <18 years, ICU stay < 24 h, acquired immune deficiency syndrome, malignant cancer, chronic kidney disease, hepatic failure, use of heparin for dialysis or treatment, use of warfarin and low molecular weight heparin (LMWH), and patients admitted to the ICU more than once. We only included the first ICU admission data from the first hospital stay among patients admitted to hospital multiple times.

## Research procedures and definitions

Data were extracted from MIMIC-IV using Structured Query Language (Jamison, 2003) with Navicat Premium (version 15.0.12) and consisted of age, sex, weight, history of disease (Hypertension, Diabetes, Chronic heart disease, Chronic pulmonary disease), vital signs (heart rate, mean arterial pressure (MAP), respiratory rate, temperature, and oxygen saturation ($SPO_2$), laboratory results [white blood cell (WBC) count, platelet count, hemoglobin, International Normalized Ratio (INR), partial thromboplastin time (PTT), and prothrombin time (PT)], acute kidney injury (AKI) stage (within 48h of ICU admission), vasopressor use, mechanical ventilation use, sepsis-induced coagulation (SIC), sequential organ failure assessment (SOFA) score, Simplified

Acute Physiology Score II (SAPS II), length of hospital stay, and length of ICU stay.

Laboratory variables of PTT were measured during the ICU stay. The chart times for the measurements and physiological values were extracted from the database. For patients with multiple measurements, the highest daily PTT value was included in the analysis for patients with multiple measurements. None of the screening variables had missing data rates exceeding 5% (Supplementary Table S1). We used the methods of previous studies to analyze this database (sepsis and sepsis-associated acute kidney injury) and analyzed the extracted patient data (Zou et al., 2022).

## Exposure and outcomes

The patients were divided into two groups: the heparin group, comprising patients who received heparin subcutaneously at preventive doses at least once in the ICU, and the control group, comprising patients who received no heparin in the ICU.The primary outcome was ICU mortality. The secondary outcomes included the 7-day, 14-day, 28-day, and in-hospital mortality rates.

## Statistical analysis

The study population was categorized into heparin (intervention) and non-heparin (control) groups according to heparin treatment status during the entire ICU stay, and categorical variables were expressed as percentages. Heparin and non-heparin groups were compared using the Chi-square or Fisher's exact test, as appropriate. Continuous variables are expressed as mean (standard deviation) or median [interquartile range (IQR)], as appropriate.

Propensity score matching (PSM) was used to account for baseline differences in the probability of receiving heparin (Zhang et al., 2019). PSM measures the probability of a patient being assigned to heparin treatment. In PSM analysis, the heparin group received heparin during the entire ICU stay. Patients in the treatment group were matched to those with untreated patients using nearest-neighbor matching. The standardized mean difference (SMD) was calculated before and after matching to examine whether PSM reduced the differences in pretreatment covariates between the treatment and control groups. Finally, a COX regression model was used to adjust for residual imbalance by including parameters with $p < 0.05$ and potential confounding judged by clinical expertise.

The dose-response relationship between subcutaneous heparin and ICU mortality was also explored by categorizing heparin into subclasses by daily dose (non-heparin, ≤ 5000IU, 5000-7500IU, 7500-10000IU, 10000-12500IU). We also explored the potential for unmeasured confounding between early prophylactic heparin prescriptions and mortality by calculating E-values (Haneuse et al., 2019). The E-value quantifies the required magnitude of an unmeasured confounder that can negate the observed association between heparin therapy and mortality.

Heparin treatment during ICU stay was considered a time-dependent variable in the marginal structural Cox model (MSCM). Potential baseline confounders, such as age, gender, weight, AKI stage, hypertension, diabetes, chronic heart disease, chronic pulmonary disease, vasopressor use, use of mechanical ventilation, SIC, SOFA, and SAPSII, were obtained on day 1 after ICU admission. APTT during the entire ICU stay was included in the model as a time-varying confounding factor, and the parameters of MSCM could be estimated using inverse probability weighting (IPW) to correct for confounding and forms of selection bias such as informative censoring (Robins et al., 2000). By weighting each patient by IPW, two pseudo-populations were created, similar to the baseline and time-dependent confounding factors and different in heparin exposure.

Stratification analysis was conducted to explore whether heparin administration and ICU or 28-day mortality differed across the various subgroups classified by gender, age, SIC, SOFA, vasopressor usage, mechanical ventilation, and AKI stage; two-tailed $p$ values < 0.05 were considered statistically significant. All statistical analyses were performed using R 4.2.1 software for Windows.

# Results

## Patient characteristics on the baseline

The initial search identified 382,278 ICU admissions from the MIMIC-IV database. In total 19,104 patients met the inclusion criteria. After excluding patients who met the exclusion criteria, 5623 eligible patients were enrolled. A total of 2410 patients were administered heparin at least once in the ICU and 3213 patients did not receive heparin treatment (Figure 1). There were no significant differences between the two groups in terms of age, Hypertension, Diabetes, Chronic heart disease, or SOFA score ($p > 0.05$). The proportion of men, percentage of patients with a history of vasopressor use, SIC,weight, $SPO_2$, WBC count, PT, APTT, and maximum INR were lower in the heparin group than in the non-heparin group ($p < 0.05$). However, Chronic pulmonary disease, mechanical ventilation use, heart rate, MAP, respiratory rate, temperature, hemoglobin level, minimum platelet count, SAPS II score, hospital stay, and ICU stay were higher in the early heparin group than in the non-heparin group ($p < 0.05$) (Table 1). After PSM, 3,374 patients were enrolled, with 1,687 in each group, except for vasopressor use and ICU stay, and the SMDs of other variables were <0.1, indicating that the baseline variables in the two groups had similar distributions (Table 1; Supplementary Figure S1).

# Outcomes

## Propensity score analysis on primary and secondary outcomes

The prematched crude ICU mortality rate was higher in patients with heparin use than in those without heparin use (11.7% vs. 11.0%, hazard ratio (HR) 0.53, 95% confidence interval (CI) [0.45-0.62] $p < 0.001$). However, after PSM, heparin was associated with reduced ICU mortality (11.7% vs. 14.6%, HR 0.75, 95% CI [0.62-0.92], $p = 0.005$) (Table 2). The 28-day

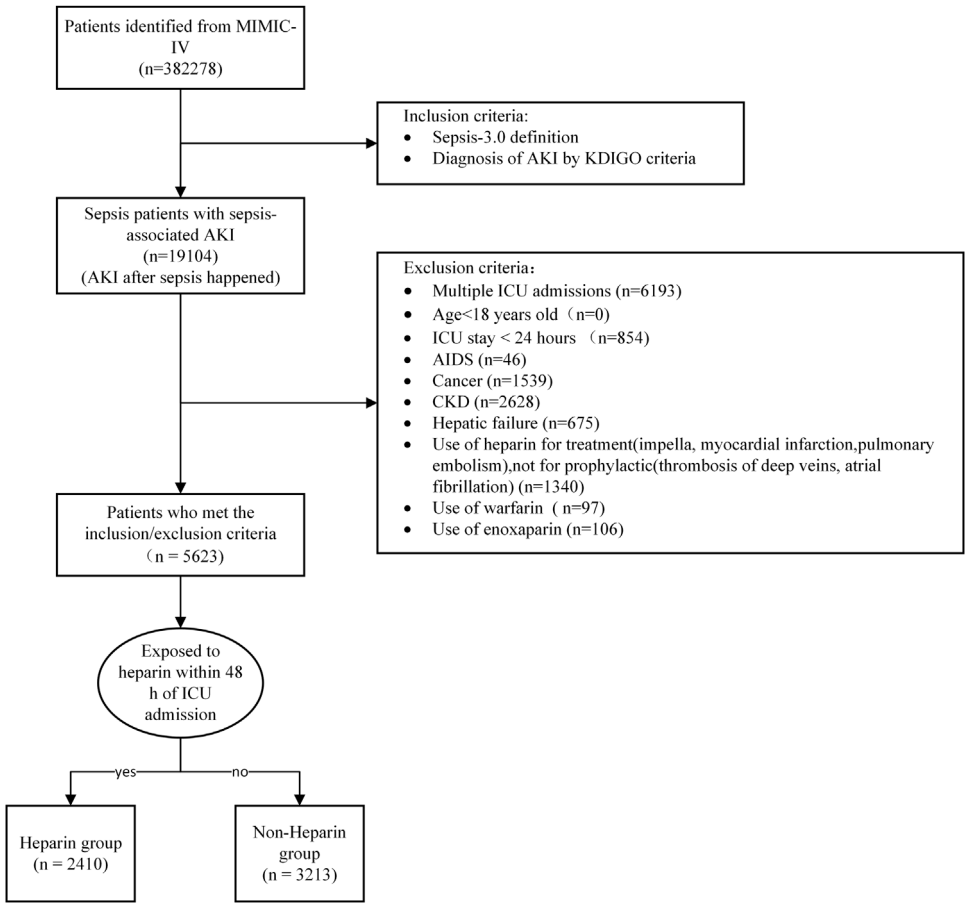


FIGURE 1
Flow chart of patient selection. Abbreviations:AKI, Acute Kidney Injury; KDIGO, Kidney Disease: Improving Global Outcomes; ICU, Intensive Care Unit; AIDS, Acquired immunodeficiency syndrome; CKD, Chronic Kidney Disease.

mortality rate in the heparin group was lower than that in the non-heparin group after PSM (postmatched 14.0% vs. 17.4%, HR 0.74, 95% CI [0.59-0.95], $p = 0.016$), and there was no significant difference in 7-day and 14-day and hospital mortality rates between the two groups ($p > 0.05$) (Table 2). Stratification analysis showed an effect only among AKI stage 3 in the primary and secondary outcomes after PSM (Table 3).

## Marginal structural cox model and stratification analysis for ICU mortality

Time-varying confounding and heparin treatments were included in the MSCM. The MSCM results showed that heparin administration was associated with significantly improved ICU mortality (HR 0.53, 95% CI 0.44-0.63, $p < 0.001$) in the overall population (Figure 2). Stratification analysis with MSCM further showed that heparin administration was associated with decreased ICU mortality at different AKI stages, regardless of gender, age, mechanical ventilation, sequential organ failure assessment (SOFA) score, and history of SIC and vasopressor use (Figure 2).

## Logistic regression model and stratification analysis of the 28-day mortality

Kaplan-Meier curves showed a significant difference between heparin use and non-heparin use after PSM ($p < 0.05$) (Figure 3A). Subgroup analysis showed that heparin use was significantly associated with reduced 28-day mortality in patients with only female, age >60 years, sepsis-induced coagulopathy (SIC), non-vasopressor use, mechanical ventilation, AKI stage 3, and SOFA score ≥ 8, with HRs of 0.79, 0.77, 0.70, 0.58, 0.70, 0.60, and 0.63, respectively ($p < 0.05$) (Figure 3B).

## Curve fitting and subgroup analysis

There was a nonlinear relationship between heparin therapy and ICU mortality with curve fitting (Supplementary Figure S2). The outcomes also showed that receiving 10000–12500 IU a day in patients with AKI stage 1, 2, and 3 was associated with decreased risk of ICU mortality as compared with the non-heparin group, similar outcomes were showed for receiving 12500–15000 IU a day in patients with AKI stage 1 and 3. For receiving less than 5000 IU,

TABLE 1 Baseline characteristics of patients with s sepsis-associated acute kidney injury before and after propensity score matching.

| Characteristics | All cohort | Propensity score matching | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | | | | After | | | |
| | | No heparin (n = 3213) | Heparin (*n* = 2410) | *p*-value | SMD | No heparin (*n* = 1687) | Heparin (*n* = 1687) | *p*-value | SMD |
| Gender, male,n(%) | 3171 (56.4) | 1973 (61.4) | 1198 (49.7) | <0.001 | 0.237 | 866 (51.3) | 886 (52.5) | 0.513 | 0.024 |
| Age (yr),median(IQR) | 67.96 (56.69,79.27) | 68.19 (57.89,78.04) | 67.47 (54.69,80.69) | 0.723 | 0.040 | 68.37 (56.25,79.74) | 68.18 (54.78,81.06) | 0.872 | 0.009 |
| Weight (kg),median(IQR) | 84.00 (70.00,99.00) | 85.00 (71.20,98.70) | 82.70 (69.00,100.00) | 0.042 | 0.016 | 84.85 (69.75,100.00) | 82.25 (68.50,99.50) | 0.226 | 0.011 |
| Hypertension,n(%) | 3412 (60.7) | 1934 (60.2) | 1478 (61.3) | 0.404 | 0.023 | 1016 (60.2) | 1019 (60.4) | 0.944 | 0.004 |
| Diabetes,n(%) | 1580 (28.1) | 913 (28.4) | 667 (27.7) | 0.562 | 0.016 | 478 (28.3) | 465 (27.5) | 0.645 | 0.017 |
| Chronic heart disease,n(%) | 369 (6.6) | 221 (6.9) | 148 (6.1) | 0.294 | 0.030 | 107 (6.3) | 107 (6.3) | 1.000 | <0.001 |
| Chronic pulmonary disease,n(%) | 1365 (24.3) | 703 (21.9) | 662 (27.5) | <0.001 | 0.130 | 435 (25.8) | 428 (25.4) | 0.813 | 0.010 |
| Heart rate (bpm) | 85 (77,96) | 84 (77,93) | 87 (77,99) | <0.001 | 0.181 | 86 (77,98) | 86 (76,98) | 0.766 | 0.011 |
| MAP (mmHg) | 77 (73,83) | 77 (73,82) | 78 (73,86) | <0.001 | 0.219 | 78 (73,85) | 78 (72,85) | 0.224 | 0.030 |
| Respiratory rate (bpm) | 19 (17,22) | 18 (16,21) | 19 (17,22) | <0.001 | 0.265 | 19 (17,22) | 19 (17,22) | 0.654 | 0.026 |
| Temperature (°C) | 36.90 (36.62,37.22) | 36.88 (36.61,37.13) | 36.92 (36.63,37.32) | <0.001 | 0.153 | 36.90 (36.65,37,26) | 36.90 (36.63,37.30) | 0.708 | 0.007 |
| Spo2 (%) | 98 (96,99) | 98 (96,99) | 97 (96,99) | 0.006 | 0.090 | 97 (96,99) | 97 (96,99) | 0.404 | 0.001 |
| WBC ($10^3$/μl) (IQR) | 14.90 (11.20,19.50) | 15.20 (11.70,19.40) | 14.40 (10.60,19.50) | <0.001 | 0.079 | 14.80 (11.10,19.10) | 14.50 (10.70,19.60) | 0.416 | 0.010 |
| Hemoglobin (g/L) (IQR) | 10.00 (8.60,11.40) | 9.70 (8.40,11.00) | 10.30 (8.90,12.00) | <0.001 | 0.312 | 10.20 (8.70,11.70) | 10.20 (8.70,11.70) | 0.766 | 0.018 |
| Minimum platelet ($10^3$/μl) (IQR) | 160 (116,218) | 147 (109,195) | 182 (129,242) | <0.001 | 0.365 | 174 (127,227) | 171 (119,229) | 0.166 | 0.043 |
| PT(s) (IQR) | 14.90 (13.20,17.20) | 15.20 (13.60,17.20) | 14.30 (12.70,17.20) | <0.001 | 0.172 | 14.50 (13.00,17.20) | 14.70 (12.90,17.20) | 0.403 | 0.034 |
| APTT(s) (IQR) | 32.10 (28.20,37.70) | 32.30 (28.50,38.40) | 31.80 (27.70,37.50) | 0.001 | 0.041 | 31.40 (27.60,37.50) | 32.30 (27.90,37.50) | 0.047 | 0.009 |
| Maximum INR (IQR) | 1.30 (1.20,1.60) | 1.40 (1.20,1.60) | 1.30 (1.10,1.60) | <0.001 | 0.179 | 1.30 (1.20,1.60) | 1.30 (1.20,1.60) | 0.835 | 0.029 |
| Vasopressor,n (%) | 3304 (58.8) | 2069 (64.4) | 1235 (51.2) | <0.001 | 0.269 | 817 (48.4) | 913 (54.1) | 0.001 | 0.114 |
| Ventilation,n (%) | 3397 (60.4) | 1889 (58.8) | 1508 (62.2) | 0.004 | 0.077 | 991 (58.7) | 1028 (60.9) | 0.206 | 0.045 |
| SIC,n (%) | 2709 (48.2) | 1811 (56.4) | 898 (37.3) | <0.001 | 0.390 | 688 (40.8) | 728 (43.1) | 0.174 | 0.048 |
| AKI stage,n (%) | | | | <0.001 | 0.215 | | | 0.978 | 0.007 |
| 1 | 1908 (33.9) | 1200 (37.3) | 708 (29.4) | | | 529 (31.3) | 534 (31.6) | | |

(Continued on following page)





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TABLE 1 (*Continued*) Baseline characteristics of patients with s sepsis-associated acute kidney injury before and after propensity score matching.

| Characteristics | All cohort | Propensity score matching | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | | | | After | | | |
| | | No heparin (n = 3213) | Heparin (*n* = 2410) | *p*-value | SMD | No heparin (*n* = 1687) | Heparin (*n* = 1687) | *p*-value | SMD |
| 2 | 2999 (53.3) | 1684 (52.4) | 1315 (54.6) | | | 914 (54.1) | 912 (54.0) | | |
| 3 | 716 (12.8) | 329 (10.2) | 387 (16.1) | | | 245 (14.5) | 242 (14.3) | | |
| SOFA score median (IQR) | 5 [4,7] | 5 [4,7] | 5 [3,8] | 0.985 | 0.013 | 5 [3,8] | 5 [4,8] | 0.112 | 0.021 |
| SAPS II score median (IQR) | 37[30,47] | 36[29,45] | 39[31,49] | <0.001 | 0.170 | 39[30,49] | 39[30,48] | 0.740 | 0.029 |
| Hospital stays (d) median (IQR) | 8.00[5.12,13.79] | 6.70[4.84,10.83] | 10.27[6.30,17.28] | <0.001 | 0.354 | 7.62[5.00,13.91] | 9.22[5.82,15.13] | <0.001 | 0.050 |
| ICU stays (d) median (IQR) | 2.88[1.63,5.85] | 2.17[1.31,3.76] | 4.54[2.49,8.61] | <0.001 | 0.558 | 2.84[1.66,5.79] | 3.94[2.22,6.89] | <0.001 | 0.124 |
| Heparin (U) median (IQR) | NA | NA | 10000[7500,11562] | | | NA | 10000[7000,11363] | | |

Abbreviations: IQR, interquartile range; MAP, mean arterial pressure; $SPO_2$, oxygen saturation; WBC, white blood cells; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; SIC, sepsis-induced coagulopathy; AKI, acute kidney injury; SOFA, sequential organ failure assessment; SAPS II, Simplified Acute Physiology Score II; ICU, intensive care unit; NA, not applicable.



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TABLE 2 Association between heparin use and clinic outcomes in patients with SAKI.

| Outcomes n (%) | Propensity score matching cohort (*n* = 3374) | | | | All eligible for propensity score (*n* = 5623) | | | |
|---|---|---|---|---|---|---|---|---|
| | No heparin *n* = 1687 | Heparin *n* = 1687 | Matched HR (95%)[a] | *p* value | No heparin n = 3213 | Heparin n =2410 | Adjusted HR (95%CI)[b] | *p* value |
| Primary | | | | | | | | |
| ICU mortality | 247(14.6) | 197(11.7) | 0.75(0.62,0.92) | 0.005 | 352(11.0) | 282(11.7) | 0.53(0.45,0.62) | <0.001 |
| Secondary | | | | | | | | |
| 7-day mortality | 314(12.4) | 206(9.2) | 0.81(0.58,1.13) | 0.209 | 384(12.0) | 120(5.0) | 0.95(0.71,1.26) | 0.710 |
| 14-day mortality | 261(15.5) | 208(12.3) | 0.76(0.58,1.00) | 0.051 | 375(11.7) | 287(11.9) | 0.95(0.75,1.20) | 0.647 |
| Hospital mortality | 289(17.1) | 241(14.3) | 0.85(0.71,1.02) | 0.073 | 405(12.6) | 344(14.3) | 0.78(0.67,0.90) | 0.001 |
| 28-day mortality | 293(17.4) | 237(14.0) | 0.74(0.59,0.95) | 0.016 | 413(12.9) | 339(14.1) | 0.93(0.76,1.14) | 0.492 |

Abbreviations: ARR, absolute risk reduction; HR, hazard ratio; SAKI, sepsis associated acute kidney injury.
[a]Results of univariable analysis of propensity score matched cohort.
[b]Adjusted results obtained from the multivariable Cox proportional hazards regression model that included the full cohort.

TABLE 3 Primary and secondary outcomes of sepsis-associated acute kidney injury stages.

| Outcomes | HR (95%CI) *p*-value | | |
|---|---|---|---|
| | Stage 1 (*n* = 1037) | Stage 2 (*n* = 1834) | Stage 3 (*n* = 503) |
| Primary | | | |
| ICU mortality | 0.60(0.39,0.93)0.022 | 0.77(0.57,1.04)0.083 | 0.59(0.40,0.88)0.009 |
| Secondary | | | |
| 7-day mortality | 0.61(0.37,1.01)0.054 | 0.90(0.63,1.28)0.543 | 0.33(0.14,0.78)0.011 |
| 14-day mortality | 0.68(0.43,1.06)0.086 | 0.87(0.63,1.19)0.371 | 0.37(0.18,0.73)0.005 |
| Hospital mortality | 0.83(0.58,1.21)0.346 | 0.86(0.65,1.12)0.259 | 0.68(0.50,0.94)0.018 |
| 28-day mortality | 0.78(0.52,1.18)0.236 | 0.81(0.60,1.10)0.174 | 0.40(0.21,0.74)0.004 |

Abbreviations: ICU, intensive care unit;HR, hazard ratio; CI, confidence interval.

5000–7500 IU and 7500–10000 IU a day, there was no significant difference in ICU mortality as compared with the non-heparin group ($p > 0.05$) (Table 4).

## Sensitivity analysis

Significant known and measured risk factors for ICU mortality after PSM within the multivariable Cox-proportional hazard model included age (HR, 1.01 [95%CI,1.01-1.02]), heart rate(HR, 1.01 [95%CI,1.00-1.01]), respiratory rate (HR, 1.10 [95%CI,1.08-1.12]), WBC(HR, 1.02 [95%CI,1.01-1.03]), PT(HR, 1.02 [95%CI,1.01-1.02]), APTT(HR, 1.01 [95%CI,1.00-1.02]), INR(HR, 1.14 [95%CI,1.10- 1.19]), vasopressor use (HR, 1.94 [95%CI,1.55-2.42]), mechanical ventilation use(HR, 1.19 [95%CI,0.94-1.50]), SIC (HR, 1.67 [95%CI, 1.39-2.01]), SAPSII (HR, 1.04 [95%CI,1.04-1.05]), SOFA (HR, 1.14 [95%CI,1.11-1.16]) (Supplementary Table S2).

We generated an E-value to assess the sensitivity to unmeasured confounding factors (https://www.evalue-calculator.com/evalue/). The primary findings were robust, unless an unmeasured confounder existed with a lower relative risk of ICU mortality, with an HR > 2.00 (upper limit 3.00), meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association >2.00 with both ICU mortality and prophylactic heparin prescriptions. Therefore, it is unlikely that an unmeasured or unknown confounder would have a substantially greater effect on ICU mortality (relative risk > 2.00) than known risk factors.

# Discussion

Our results showed that early heparin therapy improved the survival outcomes of patients with SAKI. Stratification analysis with MSCM showed that heparin administration was associated with decreased ICU mortality in different AKI stages, regardless of gender, age, mechanical ventilation, SOFA score, and the use of SIC and vasopressors. Heparin use was also significantly associated with reduced 28-day mortality in the logistic regression model in female patients, age >60 years, SIC, non-vasopressor use, mechanical ventilation, AKI stage 3, and SOFA score ≥8.

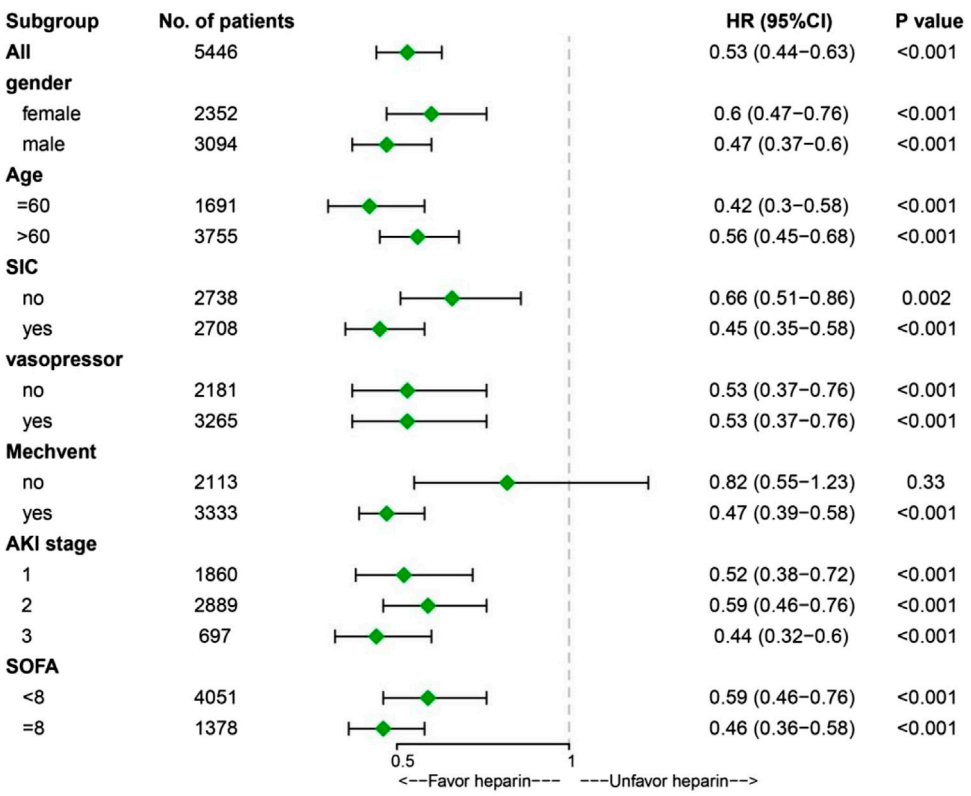


FIGURE 2
Results of ICU mortality in overall population with marginal structural Cox model and stratification analysis. Abbreviations: SIC, sepsis-induced coagulopathy; Mechvent, mechanical ventilation; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment; HR, Hazard Ratio; CI, confidence internal; ICU, Intensive Care Unit.

In our study, the early use of heparin was also significantly associated with reduced in-hospital mortality in patients with SAKI, consistent with previous studies of heparin use in sepsis (Zou et al., 2022). The prematched crude ICU mortality rate was higher in patients with heparin use than in those without heparin use (11.7% vs. 11.0%, HR 0.53, 95% CI 0.45-0.62, $p < 0.001$) and after PSM, heparin was associated with reduced ICU mortality (11.7% vs. 14.6%, HR 0.75, 95% CI [0.62-0.92], $p = 0.005$) The underline reason for this is ICU mortality was represented by percentage, while HR increased the effect of survival time on the outcome. We can see that heparin extended the length of ICU stay of patients (2.84 VS 3.94 $p < 0.001$) from in Table 1. The pathophysiology of acute kidney injury in sepsis is complex, including organ ischemia and systemic hemodynamic changes, as well as kidney inflammation and response to various septic mediators, including inflammation, microcirculatory dysfunction, ischemia-perfusion injury, and cellular adaptation to injury (De Backer et al., 2011; Gomez et al., 2014; Honore et al., 2015; Peerapornratana et al., 2019). Severe changes in systemic microvascular distribution caused by sepsis include a significant decrease in capillary density, a decrease in the proportion of capillaries with continuous flow, and an increase in the proportion of capillaries with intermittent or no flow. Based on Inflammatory and Coagulation Indicators (platelet, serum procalcitonin, prothrombin time activity) may be a robust predictor for the SAKI in patients, which providing information for timely and efficient intervention (Xin et al., 2022).

Heparin is the oldest and most widely used anticoagulant worldwide. It has been used in clinical practice for 80 years since 1935 (Wang et al., 2022). Heparin, except for its anticoagulant properties, also has anti-inflammatory activity and resistance to complement and regulate the action, such as all kinds of proteases, and its mechanism has two types: one type is adjusted by combining plasma soluble ligand, and the other is through a combination of cell surface receptors or adjusted macromolecules, which have potential effects on downstream signaling pathways. Heparin can inhibit the activation of inflammatory cells and responses by binding to inflammatory mediators and enzymes (Beurskens et al., 2020). Research in 2004 showed that NETosis is a process of density-chromatin formation consisting of nuclear DNA-histone scaffold, called NETs, that responds to a trigger (usually a pathogen), NETs are a major component of arterial and venous thrombosis, as demonstrated in several *in vivo* models and patients, heparin protects against NETosis (von Brühl et al., 2012). Histones are cytotoxic in extracellular presence and are closely related to endothelial dysfunction; sepsis, kidney ischemia, necrosis of tubular epithelial cells release histones into the extracellular space, and renal vascular endothelial and renal tubular epithelial cells produce a dose-dependent toxicity, increased vascular permeability, and neutrophils to renal parenchyma across endothelial migration. Heparin caused by severe inflammation cell damage during extracellular histones have strong affinity, which can reduce this phenomenon (Allam et al., 2012;

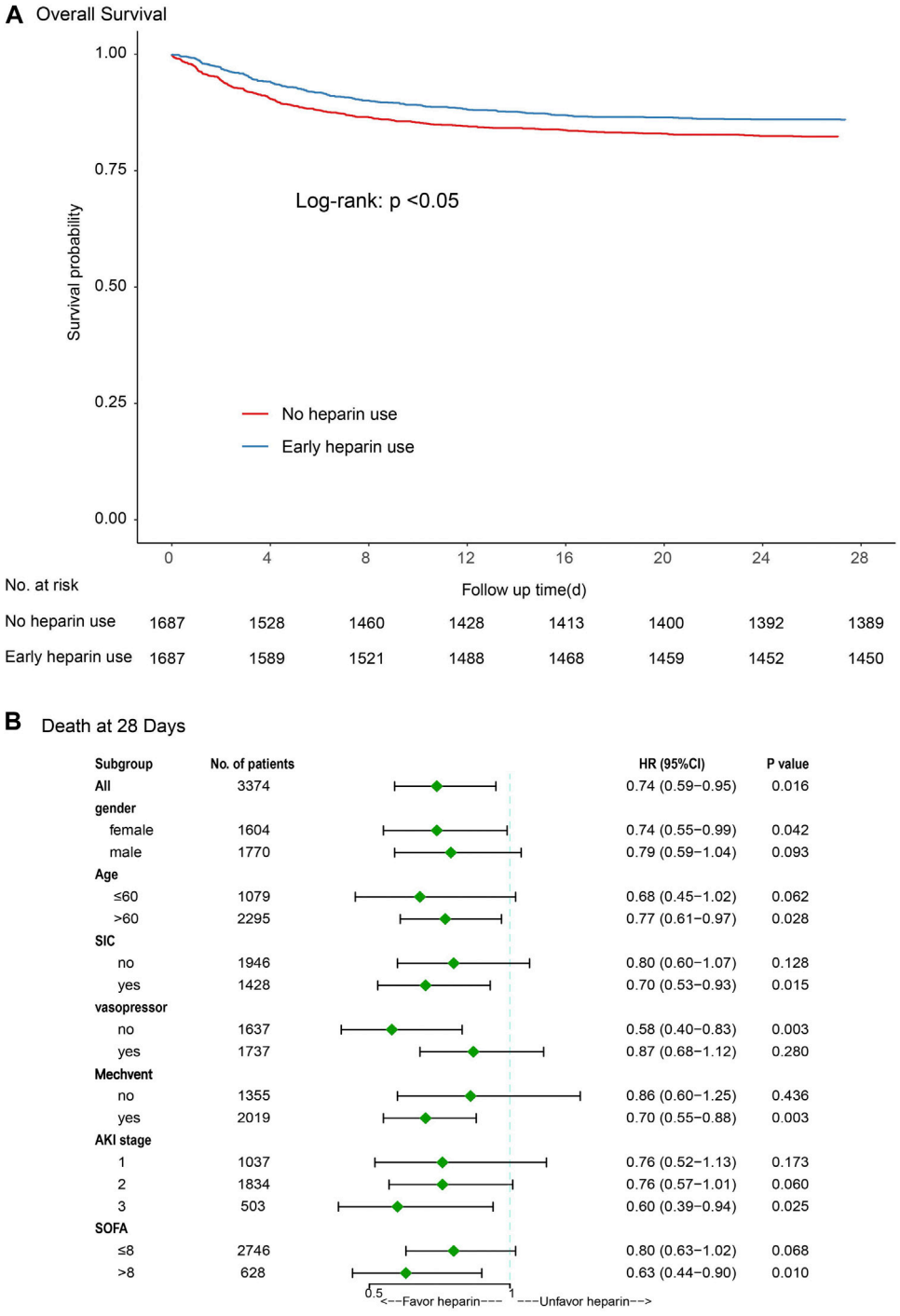


FIGURE 3
Results of 28-day mortality in overall population with logistic regression model and stratification analysis [**(A)** Kaplan-Meier curves; **(B)** Subgroup analysis]. Abbreviations: SIC, sepsis-induced coagulopathy; MV, mechanical ventilation; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment.

Saffarzadeh et al., 2012). In addition, neutrophils are known to be responsible for the development of AKI, and neutrophil-derived Heparin-binding Protein (HBP) also plays an important role in sepsis-induced AKI (Fisher et al., 2017). HBP has been shown to increase endothelial permeability, cause renal bleeding and vascular leakage, and induce inflammation in renal tubular cells (Gomez et al., 2014). Studies have shown that heparin may block GAG-binding sites on HBP and prevent their association with cell-surface GAGs, thereby attenuating HBP-induced renal vascular leakage and inflammation (Fisher et al., 2017). But there is no recommendation in the international sepsis guidelines on whether they require anticoagulation treatment in patients without venous thromboembolism (VTE) (Evans et al., 2021). The possible reason may be associated with the heterogeneity of sepsis, and it

TABLE 4 Dose-response relationship between heparin and ICU mortality in SAKI patients.

| Daily heparin usage (non-heparin group as reference) | HR (95%CI) *p*-value | | | |
|---|---|---|---|---|
| | Full cohort (*n* = 3374) | Stage 1 (*n* = 1037) | Stage 2 (*n* = 1834) | Stage 3 (*n* = 503) |
| 0U < × ≤ 5000U | 1.25 (0.89, 1.77) 0.202 | 1.57 (0.74, 3.34) 0.240 | 1.19 (0.69, 2.05) 0.543 | 1.33 (0.76, 2.33) 0.313 |
| 5000U < × ≤ 7500U | 0.69 (0.46, 1.02) 0.061 | 0.63 (0.29, 1.37) 0.240 | 0.72 (0.40, 1.28) 0.264 | 0.87 (0.41, 1.83) 0.715 |
| 7500U < × ≤ 10000U | 0.77 (0.57, 1.02) 0.069 | 0.93 (0.54, 1.59) 0.783 | 0.81 (0.54, 1.23) 0.324 | 0.59 (0.33, 1.08) 0.088 |
| 10000U < × ≤ 12500U | 0.39 (0.27, 0.56) <0.001 | 0.40 (0.19, 0.82) 0.013 | 0.52 (0.31, 0.85) 0.009 | 0.26 (0.13, 0.54) <0.001 |
| 12500U < × ≤ 15000U | 0.50 (0.31, 0.81) 0.005 | 0.30 (0.11, 0.87) 0.026 | 0.93 (0.51, 1.66) 0.795 | 0.30 (0.09, 1.00) 0.050 |
| *p* value for trend | <0.001 | 0.002 | 0.021 | <0.001 |

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval; SAKI, sepsis-induced acute kidney injury.

is necessary to pay attention to the onset stage of sepsis and heparin dosage for clinicians.

The optimal dosage of heparin in patients with sepsis remains controversial. In our study, 1000–20000 IU/day was shown to reduce adverse outcomes and improved patient prognosis. Heparin-related side effects, including bleeding and thrombocytopenia, should not be ignored. In some related studies, the use of intravenous heparin was not associated with increased gastrointestinal or intracranial bleeding (Zarychanski et al., 2008; Liu et al., 2014). However, it is necessary to closely observe and monitor relevant indicators when using them.

In our stratified analysis, heparin use in women was significantly associated with reduced 28-day mortality, which may be mediated by differences in steroid hormone levels (O'Brien et al., 2019). Men may be more susceptible to infection than women, not only because androgens reduce immunity but also because steroid hormones affect disease-fighting genes and behavior (Klein, 2000). Elderly patients are independent risk factors for venous thromboembolism, and it has been reported that pharmacodynamic changes in sensitivity to drugs are better in the elderly (Mangoni and Jackson, 2004); for example, besides antithrombin unfractionated heparin combined with many plasma proteins, these factors may help heparin in the elderly with unpredictable pharmacokinetic and pharmacodynamic properties (Dorobantu and Bogdan, 2016). Heparin is a glycosaminoglycan with anticoagulant and anti-inflammatory effects (Robertson, 2006). Studies have shown that in patients with SAKI with coagulopathy, the use of heparin can improve the prognosis of patients, which is related to the anticoagulant and non-anticoagulant effects of heparin (Li et al., 2011). Heparin is used as an anticoagulant, and its main effect is to increase the inactivation of factor Xa and thrombin mediated by antithrombin, thus effectively limiting the production of thrombin (Evans et al., 2021). As thrombin production is closely related to inflammation, heparin also plays an anti-inflammatory role. Heparin neutralizes endotoxins and increases serum tumor necrosis factor-binding protein-1, directly limiting coagulation and inflammation activation (Schultz and Becker, 1967).

Notably, our results must be interpreted in the context of the limitations of our study. First, it was a retrospective study. Due to the large time span, there may be measurement bias; therefore, we used PSM analysis to reduce this bias. Second, some patient variables were not extracted from the database, which may have led to confusion. Third, due to the large time span of the data, sepsis-related definitions have changed in clinical practice studies, which may lead to the results not being generalized to current practice. Lastly, according to the KDIGO criteria, AKI can be classified into two categories: persistent AKI, defined as continuing AKI for more than 48 h from onset, and transient AKI, where there is complete reversal of AKI within 48 h of onset (Cardoso et al., 2022). Thus, additional research is needed to assess the effectiveness of heparin in both transient and persistent AKI.

## Conclusion

The present study suggests that early heparin administration to patients with SAKI who received 10000–15000 IU/day appears to be associated with improved ICU mortality at different AKI stages, regardless of gender, age, mechanical ventilation, sequential organ failure assessment (SOFA) score, and history of SIC and vasopressor use. Patients with female, age >60 years, sepsis-induced coagulopathy (SIC), non-vasopressor use, mechanical ventilation, AKI stage 3, and SOFA score ≥ 8 who received heparin had decreased 28-day mortality. A prospective randomized controlled study should be conducted to further verify these findings.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: these data are available at https://mimic-iv.mit.edu/.

## Ethics statement

The studies involving humans were approved by the Research Ethics Committee of Shenzhen Second People's Hospital (20220519001-MC01). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of

written informed consent for participation from the participants or the participants' legal guardians/next of kin because the need for informed consent from individual patients was waived because of the retrospective and observational nature of the study.

## Author contributions

Z-PZ: Data curation, Software, Writing–original draft. LZ: Writing–original draft, Funding acquisition. YL: Data curation, Software, Writing–review and editing. Z-JY: Methodology, Resources, Writing–original draft. J-JH: Writing–original draft, Data curation, Formal Analysis. D-ZL: Data curation, Writing–original draft, Investigation. Y-HC: Data curation, Writing–original draft, Methodology. Y-YL: Conceptualization, Resources, Writing–review and editing. Y-MY: Resources, Writing–review and editing, Validation, Visualization. MW: Writing–review and editing, Conceptualization, Funding acquisition, Supervision.

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## Conflict of interest

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

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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.2023.1261305/full#supplementary-material

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# Strengths and opportunities to clinical trial enrollment among BIPOC, rural dwelling patients in the northwest United States: a retrospective study

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**Introduction:** Clinical trials investigating the safety and efficacy of experimental drugs and devices are the cornerstone of medicinal advancement. Enrolling sufficient participants in these trials is vital to ensure adequate statistical power and generalizability. Clinical trial participation is particularly low among certain populations, including medically underserved communities (i.e., rural areas) and Black, Indigenous, and People of Color (BIPOC).

**Methods:** A retrospective study design was used to understand patient outcomes and access/barriers to clinical trial participation in the rural northwest United States. A quantitatively focused retrospective chart review was conducted for adult participants enrolled in at least one clinical trial in a single northwest health system between 1999 and 2022. Descriptive and inferential statistical analyses were performed to assess trial outcomes at a significance level 0.05.

**Results:** The retrospective chart review yielded 833 clinical trial records with 753 individual enrolled participants. The all-cause relative frequency of death at last known follow-up amongst clinical trial participants was 8.90% (n = 67). Based on logistic regression, the death was significantly associated with the participants' age at initial trial screening ($\beta$ = 0.09, $p$-value <0.001), those that resided in non-metro areas ($\beta$ = −0.86, $p$-value = 0.045), and those that lived in Northeastern Montana ($\beta$ = 1.27, $p$-value = 0.025). Additionally, death at last known follow-up was significantly associated with enrollment in 2021–2022 ($\beta$ = −1.52, $p$-value <0.001), enrolled in more than one study ($\beta$ = 0.84, $p$-value = 0.023), in internationally sponsored trials ($\beta$ = −2.08, $p$-value <0.001), in Phase I ($\beta$ = 5.34, $p$-value <0.001), in Phase II trials ($\beta$ = 1.37, $p$-value = 0.013), diabetes as a primary trial target ($\beta$ = −2.04, $p$-value = 0.003).

**Conclusion:** As decentralized trial design and remote or virtual elements of traditional trials become normative, representation of rural and frontier populations is imperative to support the generalizability of trial data encouraged by the FDA.

KEYWORDS

**clinical trial enrollment, access barriers, rural, frontier, decentralized trial**

# 1 Introduction

Clinical trials (CTs), the cornerstone of medicinal advancement, offer patients the opportunity to receive state-of-the-art treatments and access to potentially effective options before they are approved for routine use (Krzyzanowska et al., 2011). Emerging technologies administered as part of CTs may improve health outcomes (i.e., cancer control) and improve quality of life or shorten treatment times, thus change the overall burden of a life-threatening illness. Over the past decade, the number of drugs developed for gynecological and breast cancers based on CTs has increased (Workman, 2003; Doisneau-Sixou and Harbeck, 2014; Beaver et al., 2019). Enrolling sufficient participants in these trials is vital to ensure adequate statistical power and generalizability. Yet, participation in CTs has remained low for more than 20 years, particularly among community sites (4%) when compared to National Cancer Institute (NCI) designated sites (19%) (Unger and Fleury, 2021). In addition to the practice site, health status, race and ethnicity, rurality, and socioeconomic status influence clinical trial enrollment (Caston et al., 2022a; Caston et al., 2022b).

Clinical trials should be equally accessible to all populations for many reasons, including access to novel treatments that may not otherwise be available. Specific populations are often underrepresented, including racial and ethnic minorities, uninsured, socioeconomically disadvantaged, elderly, and rural populations. This underrepresentation limits the ability to generalize trial results to diverse patient populations. Lack of CT representation is well documented for patients who are Black, Indigenous, People of Color (BIPOC), rural residents, or patients living in disadvantaged areas (Caston et al., 2022a; Caston et al., 2022b). Lack of CT representation is particularly low among indigenous populations; only 1% of participating individuals are American Indian/Alaska Native (AI/AN) - a disproportionately low level (Mainous et al., 2023). Patients in rural areas have decreased participation in clinical trials, with about one in three clinical trial participants are rural residents compared to one in five in the general population (Unger et al., 2018; Bharucha et al., 2021)). Multilevel barriers to clinical trial participation disproportionately affect certain groups that are prevalent in older adults and rural residents, resulting in underrepresentation in clinical trials (Hamel et al., 2016). Economic, social, cultural, and medical barriers to CT representation have been suggested, including unequal access to the healthcare system, mistrust of clinical research, poor past experiences with the healthcare system, lack of insurance, lack of transportation, and vast geographical distances to seek healthcare (Iglehart, 2018; Wercholuk et al., 2022).

Such discrepancies in CT participation opportunities may exacerbate known cancer-related health disparities among underserved populations. Differences in cancer risk and biology among underserved populations may also contribute to outcome disparities, especially if these groups are underrepresented in clinical trials, as the impact of newer therapies could be inadequately studied in these populations (Johnson et al., 2014; Geana et al., 2017; Batai et al., 2018; Rayford et al., 2021). For example, recent data from the Carolina Breast Cancer Study suggests that Black women more often have higher-risk, harder-to-treat breast cancer than women of other racial groups (Troester et al., 2018). While clinical trial participation is associated with decreased mortality (Unger et al., 2014; Unger et al., 2018), it should be noted that high area-level socioeconomic deprivation has been found to result in persistent disparities even with clinical trial enrollment (Unger et al., 2021). A SWOG Cancer Research Network report demonstrates that access to clinical trials narrows the gap in cancer care disparity among patients in urban and rural communities (Seidler et al., 2014; Perni et al., 2021).

In recognition of these issues and the challenges faced by the BIPOC, rural, and underserved individuals it serves, our large healthcare organization in the rural Northwest undertook a comprehensive effort to explore the strengths and opportunities of clinical trials specific to our region. Within our healthcare area, patients travel considerable distances (e.g., 500 miles) across the vast geographic expanse of Montana, Wyoming, and North Dakota to attend study visits. Unique structural and cultural factors further impede access to care within the region including avoidance of care, fear of anonymity, perceived lack of confidentiality due to small community, and mistrust of unfamiliar staffing (Burch, 2022). Diversity exists due to the rurality of the patient population and the limited number of specialists throughout the region. Due to the complexity of CTs, challenges occur in implementing virtual and regional models based on the availability and lack of trained staff in rural communities. Virtual visits can be implemented; however, limitations exist without adequately trained staff to conduct study-specific procedures. Yet, there remains a lack of literature exploring such limitations and opportunities for clinical trial participation among diverse populations. Therefore, the aims of this retrospective chart review were two-fold: 1) explore the strengths and opportunities of clinical trial participation among BIPOC, rural, and underserved individuals, and 2) objectively understand enrollment, utilization, and outcomes of clinical trial participants in the rural Northwest.

# 2 Materials and methods

## 2.1 Study design

This retrospective chart review (RCR) explored all known clinical trial participants who were provided care between 1999 and 2022 at a large healthcare organization in the rural

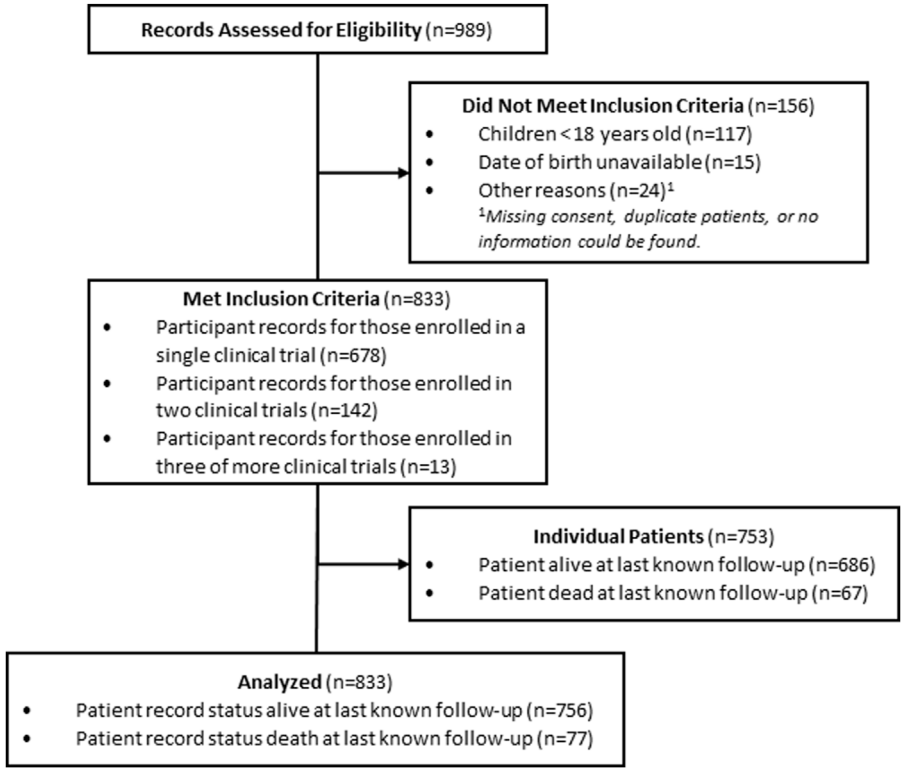


FIGURE 1
RCR chart screening, inclusion and analysis.

Northwest. The quantitative data described participant attributes, including demographics, clinical trial study details, insurance information, and hospital discharge information.

### 2.1.1 Data management

Clinicians and research staff employed at the large healthcare organization were responsible for all data collection and management aspects throughout the study period and subsequent dissemination. Investigators complied with data stewardship and other applicable standards for data collection, data entry and management, data analysis, and dissemination activities.

### 2.1.2 Data collection

Given that this was an RCR, the request for waiver of informed consent for medical record review was sought and approved by the Montana State University Institutional Review Board (Protocol # 2023–604) and the hospital organization's Privacy & Exemption Committee on 19 April 2023. After approval, a list of all the names and medical record numbers of adult patients (age 18 and over) with a record of clinical trial participation in calendar year 1999 (starting 01 January 1999) through calendar year 2022 (ending 31 December 2022) were collected and managed by healthcare research staff and clinicians. Data were then de-identified and securely transferred for statistical analyses. All consecutive patient charts were then retrospectively reviewed from a large healthcare system in the rural Northwest. This rural healthcare system has 40 affiliated facilities and a primary service area that spans Montana, northern Wyoming, and part of eastern North Dakota. The RCR identified all patients previously or currently enrolled in any clinical trial at any of the 40 affiliated facilities.

### 2.1.3 Screening and inclusion criteria

The healthcare system's electronic and hardcopy medical records were reviewed to identify any patients enrolled in a clinical trial from 1999 to 2022. A total of 989 participant records were extracted from the electronic database and physical charts (Figure 1). Patients were included in this RCR if they were provided care at one of the 40 affiliated healthcare system sites; enrolled in at least one clinical trial between 1999 and 2022; and were adults aged ≥18 years at trial enrollment. Patients were excluded if not enrolled in a clinical trial between 1999 and 2022; children less than 18 years old; date of birth was missing/unavailable; or consent form(s) were missing/unavailable from electronic files. The final dataset encompassed 833 records, which included 753 individual patients (75 patients participated in more than one trial during the study period).

### 2.1.4 Data attributes

The extracted dataset comprised a total of 20 key attributes. These attributes included participant demographic backgrounds, clinical trial study details, insurance information, and hospital discharge information (Table 1). Due to the limited number of participants enrolled in more than one study, the number of studies enrolled for each participant was summarized into two levels (one study vs. more than one study). To balance the study distribution across categories, the ten Rural-Urban Commuting Area (RUCA)

TABLE 1 Extracted dataset attributes.

| Attributes (total attributes k = 20) | Descriptive analysis | Inferential analysis |
|---|---|---|
| Age at screening | Continuous, years | Continuous, years |
| Number of studies enrolled | Dichotomous, 2 levels | Dichotomous, 2 levels: One study \| More than one study |
| Gender | Dichotomous, 2 levels | Dichotomous, 2 levels: Female \| Male |
| Marital status | Categorical, 3 levels | Categorical, 3 levels: Married & Live partner \| Single \| Divorced, Separated & Widowed |
| Race | Categorical, 3 levels | Categorical, 3 levels: White \| American Indian or Alaska Native \| Other |
| RUCA[a] | Dichotomous, 2 levels | Dichotomous, 2 levels: Metro Area \| Nonmetro Area |
| RUCC[b] | Dichotomous, 2 levels | Dichotomous, 2 levels: Metro Area \| Nonmetro Area |
| MT area code | Categorical, 4 levels | Categorical, 4 levels |
| | | Northeastern \| Eastern \| North Central, South Central & Western \| Outside MT |
| International study | Dichotomous, 2 levels | Dichotomous, 2 levels: Domestic \| International |
| Trial sponsor type | Categorical, 4 levels | Categorical, 4 levels: Academic Institute/Healthcare Organization \| Biotech/Device \| |
| | | Consortium/Network/Foundation \| Pharmaceutical/Biopharmaceutical |
| Primary sponsor type | Categorical, 3 levels | Categorical, 3 levels: Commercial \| Government \| Other |
| Secondary insurance type | Categorical, 3 levels | - |
| Insurance status | Categorical, 3 levels | Categorical, 3 levels: Single Insurance \| Two Insurances \| No insurance |
| Study enrolled year | Categorical, 5 levels | Categorical, 2 levels: 2020 and prior \| 2021–2022 |
| Study status | Categorical, 6 levels | - |
| Study phases | Categorical, 6 levels | Categorical, 6 levels: Observational \| Pilot \| Phase I \| Phase II \| Phase III \| Phase IV |
| Disease site | Categorical, 7 levels | Categorical, 3 levels: Cancer, Breast & GYN \| Diabetes \| Other |
| Deceased status | Dichotomous, 2 levels | Dichotomous, 2 levels: Deceased \| Not deceased |
| Last Encounter type | Categorical, 4 levels | - |
| Days to deceased | Continuous, days | - |

[a]Metro area: RUCA, 1-6, Nonmetro area: RUCA, 7–10.
[b]Metro area: RUCC, 1-3, Nonmetro area: RUCC, 4–9.

Codes were recategorized into metropolitan (metro) areas and nonmetropolitan (nonmetro) areas. Both primary and secondary insurance types included commercial (e.g., BlueCross BlueShield), government (i.e., Medicaid, Medicare, Tricare, Veterans Affairs, and Indian Health Service), and other insurance types (i.e., no insurance, charity care, self-pay). Due to limited information (e.g., unreported), secondary insurance types were excluded from inferential analyses. However, a composite variable for known primary and secondary insurance types was included to understand access/barriers to advanced care, such as clinical trials. This composite insurance variable was summarized into three levels (i.e., no insurance, single insurance, two or more insurances). Study status, last encounter type, and days to a deceased endpoint were excluded from inferential analysis because of class imbalance (i.e., skewed distributions) for deceased participants. Lastly, the trial enrollment year and disease site were aggregated across levels based on expert input (EJ and JB) for inferential analyses.

### 2.1.5 Statistical analyses

Both descriptive and inferential analyses were completed using the R programming language (Version R-4.3.0) (R Core Team, 2013) with Tidyverse packages (Wickham et al., 2019). A descriptive analysis was conducted for all 20 attributes. Means and standard deviations were calculated for continuous attributes. Frequency and relative frequency were summarized for dichotomous and categorical attributes. Inferential analysis includes association and logistic regression analysis for 16 attributes (Table 1). Analysis of variance and Chi-square analyses were used to determine relationships amongst and between features. The logistic model used death at last known follow-up (yes, no) as the dependent variable and selected predictors (i.e., screening via backward selection method) analysis as independent variables (Borboudakis and Tsamardinos, 2019). Two-sided significance level was set at 0.05 for all inferential analyses.

TABLE 2 Patient demographics at first trial screening by status at last known follow-up.

| | All patients (n = 753) | Alive (n = 686) | Dead (n = 67) |
|---|---|---|---|
| Age[a] | 57.5 (15.1) | 56.4 (15.0) | 68.1 (11.4) |
| Age Interval[b] | | | |
| 18–44 | 167 (22.2) | 164 (23.9) | 3 (4.5) |
| 45–64 | 308 (40.9) | 285 (41.5) | 23 (34.3) |
| 65–69 | 111 (14.7) | 103 (15.0) | 8 (11.9) |
| 70–74 | 96 (12.8) | 84 (12.2) | 12 (17.9) |
| 75–79 | 44 (5.8) | 34 (5.0) | 10 (14.9) |
| ≥80 | 27 (3.6) | 16 (2.3) | 11 (16.4) |
| Female[b] | 468 (62.2) | 428 (62.4) | 40 (59.7) |
| Marital Status[b, c] | | | |
| Married or Domestic Partnership[d] | 479 (63.6) | 438 (63.8) | 41 (61.2) |
| Single | 161 (21.4) | 149 (21.7) | 12 (17.9) |
| Divorced, Separated & Widowed | 108 (14.3) | 94 (13.7) | 14 (20.9) |
| Race[b, c] | | | |
| White | 694 (92.2) | 632 (92.1) | 62 (92.5) |
| American Indian or Alaska Native | 34 (4.5) | 30 (4.4) | 4 (6.0) |
| Other[e] | 22 (2.9) | 21 (3.1) | 1 (1.5) |
| RUCA Code[b, f] | | | |
| Metropolitan Counties | 517 (68.7) | 471 (68.7) | 46 (68.7) |
| Nonmetropolitan Counties | 236 (31.3) | 215 (31.3) | 21 (31.3) |
| Montana Region[b] | | | |
| North Eastern | 73 (9.7) | 64 (9.3) | 9 (13.4) |
| Eastern | 535 (71.1) | 489 (71.3) | 46 (68.7) |
| North Central | 9 (1.2) | 9 (1.3) | - |
| South Central | 49 (6.5) | 43 (6.3) | 6 (9.0) |
| Western | 9 (1.2) | 8 (1.2) | 1 (1.5) |
| Outside Montana[g] | 78 (10.3) | 73 (10.3) | 5 (7.5) |
| Primary Insurance Type[b] | | | |
| Commercial | 352 (46.8) | 334 (48.7) | 18 (26.9) |
| Government Insurance | 372 (49.4) | 327 (47.7) | 45 (67.1) |
| Other | 29 (3.8) | 25 (3.6) | 4 (6.0) |
| Insurance Status[b] | | | |
| Single Insurance | 471 (62.6) | 442 (64.4) | 29 (43.3) |
| Two Insurances | 253 (33.6) | 219 (31.9) | 34 (50.7) |
| No Insurance | 29 (3.8) | 25 (3.6) | 4 (6.0) |

(Continued on following page)

TABLE 2 (*Continued*) Patient demographics at first trial screening by status at last known follow-up.

| | All patients (n = 753) | Alive (n = 686) | Dead (n = 67) |
|---|---|---|---|
| Enrolled in more than one trial[b] | 75 (10.0) | 67 (9.8) | 8 (11.9) |

[a]Mean (Standard Deviation).
[b]Frequency (Relative Frequency).
[c]Missing marital status (n* = 5) and Race (n* = 3).
[d]Married (62.2%) and Domestic partnerships (1.46%).
[e]Other races included Asian (1.20%), Black/African American (1.20%), Native Hawaiian/Pacific Islander (0.27%), multiple races/not reported (1.20%).
[f]Defined using the rural-urban commuting area codes. RUCA, is a classification system used to categorize geographic areas based on their level of urbanization and commuting patterns.
[g]Wyoming (8.76%), Minnesota (0.40%), South and North Dakota (0.40%), and other states (0.80%).

# 3 Results

## 3.1 Patient characteristics

Of the 833 clinical trial participant records, 753 adult patients (75 participated in more than one trial during the study period) were included in this retrospective chart review (RCR). As detailed in Table 2, participants were, on average, 57.5 (standard deviation 15.0) years old at first clinical trial screening, most were female (62.2%), White (92.2%), and married/domestic partnership (63.6%). Patients' primary health insurance included a nearly equivalent frequency of commercial (46.8%) and government (49.4%) insurance types. Over 33% of participants had two or more insurance types. A larger than expected proportion of 3.6% of older adults (≥80 years old) were enrolled in clinical trials.

## 3.2 Clinical trial characteristics

There were 833 clinical trial participants from 1999 to 2022, supported by 753 individual patients (i.e., 75 patients were enrolled participants in more than one study) (Table 3). Most trials began in 2021 (209, 25.1%), with only a few trials per year from 1999 to 2018 (178, 21.4%). Domestic (US-based) clinical trials were most prevalent (601, 72.1%), and most trials were sponsored by biotechnology/medical device companies (292, 35.1%). While all study phases (pilot, phases I-IV, and observational) were conducted, a vast majority were observational trials (448, 53.8%). Trials primarily focused on the treatment of diabetes (34.1%), breast or gynecological cancer (20.6%), and other forms of cancer (19.6%). Due to specialty availability, very few Biobank/Repository (4.8%) and lung-related (3.0%) trials were conducted.

## 3.3 Trial participation by rurality

As of 2023, this large healthcare organization in the rural Northwest is the only Level I Trauma Center serving the states of Montana and Wyoming across 244,854 square miles (about the area of Texas), which are primarily designated as rural areas (i.e., 27.5% RUCA Code 10: primary flow to a tract outside of an urban area or urban center) (U.S. Department of Agriculture, 2019) (Figure 2). Patients from metropolitan tracts (i.e., RUCA codes 1 and 2) accounted for most trial participants (63%) (Table 4), yet nearly 22% of study participants lived in non-metropolitan areas (RUCA codes 4–8). Only 15% of participants lived in the most rural, isolated areas (RUCA 10). Across the state of Montana, most participants resided in Eastern Montana (71.9%), coinciding with the rural hospital's main location. In conjunction with the hospital's service area, the next greatest regional enrollment came from northern Wyoming (10.3%).

## 3.4 End of trial status

Across all clinical trial participants, 678 were enrolled in only one study, and 75 participants were enrolled in two or more clinical trials (Table 2). A total of 67 participants were reported as deceased as the final clinical or follow-up endpoint for an all-cause relative frequency of death of 8.90%. Deceased participants were, on average, 10 years older than surviving patients. Over 22% of enrolled participants were aged 70 years and older. Half (49.4%) of deaths occurred in those aged 70 years and older. The frequency of death was marginally higher amongst females (59.7%) and those divorced/separated/widowed (20.9%). Deaths were higher in metropolitan tracts (67.5%) compared to non-metro tracts (32.5%).

Most deaths occurred amongst participants enrolled in one clinical trial (Table 5). Since only one hospital system participated in the RCR, only encounters within the health system's affiliated hospitals were available to categorize deceased participants' last known encounter type. The last recorded encounter type for deceased patients was either an inpatient (46.3%) or outpatient (46.3%) visit. On average, the duration from the previous encounter to the date of death was 37.8 days. Duration's distribution was negatively skewed, with extreme outliers resulting in a very large standard deviation of 88.1 days.

The binary logistic regression model identified eight variables associated with trial death at last known follow-up (Table 6). Age at initial trial screening, residence region, and residence rurality were significantly associated with trial death. Specifically, older age, those residing in Northeastern Montana, and those living in metropolitan RUCA codes had significantly higher odds of death. Furthermore, participants enrolled from 1999 to 2020 and in more than one trial had significantly higher odds of death. Participants undergoing cancer treatment and those in Phase 1 or 2 trials had exceptionally high odds of death. While domestic trial sponsors had significantly higher odds of death, the type of trial sponsor (e.g., academic institute) was of no predictive value. Marital status, gender, race, insurance status, insurance type, and study status were each eliminated as highly non-significant factors during the backward selection methodology to fit the logistical regression mode.

TABLE 3 Clinical trial characteristics.

| | Trial participation (n = 833) | End of trial status: Alive (n = 756) | End of trial status: Dead (n = 77) |
|---|---|---|---|
| Trial enrollment year[a] | | | |
| 2018 and prior | 178 (21.4) | 160 (21.2) | 18 (23.4) |
| 2019 | 150 (18.0) | 126 (16.7) | 24 (31.2) |
| 2020 | 131 (15.7) | 109 (14.4) | 21 (28.6) |
| 2021 | 209 (25.1) | 198 (26.2) | 11 (14.3) |
| 2022 | 165 (19.8) | 163 (21.6) | 2 (2.6) |
| Domestic vs. International Trials[a] | | | |
| International Trials | 232 (27.9) | 216 (28.6) | 16 (20.8) |
| Domestic Trials | 601 (72.1) | 540 (71.4) | 61 (79.2) |
| Trial Sponsor Type[a] | | | |
| Academic Institute/Health Organization | 178 (21.4) | 169 (22.4) | 9 (11.7) |
| Biotechnology/Device Company | 292 (35.1) | 277 (36.6) | 15 (19.5) |
| Consortium/Network/Foundation | 270 (32.4) | 231 (30.6) | 39 (50.6) |
| Pharmaceutical/Biopharmaceutical | 93 (11.2) | 79 (10.4) | 14 (18.2) |
| Study Phases[a] | | | |
| Pilot | 52 (6.2) | 51 (6.7) | 1 (1.3) |
| Phase I | 10 (1.2) | 3 (0.4) | 7 (9.1) |
| Phase II | 35 (4.2) | 26 (3.4) | 9 (11.7) |
| Phase III | 169 (20.3) | 158 (20.9) | 11 (14.3) |
| Phase IV | 119 (14.3) | 104 (13.8) | 15 (19.5) |
| Observational | 448 (53.8) | 414 (54.8) | 34 (44.2) |
| Disease/Disorder Target[a,b] | | | |
| Biobank/Biospecimen Repositories | 40 (4.8) | 35 (4.6) | 5 (6.5) |
| Breast/Gynecological Cancers | 172 (20.6) | 149 (19.7) | 23 (29.9) |
| Cancer | 163 (19.6) | 135 (17.9) | 28 (36.4) |
| Cardiovascular | 50 (6.0) | 38 (5.0) | 12 (15.6) |
| Diabetes | 284 (34.1) | 277 (36.6) | 7 (9.1) |
| Lung-related | 25 (3.0) | 24 (3.2) | 1 (1.3) |
| Neurological-related | 99 (11.9) | 98 (13.0) | 1 (1.3) |
| Trial Participant Enrollment Status[a,c] | | | |
| Complete | 410 (49.2) | 410 (54.2) | N/A |
| Deceased | 77 (9.2) | - | 77 (100.0) |
| Early Termination[d] | 39 (4.7) | 39 (5.2) | N/A |
| Trial Monitoring[e] | 161 (19.3) | 161 (21.3) | N/A |
| Randomized[f] | 80 (9.6) | 80 (10.6) | N/A |

(Continued on following page)

TABLE 3 (*Continued*) Clinical trial characteristics.

| | Trial participation (n = 833) | End of trial status: Alive (n = 756) | End of trial status: Dead (n = 77) |
|---|---|---|---|
| Screen Fail[g] | 66 (7.9) | 66 (8.7) | N/A |

[a]Frequency (Relative Frequency).
[b]Biobank/Biospecimen Repositories (Biorepository, Caris Biorepository, Diabetes Related Antibodies, and Polycythemia Vera), Breast/Gynecological Cancers (Breast, Breast Pre-Biopsy Blood Collection, GYN, and Ovarian), Cancer (Circulating Tumor Cells, Multiple Myeloma, Cancer Health Disparities, Tumors, Cancer Central Nervous System, Colon Cancer, GI, glioblastoma; GU, Head & Neck Cancer, Leukemia, Lymphoma, Melanoma, Prostate Cancer, and Renal Cell), Cardiovascular (Endotak Reliance, Heart Failure, and Watchman Device–Afib), Diabetes (T1DM, T2DM, and Diabetes), Lung-related (Cystic Fibrosis, Lung, and Lung Cancer), Neurological-related (MS, and Pain).
[c]NR: Not reportable due to sample size <5; N/A: Not Applicable.
[d]Patients who either revoked consent or had to stop trial due to other circumstances (serious adverse events, moving out of area, etc.).
[e]Patients complete with active treatment but were monitored for recurrence and death. This status is typically only used for cancer trials.
[f]Patient signed consent, and was actively receiving treatment.
[g]Patient signed consent, however, did not receive study drug. Usually excluded from study based on disease severity and/or specific inclusion/exclusion criteria of the clinical trial.

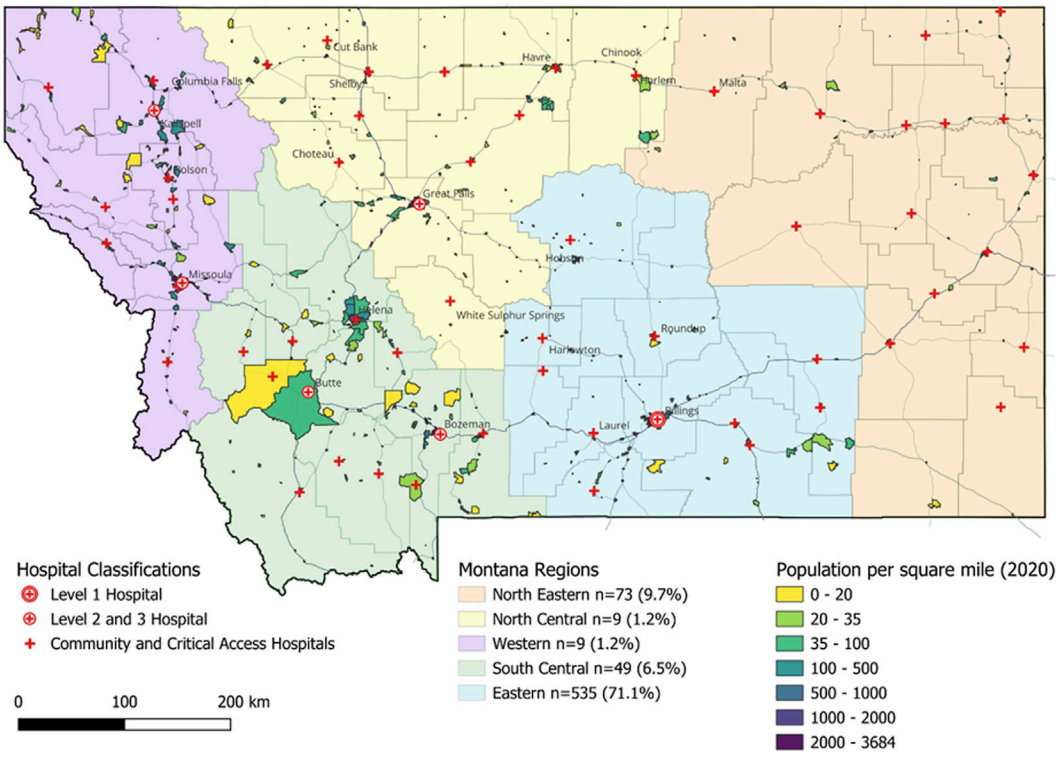


FIGURE 2
Hospital locations, population and trial participants across Montana Regions. 56 community and critical access hospitals. 6 level 2 and 3 hospitals. 1 level 1 hospital. Montana has three metro core areas: Billings, Missoula and Great Falls. And it has four micro core areas: Kalispell, Bozeman, Helena and Butte.

## 4 Discussion

This retrospective chart review examined patients' medical records enrolled in a clinical trial between 1999 and 2022 at a large healthcare organization in the rural Northwest. The final dataset of 833 records included 753 individual participants, with 75 patients participating in more than one trial during the study period. Numerous other studies have been conducted on this topic; however, none were found relevant to the rural frontier population of our service area.

Research participants were, on average, 57.5 years of age at their first clinical trial screening, and 3.6% of participants enrolled in clinical trials were 80 years or older, a larger number than expected. These findings do not align with the current literature, where clinical trial participants are, on average, 55 years of age or younger (NIH, 2021). However, the findings do align with a recent report from the US Census Bureau stating that older adults comprise 17.5% of the rural population, in contrast to urban centers at 13.8% (Smith and Trevelyan, 2019).

Most clinical trial participants in this sample were women (62.2%), which is a higher number than reported in the literature. A recent study found that low recruitment of women remains an issue in industry-sponsored early-phase trials, with

TABLE 4 Clinical trial participation comparison based on Montana RUCA Codes.

| Primary RUCA Code[a] | Metropolitan or Non-Metropolitan[b] | MT RUCA tracts (n = 271)[c] | All patients (n = 753)[d] | Participation difference[e] (%) |
|---|---|---|---|---|
| 1 | Metropolitan area core | 61 (22.51%) | 358 (47.54%) | +25.03 |
| 2 | Metro area high commuting | 23 (8.49%) | 118 (15.67%) | +7.18 |
| 4 & 5 | Non-metro micropolitan areas | 51 (18.82%) | 41 (5.44%) | −13.38 |
| 7 | Non-metro, small-town core | 39 (14.39%) | 111 (14.74%) | +0.35 |
| 8 | Non-metro, small-town high commuting | 11 (4.06%) | 13 (1.73%) | −2.33 |
| 10 | Non-metro, rural areas | 86 (31.73%) | 112 (14.87%) | −16.86 |

[a]Defined using the rural-urban commuting area codes. RUCA, is a classification system used to categorize geographic areas based on their level of urbanization and commuting patterns (U.S., department of agriculture, 2019). There are no RUCA, Codes 3 and 9 in the State of Montana; RUCA, codes 4 and 5 combined due to low sample sizes.
[b]Metro counties are according to the population size of the metro area—those in "large" areas have at least 1 million residents and those in "small" areas have fewer than 1 million residents. Nonmetro counties include all counties outside metro areas and are classified as micropolitan, small town or rural area (U.S., department of agriculture, 2013).
[c]Frequency (relative frequency) by total number of FIPS, tracts in that state of Montana is 271 (U.S., census bureau, 2017).
[d]Frequency (relative frequency) for Montana patients.
[e]Computed by subtracting the relative frequency of tracts by RUCA, code from study participation (All Patients-RUCA, Tracts).

TABLE 5 Deaths across all trial participants.

| Number of enrolled trials[a] | |
|---|---|
| One study | 59 (88.1) |
| More than one study | 8 (11.9) |
| Last encounter type[a,b] | |
| Outpatient | 31 (46.3) |
| Inpatient | 31 (46.3) |
| Research | 4 (6.0) |
| Emergency Department | 1 (1.5) |
| Days to death from last encounter[c,d] | 37.8 (88.1) |

[a]Frequency [Relative Frequency (%)].
[b]Only encounters within the health system's affiliated hospitals were available to categorize the last known encounter type for deceased participants.
[c]Mean (Standard Deviation).
[d]Calculated as the difference between the last known encounter date and date of death.

females accounting for 29%–34% of participants (Cottinham and Fisher, 2022). However, the higher-than-average participation of women in clinical trials in our region correlates with clinical service delivery as breast and gynecological cancers are two of the five top-treated cancers at our healthcare facility. In this sample, 172 (20.6%) of patients participated in breast/gynecological clinical trials, just behind 284 (34.1%) participants enrolled in diabetes clinical trials. Most trials in our sample were observational; however, interventional clinical trials continue to increase and diversify across the region. Clinical trials in our area primarily focus on diabetes, breast or gynecological cancer, and other forms of cancer. Due to the region's lack of availability of specialty services, very few Biobank/Repository and lung-related trials were conducted.

While most participants were white, 4.5% of participants in this study were American Indian/Alaska Native, a percentage much higher than the national average of 1% (Mainous et al., 2023). This percentage is comparable to our service area metrics which show around 5% of our population is American Indian/Alaskan Native. This higher number may be attributed to the large service area of our region, including 7 American Indian reservations and 12 American Indian tribes (OPI, 2015). As the largest healthcare system in the rural Northwest, clinical service reaches a diverse population of varying ethnical and racial backgrounds across Montana, Wyoming, Idaho, and the Dakotas.

In analyzing our dataset, we found that 46.8% had commercial insurance and 49.4% had government-issued insurance. We also identified that over 33% had two or more insurances which would align with the aging population served in clinical trials. Even though the majority of services may be covered under the standard of care or via clinical trial benefits, patients may still be expected to pay copays and coinsurance, which may deter clinical trial participation (Unger et al., 2021; Brøgger-Mikkelsen et al., 2022).

While most participants were from metropolitan areas (i.e., RUCA 1 and 2), nearly 22% of participants lived in rural areas, with 10% living in frontier areas. Most participants (71.9%) lived closest to the large healthcare center. This finding aligns with current literature where the distribution of clinical trial participants is largely urban versus rural (Seidler et al., 2014; de Jong et al., 2022). From a practical standpoint of conducting clinical research, it is understandable to see a greater number of participants from urban areas with improved access to healthcare services. With only seven NIH top research centers in rural areas compared to the 49 in urban centers, the awareness and socialization of populations to research remains different between geographic regions (Brogger-Mikkelsen et al., 2022). Expanding clinical research to rural areas and exploring opportunities for innovative trial methodologies and designs, such as decentralized trials, may improve the heterogeneity of the sample population and the generalizability of the research findings.

Deceased participants were, on average, 10 years older than surviving participants, with half of the deaths occurring in those aged 70 years and older and among participants enrolled in one clinical trial. Most notably, death was highest among metropolitan tracts (67.5%) compared to non-metro tracts (32.5%). Specifically, participants who were older, living in the Northeastern Montana region, and residing in a metropolitan area had significantly higher mortality odds. Participants undergoing cancer treatment and those in Phase 1 or 2 trials had exceptionally high odds of death. When comparing deaths among Montana residents to the US average

TABLE 6 Logistic regression model for trial death.

| Factor[a] | Odds ratios for predictors | | | Coefficients[c] | |
|---|---|---|---|---|---|
| Level A | Level B[b] | OR | Or 95% CI | β | *p*-value |
| Age at screening | - | 1.09 | (1.06, 1.12) | 0.09 | <0.001** |
| Study phases Observational | Pilot | 0.47 | (0.02, 4.65) | −0.75 | 0.557 |
| | I | 209.1 | (32.6, 1,684.5) | 5.34 | <0.001** |
| | II | 3.93 | (1.30, 11.51) | 1.37 | 0.013* |
| | III | 2.42 | (0.80, 7.06) | 0.88 | 0.109 |
| | IV | 0.63 | (0.19, 2.11) | −0.46 | 0.447 |
| Montana region Eastern | Central & Western | 2.26 | (0.77, 6.12) | 0.81 | 0.120 |
| | Northeastern | 3.55 | (1.18, 11.05) | 1.27 | 0.025* |
| | Outside MT | 0.46 | (0.11, 1.51) | −0.79 | 0.231 |
| Disease Site Cancer, Breast & Gynecological | Diabetes | 0.13 | (0.03, 0.50) | −2.04 | 0.003** |
| | Other | 2.91 | (0.95, 9.62) | 1.07 | 0.069 |
| Study Type Domestic | International | 0.13 | (0.05, 0.33) | −2.08 | <0.001** |
| RUCA Metropolitan | Non-metropolitan Area | 0.42 | (0.17, 0.95) | −0.86 | 0.045* |
| Enrolled Year 2020 and prior | 2021–2022 | 0.22 | (0.09, 0.48) | −1.52 | <0.001** |
| Trials enrolled One study | More than one study | 2.31 | (1.11, 4.74) | 0.84 | 0.023* |
| Sponsorship Biotechnology/Device | Academic institute/Health Org | 0.29 | (0.07, 1.07) | −1.25 | 0.073 |
| | Consortium/Network/Foundation | 0.48 | (0.13, 1.73) | −0.74 | 0.258 |
| | Pharmaceutical/Biopharmaceutical | 2.01 | (0.61, 6.35) | 0.70 | 0.240 |

[a]Only statistically significant factors/levels and near/close to be significant factors and their levels were listed.
[b]Odd ratios for level A to level B.
[c]Coefficients of level A: * *p*-value is less than 0.05; ** *p*-value is less than 0.01.
[d]Median number of diagnoses was 10, median of the number of procedures was 2, and median length of stay was 5 days.

TABLE 7 Difference for RCR study's relative death frequency and current Mortality US rates (Census 2020).

| Age interval (years) | Trial death frequency (all causes) (%) | US mortality rate (all causes) (%) | Montana mortality rate (all causes) | US mortality rate (cancer) (%) | Montana mortality rate (cancer) (%) | Montana mortality rate (heart diseases) (%) |
|---|---|---|---|---|---|---|
| 18–44 | 7.8 | 0.5[a] | 1.5%[a] | 0.07[a] | 0.04[a] | 0.03[a] |
| 45–64 | 31.2 | 1.5 | 3.3% | 0.7 | 0.3 | 0.3 |
| ≥65 | 61.0 | 22.3 | 30.4 | 4.7 | 3.2 | 5.2 |

[a]Includes mortality rate statistics for 15–18 age interval.

(Table 7), Montana participants (≥65 years old) in cancer clinical trials have lower death rates (3.2%) than the national mortality average of 4.7% (Census 2020). Future research is needed to further explore mortality differences among urban and rural clinical trial research participants using epidemiological surveillance.

These findings suggest a need for targeted interventions to improve access to and education about clinical trials in rural and frontier areas. Additional work needs to be conducted to continue to gain trust in the rural communities and find ways to help with socioeconomics considerations of these patients. As the populations of our rural communities continue to age, an increased need for research services closer to patients' homes will become vitally important.

## 5 Conclusion

This RCR described the adult clinical trial participation landscape across a large healthcare organization in the rural Northwest between 1999 and 2022. While the majority of trials

were observational in nature, there were significant portions of the enterprise portfolio that centered on interventional research with industry partners, particularly surrounding diabetes and cancer. The older age of the sample population aligns with the general population of Montana and demonstrates a willingness of older adults to engage in research. While a higher likelihood of death was associated with early-phase and cancer-related research, this aligns with national assumptions with safety/efficacy studies with accelerated, varied disease processes such as cancer.

As decentralized trial design and remote or virtual elements of traditional trials become normative, representation of rural and frontier populations is not only possible but imperative to support the generalizability of trial data encouraged by the FDA. The increase in participation during and after the pandemic demonstrates the successful engagement of non-urban communities, which is critical to future awareness initiatives with novel therapies and technologies (e.g., remote patient monitoring). Retrospective chart reviews, such as the one conducted, support organizational readiness for expanded and varying the types of clinical trials within the enterprise portfolio, given the projection potential derived from historical data. Furthermore, a critical analysis of safety management policies and procedures is possible, given population-based mortality data and aggregated participant demographic information. Healthcare systems serving rural and frontier populations, empowered by historical data analysis, can lead change in expanding opportunity equity and conducting culturally congruent clinical trials in the communities served.

## 6 Limitations

Logistic regression analysis is a statistical technique to evaluate the relationship between predictor variables and a dichotomous outcome, which may have been impacted by concurrent effects of several predictor factors not controllable during the current study. While care was taken to capture all clinical trial participants within the review period, there is a possibility of missing potential eligible cases due to transcription error at the time of record creation or lack of consent form upload into the EHR. Additionally, survival analysis is the best practice to analyze clinical trial treatment efficacy. This study's RCR was unable to capture critical temporal effects (e.g., longitudinal follow-up data across many times points) except trial status at last known follow-up. This study was also unable to prospectively enroll participants in trials or treatment types. Future studies based on the results of this exploratory analysis of an extremely heterogenous mixtures of trials will utilize survival analysis to understand trial enrollment, barriers, and treatment efficacy for rural participants.

Due to low sample sizes, IRB restrictions and confidentiality, this RCR was unable to complete and/or report detailed findings related to race, ethnicity, and rurality. Future prospective studies will capture the necessary consent and data to better understand clinical trial barriers particularly among BIPOC and frontier residents.

This RCR did not include children and youth under the age of 18, which limited the interpretation to characteristics of clinical trial participation to adults. However, pediatric clinical trials are conducted at the organization, and future research will include a sub-set examination of children's enrollment in research.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Deidentified data available upon request. Requests to access these datasets should be directed to JN, jbesel@billingsclinic.org.

## Ethics statement

The studies involving humans were approved by the Montana State University IRB; Billings Clinic Privacy and Exemption Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

JN: Conceptualization, Funding acquisition, Investigation, Methodology, Writing–original draft, Writing–review and editing, Supervision. EJ: Conceptualization, Funding acquisition, Investigation, Methodology, Writing–original draft, Writing–review and editing, Supervision. BK: Data curation, Writing–review and editing. BM: Data curation, Formal Analysis, Writing–original draft, Methodology. JM: Data curation, Formal Analysis, Writing–original draft, Methodology.

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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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# Impact of a pharmacist-led educational intervention on knowledge, attitude, and practice toward the rational use of antibiotics among healthcare workers in a secondary care hospital in Punjab, Pakistan

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**Introduction:** Growing antimicrobial resistance (AMR) and decreasing efficacy of the available antimicrobials have become a significant public health concern. The antimicrobial stewardship program (ASP) ensures the appropriate use of antimicrobials and mitigates resistance prevalence through various interventions. One of the core components of the ASP is to educate healthcare workers (HWs). Therefore, this study aims to identify the impact of a pharmacist-led educational intervention targeting knowledge, attitude, and practices regarding rational antibiotic use among healthcare professionals in a secondary care hospital in Punjab.

**Methods:** This is a single-center, questionnaire-based, pre–post interventional study conducted over a six-month time period. Data analysis was conducted using SPSS version 26.

**Results:** Regarding the pre-interventional knowledge, attitude, and practice (KAP) score of the respondents, 90.3% had a good knowledge score, 81.5% had a positive attitude, and 72.3% of HWs (excluding doctors) had a good practice score. Additionally, 74.6% of the doctors had a good practice score. After educational intervention, there was a significant improvement in the knowledge, attitude, and practice of the respondent HWs ($p$-value <0.001). Furthermore, males have higher knowledge scores compared to females in the pre- and post-intervention stages ($p$-value <0.05), and doctors differ from nurses regarding knowledge scores in both pre- and post-intervention stages.

**Conclusion:** Considering educational programs as the backbone of the ASP, it is imperative to sustain efforts in the ongoing educational programs of HWs to foster high awareness and adherence to the ASP among HWs.

KEYWORDS

**rational antibiotic use, ASP, antimicrobial resistance, knowledge attitude and practice, pharmacist-led educational intervention**

# 1 Introduction

Since the discovery of antibiotics, the affirmation of a marked decrease in mortality has been indisputable. The World Health Organization (WHO) has declared inappropriate antibiotic use as a "global threat to public health" and a significant contributor toward antimicrobial resistance, causing 1.27 million deaths globally in 2019 (CDC, 2022), which could reach up to 10 million deaths per year and cost 100 trillion dollars to the global economy by 2050 (Jim O'Neill, 2016; Amaha et al., 2019; CDC, 2022; Murray et al., 2022). Thus, it is imperative to rationalize the use of antibiotics to sustain their effectiveness (Broom et al., 2015). The terminology most often used for the rational use of antibiotics within hospitals is referred to as "Antimicrobial Stewardship" (Laxminarayan et al., 2013). An essential goal of the antimicrobial stewardship program (ASP) is to ensure the appropriate usage of antimicrobials today to render them effective for those needing them in the future (Cox et al., 2017; Dyar et al., 2017).

The ASP is designed to optimize antibiotic use; education and training complement the effectiveness of ASP activities in hospitals (Apisarnthanarak et al., 2018). Educational intervention is considered a valuable tool for promoting appropriate antibiotic use (Harbarth et al., 2015; Barlam et al., 2016; Cox et al., 2017; Godman et al., 2021). In a study conducted at the National Liver Institute, Egypt, an educational program was offered to healthcare providers as an intervention to the ASP, and improvement in the knowledge, attitude, and practice of healthcare providers was observed as a result of the intervention (Tahoon et al., 2020). Various other studies have also shown significant improvements in the rational utilization of antibiotics after the educational intervention, particularly led by pharmacists (Monmaturapoj et al., 2021; Lai et al., 2022; Otieno et al., 2022; Xu et al., 2022; Almutairi et al., 2023; Lutfiyati et al., 2023). The ASP requires multidisciplinary healthcare workers to perform as a single unit, and education based on updated information is a requisite for informed decision making (Laxminarayan et al., 2013; Cosgrove et al., 2014).

Pakistan faces irrational prescribing and dispensing adversities leading to high antimicrobial resistance (AMR) (Saleem et al., 2018; Rakhshani et al., 2022). The antibiotic armamentarium has been severely compromised due to the non-judicious use of broad-spectrum antibiotics (Haseeb et al., 2022). A point prevalence survey concluded a staggering 77.6% of antibiotic use within the included hospitals of Punjab (Saleem et al., 2019), and two separate simulated client studies observed an astounding 90.5% and 96.9% of antibiotics being dispensed without prescription from pharmacies and medical stores of Pakistan (Saleem et al., 2020; Ahmad et al., 2022). Furthermore, the Pakistani pharmaceutical market is overwhelmed with "me too" generics of antibiotics, especially from the "Watch" category of WHO AWaRe classification for antibiotics, posing an extreme strain on marketing these brands and eventually increasing consumption through prescribers, ultimately taking Pakistan to the top antimicrobial consumers among developing countries (Malik and Figueras, 2019).

Pakistan's National Action Plan (NAP) against AMR emphasizes the need for an ASP in hospital settings under the fourth strategic priority (M.o.N.H.S.R.C, 2017). However, currently, available literature portrays substantial barriers that are unaddressed, consequently leading to meager implementation (Khan et al., 2020; Saleem and Pethani, 2020; Atif et al., 2021; Mubarak et al., 2021; Chang et al., 2022). Pakistan, a resource-limited country, struggles to properly implement the ASP due to the oblivious attitude of the health professional community and the non-existence of guidelines advocating for prescribing discipline regarding the rational use of antibiotics and an effective infection control program (Atif et al., 2021). Considering AMR, a looming threat, healthcare professionals in Pakistan showed a positive attitude toward ASP implementation and offered to be obtainable to educational activities despite their lack of familiarity with the program (Hayat, Rosenthal, Gillani, et al., 2019; Hayat et al., 2020). The optimal implementation of an ASP in a hospital is a collaborative effort of all health professionals, including physicians, pharmacists, nurses, and other allied health professionals dealing with antibiotics in their roles and at different stages of a treatment cycle (Saleem et al., 2022). Pharmacists, being experts in antimicrobials and a core component of a stewardship team, can play a significant role in preventing inappropriate antimicrobial use (Goff and Rybak, 2015, p. 2015; Pollack et al., 2016). A systematic review concluded that educational intervention concomitant with other antimicrobial stewardship interventions introduced by pharmacists produced beneficial outcomes and reduced the duration of antimicrobial therapy (Monmaturapoj et al., 2021). However, limited literature is available concerning educational intervention led by pharmacists in Pakistan (Butt et al., 2019; Khan and Fang, 2021). Moreover, literary resources covering secondary care facilities concerning ASP interventions and implementation are also scarce (Rupali and Kumar, 2022). Therefore, this study aims to identify the impact of a pharmacist-led educational intervention targeting knowledge, attitude, and practices regarding rational antibiotic use among healthcare professionals in a secondary care hospital in Punjab.

# 2 Materials and methods

## 2.1 Study design and setting

A pre–post interventional cohort study was guided via a self-administered questionnaire. The educational intervention was

conducted via a face-to-face lecture, assisted by an educational guide. The study was conducted in Jhelum, in Punjab province, between November 2022 and April 2023 at District Headquarter (DHQ) Hospital. It has several wards, such as the medical ward, gynecology and obstetrics ward, and pediatric ward, along with a nursery, surgical ward, cardiology ward, dialysis center, and outpatient department (OPD), offering a wide range of health services. The hospital also has an OPD pharmacy and a pharmacy in the emergency department. In general, it is a secondary care hospital with a 400-bed capacity, operating under the administrative control of the Primary & Secondary Healthcare Department, Government of Punjab.

## 2.2 Study participants

All healthcare workers (HWs) involved in prescribing, dispensing, and administering antibiotics within the confines of the health facility, including doctors, nurses, pharmacists, dispensers, and technicians/technologists, and employed by the health facility constitute the study population. A total of 256 HWs eligible for inclusion in the study were identified.

### 2.2.1 Inclusion criteria

Eligible HWs who are acquiescent to participate fulfilled the inclusion criteria.

### 2.2.2 Exclusion criteria

The reverse applies to exclusion criteria where HWs are non-consenting to participate and are not directly involved in prescribing, dispensing, and administering antibiotics. Moreover, HWs who are not employed in the said setup are also excluded.

## 2.3 Sampling technique and sample size

All HWs (256) fulfilling the inclusion criteria were approached throughout the study and requested to participate. More than 100 HWs could not be included because of different working shifts. Collectively, 150 HWs from all cadres agreed to participate. Among them, 20 out of 150 agreed participants who filled the pre-proforma withdrew their participation, and 6 participants were transferred to other facilities, so post-proforma could not be filled. Therefore, data collection concluded with a total of 124 participants.

## 2.4 Educational intervention

Each participant was handed the questionnaire after briefly describing the study; it was identified as pre-proforma. It took almost 10 min to fill the proforma on average. Afterward, the author provided an educational intervention via a face-to-face lecture, supported by an educational guide presented via PowerPoint. Each session lasted between 30 and 40 min. The author created the educational guide from the literature and educational material available on the CDC website (Lambrini et al., 2017; CDC, 2023). In general, the content of the educational guide comprised an introduction and classification of antibiotics, an introduction and mechanism of antibiotic resistance, the importance of rational utilization of antibiotics, and an introduction to and the importance of the ASP in healthcare facilities. Cadre-specific content included basic prescribing principles and factors to consider before prescribing for doctors, factors to consider before administering antibiotics, the mechanism of action of antibiotics, and the importance of correct dispensing and patient counseling for nurses, pharmacists, and others. It was presented by the lead author and assessed by the two experts in the field of clinical pharmacy. The author collected the data from HWs in small batches ranging from 8 to 10 participants on any day except for doctors who were being visited in groups of 2–3 participants each time. After the gap of 15 days, the author contacted each participant at their workstation and requested to fill the post-proformas.

## 2.5 Data collection tool

The questionnaire was acquired from a few similar studies and adopted as per the objectives of our study (Tegagn et al., 2017; Sarwar et al., 2018). The five-part questionnaire included a demographic section (gender, age, profession, and experience), a knowledge section (inquiring about the knowledge of HWs regarding antibiotics and AMR) including 10 questions, a section regarding familiarity with related terminologies (3 questions/terms), an attitude section (probing general attitude about antibiotics and AMR) including 6 questions, and a two-part practice section, where one part covered the generalized practices of all HWs other than doctors (nine questions) and the second part consisted of four questions, for which the doctors were meant to fill in regarding their prescribing practice. The total count of questions was 32, excluding demographics. Each question was based on a 5-point Likert scale (1 = no opinion, 2 = strongly disagree, 3 = disagree, 4 = agree, and 5 = strongly agree) except Section 3, where familiarity related to terminologies (AMR, rational antibiotic use, and ASP) was evaluated using a five-item scale [1 = not at all familiar (I have never heard of it), 2 = not familiar (I have heard the term, but I am not sure what it is), 3 = somehow familiar, 4 = familiar (I have heard the term and have some familiarity), and 5 = very familiar (engaged in practice)]. Outcome scoring was performed dichotomously as "Good" and "Poor" for the knowledge section, familiarity with terminologies and practice sections. A score of ≥70% was considered a "Good" score. For the attitude section, outcomes were dichotomized as "Positive" and "Negative," and a score of ≥65% was considered a positive attitude.

## 2.6 Data analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (frequencies, percentages, mean, and standard deviation) were applied to independent variables (demographics). Data were presented in a tabulated form. A normality check for data was carried out using the Shapiro–Wilk test (where $p$-value <0.05, indicating not normally distributed data). Non-parametric statistics, including the Wilcoxon signed-rank test, was applied to continuous variables to

TABLE 1 Details of the demographic characteristics of the sample.

| | — | n | % |
|---|---|---|---|
| Gender | Male | 38 | 30.6 |
| | Female | 86 | 69.4 |
| Age | 20–29 | 48 | 38.7 |
| | 30–39 | 47 | 37.9 |
| | 40–49 | 21 | 16.9 |
| | 50–59 | 8 | 6.5 |
| Profession | Doctor | 59 | 47.6 |
| | Pharmacist | 4 | 3.2 |
| | Nurse | 51 | 41.1 |
| | Dispenser | 9 | 7.3 |
| | Other | 1 | 0.8 |
| Experience (years) | <5 | 49 | 39.5 |
| | 5–10 | 34 | 27.4 |
| | >10 | 41 | 33.1 |

Sample demographics ($n$ = 124).

check the differences in pre–post data, and McNemar's test was applied to categorical variables to evaluate the differences in pre–post data. Furthermore, the independent-sample Mann–Whitney U test and Kruskal–Wallis test, followed by the Bonferroni-adjusted *post hoc* test where necessary, were applied to independent variables such as gender, age, profession, and experience. These tests were employed to check the variations within these categories concerning knowledge, attitude, and practice. A $p$-value of <0.05 was considered statistically significant, except for the *post hoc* test where Bonferroni-adjusted $p$-value was used, and all tests were two-tailed.

## 2.7 Ethical approval

Hamdard University provided ethical approval for the study to the author vide no. HU/DRA/2023/068 dated 6 February 2023. Moreover, the author was granted permission from the hospital's medical superintendent to collect data from the participants. The objectives of the study were communicated to all the participants, and verbal consent was obtained before data collection. Participants were also ensured data confidentiality. After seeking proper consent, the questionnaire was served to the participants. Participants also had the right to withdraw from the study at any stage.

# 3 Results

## 3.1 Demographics

The sample comprised 124 HWs, primarily female, $n$ = 86 (69.4%), while only $n$ = 38 (30.6%) were male. Most of the HWs, $n$ = 48 (38.7%), are from the 20–29 years age group category, followed by the 30–39 years age group category, $n$ = 47 (37.9%). Most of the HWs, $n$ = 59 (47.6%), are doctors, followed by nurses, $n$ = 51 (41.1%). Pharmacists, dispensers, and others were 3.2%, 7.3%, and 0.8%, respectively. Most HWs marked experience in the category of <5 years with $n$ = 49 (39.5%), followed by the >10 years of experience category with $n$ = 41 (33.1%). Table 1 depicts the details of the demographic characteristics of the sample.

## 3.2 Difference between pre and post knowledge scores

Regarding the statement "inappropriate antibiotic use can lead to resistance," 47.6% of HWs agreed and 37.1% strongly agreed to it in the pre-intervention stage as compared to the post-intervention stage, where 42.7% agreed and 57.3% strongly agreed (Figure 1). The statement "inappropriate use of antibiotics can lead to ineffective treatment" was agreed by 58.9% and strongly agreed by 34.7% in the pre-intervention stage, whereas the post-intervention stage showed that 46% agreed and 53.2% strongly agreed to it (Figure 1). In another statement, "inappropriate use can lead to increased adverse effects," 71% of the respondents agreed and 20.2% strongly agreed to it in the pre-intervention stage as compared to the post-intervention stage, where 50% agreed and 46% strongly agreed (Figure 1). For the statement "inappropriate antibiotic use gives an additional burden on medical costs for the patient," 50.8% of respondents agreed and 38.7% strongly agreed in the pre-intervention stage as opposed to the post-intervention stage, where 42.7% agreed and 57.3% strongly agreed (Figure 1).

Educational intervention regarding the rational use of antibiotics improved the percentage of "Good" knowledge among HWs. In total, 90.3% of them possessed "Good" knowledge in the pre-intervention stage compared to 100% in the post-intervention, which is a statistically significant result with a $p$-value <0.001 (Table 2). Moreover, there is a difference of mean in the pre-intervention knowledge score of HWs and post-intervention knowledge score from 78.48 ± 7.291 to 83.73 ± 6.413, which is also statistically significant with $p$-value <0.001 (Table 3).

Furthermore, the independent-sample Mann–Whitney U test was applied to investigate the difference across gender categories, and a statistically significant difference ($p$-value <0.05) was found in both the pre- and post-intervention knowledge scores of the respondents. Males have higher knowledge scores than females in the pre- and post-intervention stages (mean rank = 73 and 74.93, respectively) (Table 4). The independent-sample Kruskal–Wallis test was applied to independent variables (age, profession, and experience), and a statistically significant difference ($p$-value <0.05) was found across all the independent variables for knowledge scores of the respondents in the pre-intervention stage. Except for age, a statistically significant difference ($p$-value <0.05) was found across the independent variables (profession and experience) for the knowledge scores of the respondents in the post-intervention stage (Tables 4, 5). Moreover, statistically significant variables for both pre- and post-intervention stages were subjected to the Bonferroni-

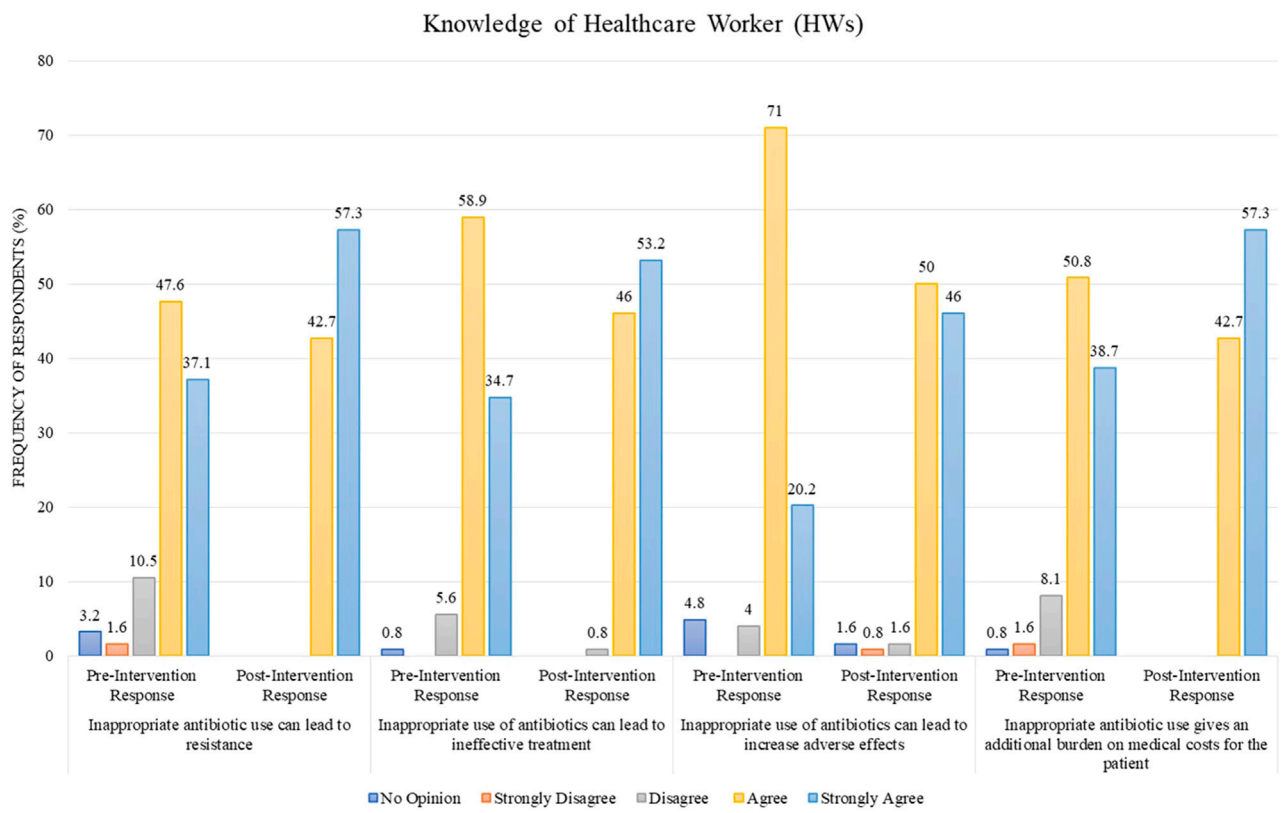


FIGURE 1
Comparison of pre- and post-intervention responses regarding the knowledge of healthcare workers.

TABLE 2 Total knowledge, attitude, and practice score of healthcare workers and doctors regarding the rational use of antibiotics.

| | Pre-intervention | | Post-intervention | | *p*-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Total knowledge score** | | | | | |
| Good (≥70%) | 112 | 90.3 | 124 | 100 | <0.001* |
| Poor (<70%) | 12 | 9.7 | 0 | 0 | |
| **Total attitude score** | | | | | |
| Positive (≥65%) | 101 | 81.5 | 123 | 99.2 | <0.001* |
| Negative (<65%) | 23 | 18.5 | 1 | 0.8 | |
| **Practice of healthcare workers** | | | | | |
| Good (≥70%) | 47 | 72.3 | 64 | 98.5 | <0.001* |
| Poor (<70%) | 18 | 27.7 | 1 | 1.5 | |
| **Prescribing practice of doctors** | | | | | |
| Good (≥70%) | 44 | 74.6 | 58 | 98.3 | 0.001* |
| Poor (<70%) | 15 | 25.4 | 1 | 1.7 | |

Data were interpreted using McNemar's test at $p < 0.05$.

adjusted *post hoc* test, which indicated that doctors were different from dispensers and nurses ($p$-value = 0.00) in the pre-intervention stage. In contrast, in the post-intervention stage, doctors differ from nurses ($p$-value = 0.00). For details, refer to Table 4.

## 3.3 Difference between pre and post familiarity with terminologies

Regarding familiarity with terminologies, 28.2% of HWs in the pre-intervention stage were familiar with the term "antimicrobial

TABLE 3 Knowledge, attitude, and practice (healthcare workers/doctors) regarding the rational use of antibiotics.

| | Pre-intervention | Post-intervention | *p*-value |
|---|---|---|---|
| Knowledge | 78.48 ± 7.291 | 83.73 ± 6.413 | <0.001* |
| Attitude | 73.63 ± 10.429 | 83.44 ± 9.532 | <0.001* |
| Practice of healthcare workers | 75.45 ± 7.396 | 81.81 ± 5.745 | <0.001* |
| Prescribing practice of doctors | 75.34 ± 12.065 | 86.53 ± 7.614 | <0.001* |

Data values are represented as mean and interpreted using the Wilcoxon signed-rank test with $p < 0.05$.

resistance" as compared to 51.6% in the post-intervention stage (Figure 2). For familiarity with the term "rational antibiotic use," 27.4% HWs were familiar in the pre-intervention stage as opposed to 48.4% in the post-intervention stage (Figure 2). Only few HWs (5.6%) were familiar with the term "antimicrobial stewardship program" in the pre-intervention stage as compared to 56.5% in the post-intervention stage (Figure 2).

## 3.4 Difference between pre and post attitude scores

In the pre-intervention stage, the response of HWs for the statement "antimicrobials are overused at my hospital/facility" was 40.3% in agreement and 37.1% in disagreement, but after the intervention, the percentage of disagreement decreased to 20.2%, with the simultaneous increase in the percentage of agreement to 54.8% (Figure 3). For the statement "antimicrobial resistance is a great problem in my hospital/facility," the post-intervention agreement percentage was 62.9% as compared to the pre-intervention stage, where only 43.5% agreed (Figure 3). In another statement, "antibiotic resistance is an important and serious public health issue faced worldwide," the respondents were 53.2% in agreement before the intervention, but after the intervention, the response for this statement was converted to "strongly agree" by a percentage of 63.7% (Figure 3). The same trend was observed for the statement "I would like more education on the appropriate use of antibiotics," with a pre-intervention agreement percentage of 62.9% as compared to the post-intervention stage where the response "strongly agree" for this statement was 59.7% (Figure 3).

The overall educational intervention improved the percentage of "Positive" attitudes in HWs regarding the rational use of antibiotics from 81.5% (pre-intervention) to 99.2% (post-intervention). This result is also statistically significant ($p$-value <0.001) (Table 2). The difference in mean between pre–post intervention scores is 73.63 ± 10.429 vs. 83.44 ± 9.532. This difference is also statistically significant, with a $p$-value <0.001 (Table 3).

## 3.5 Difference between pre and post practice scores

Most of the HWs, other than doctors ($n$ = 65, 52.4%), either disagree or strongly disagree (24.2% or 18.5%) with the statement "I dispense/administer antimicrobials without a prescription" in the pre-intervention stage as compared to the post-intervention stage where the percentage increase in the response "disagree" was observed to be 33.1%. In comparison, the response "strongly disagree" remains the same (18.5%) (Figure 4). For the statement "I dispense/administer antimicrobial agents for durations longer than prescribed by the physician on a patient's request," the percentage of disagree/strongly disagree response increased from 28.2%/14.5% before the intervention to 34.7%/17.7% after the intervention (Figure 4).

The percentage of HWs' practice (other than doctors) was presented as "Good" regarding the rational use of antibiotics in response to the educational intervention; 98.5% of the respondents improved their practice after the intervention as compared to 72.3% in the pre-intervention stage, with the result being statistically significant with a $p$-value of <0.001 (Table 2). The difference in mean between pre–post intervention scores is 75.45 ± 7.396 vs. 81.81 ± 5.745. This difference is also statistically significant, with a $p$-value <0.001 (Table 3).

## 3.6 Difference between pre and post prescribing practice scores

Regarding the prescribing practice of doctors (n = 59, 47.6%), most of them agreed and strongly agreed with the statement "if medically appropriate, IV antibiotics should be stepped down to an oral alternative after 3 days," with the cumulative percentage of "agree and strongly agree" response being 38.8%/47.6% before the intervention as opposed to 46.8%/47.6% after the intervention (Figure 5).

For the statement "broad-spectrum antibiotics should be used in place of narrow-spectrum antibiotics to reduce resistance," a range of responses were observed during the pre-intervention stage. However, after the intervention, the cumulative percentage for the responses "disagree and strongly disagree" increased to 44.3% out of 47.6% (Figure 5).

The prescribing practice of respondent doctors has been concluded as "Good" regarding the rational use of antibiotics in response to the educational intervention. During the pre-intervention, 74.6% of doctors had "Good" practice; educational intervention improved the practices, so after the intervention, 98.3% of doctors had shown "Good" practice. This result is statistically significant, with a $p$-value of 0.001 (Table 2). The difference in mean between pre–post intervention scores is 75.34 ± 12.065 vs. 86.53 ± 7.614. This difference is also statistically significant, with $p$-value <0.001 (Table 3).

TABLE 4 Comparison of the characteristics of healthcare workers and doctors with total knowledge and attitude scores before and after an intervention.

| Variable | Category | Pre-intervention (knowledge) | | | Post-intervention (knowledge) | | | Pre-intervention (attitude) | | Post-intervention (attitude) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Rank | *p*-value | Pairwise difference[a] | Rank | *p*-value | Pairwise difference[a] | Rank | *p*-value | Rank | *p*-value |
| Gender[b] | Male | 73.00 | 0.03~ | NA | 74.93 | 0.01~ | NA | 54.58 | 0.101 | 58.99 | 0.466 |
| | Female | 57.86 | | | 57.01 | | | 66.00 | | 64.05 | |
| Age (years)[c] | 20–29 | 73.27 | 0.004~ | Between 20–29 and 40–49; $p = 0.002$ | 70.75 | 0.066 | No significant difference | 56.63 | 0.125 | 62.59 | 0.868 |
| | 30–39 | 61.95 | | | 62.80 | | | 69.40 | | 63.88 | |
| | 40–49 | 39.38 | | | 49.17 | | | 54.38 | | 63.05 | |
| | 50–59 | 61.81 | | | 46.25 | | | 78.50 | | 52.38 | |
| Profession[c] | Doctors | 80.20 | <0.001~ | Between doctor and nurse; $p = 0.00$ | 74.41 | <0.001~ | Between doctor and nurse; $p = 0.001$ | 64.19 | 0.001~ | 62.73 | 0.165 |
| | Pharmacist | 92.25 | | | 100.63 | | | 105.13 | | 96.38 | |
| | Nurse | 45.43 | | | 47.46 | | | 62.76 | | 59.12 | |
| | Dispenser | 25.33 | | Between doctor and dispenser; $p = 0.00$ | 46.78 | | | 24.44 | | 59.06 | |
| | Other | 104.00 | | | 116.00 | | | 121.00 | | 117.00 | |
| Experience (years)[c] | <5 | 73.71 | 0.009~ | Between <5 and >10; $p = 0.007$ | 70.41 | 0.044~ | No significant difference | 60.90 | 0.864 | 64.13 | 0.134 |
| | 5–10 | 60.53 | | | 64.09 | | | 65.18 | | 70.31 | |
| | >10 | 50.73 | | | 51.73 | | | 62.20 | | 54.07 | |

[a]Bonferroni-adjusted *post hoc* test, $p < 0.05$.
[b]Independent-sample Mann–Whitney U test.
[c]Independent-sample Kruskal–Wallis test.





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TABLE 5 Comparison of the characteristics of healthcare workers and doctors with total practice scores before and after an intervention.

| Variable | Category | Pre-intervention (practice HWs) | | Post-intervention (practice HWs) | | Pre-intervention (practice doctors) | | Post-intervention (practice doctors) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rank | *p*-value | Rank | *p*-value | Rank | *p*-value | Rank | *p*-value |
| Gender[a] | Male | 24.06 | 0.125 | 24.17 | 0.119 | 29.29 | 0.754 | 32.69 | 0.226 |
| | Female | 34.44 | | 34.42 | | 30.68 | | 27.40 | |
| Age (years)[b] | 20–29 | 39.50 | 0.061 | 40.13 | 0.025 | 27.98 | 0.547 | 27.88 | 0.381 |
| | 30–39 | 33.43 | | 33.74 | | 34.83 | | 29.53 | |
| | 40–49 | 22.60 | | 21.40 | | 28.17 | | 40.42 | |
| | 50–59 | 40.90 | | 40.70 | | 26.17 | | 34.67 | |
| Profession[b] | Doctors | — | 0.204 | — | 0.456 | N/A | | N/A | |
| | Pharmacist | 42.00 | | 34.50 | | | | | |
| | Nurse | 33.40 | | 34.26 | | | | | |
| | Dispenser | 24.06 | | 24.17 | | | | | |
| | Other | 57.00 | | 42.00 | | | | | |
| Experience (years)[b] | <5 | 35.38 | 0.821 | 35.04 | 0.511 | 29.88 | 0.242 | 29.54 | 0.881 |
| | 5–10 | 33.44 | | 35.42 | | 37.00 | | 29.00 | |
| | >10 | 31.52 | | 29.98 | | 24.96 | | 32.04 | |

[a]Independent-sample Mann–Whitney U test.
[b]Independent-sample Kruskal–Wallis test.

## 4 Discussion

To the best of our knowledge, this is the first educational intervention study led by a pharmacist ascertaining the KAP of HWs regarding the rational use of antibiotics performed in a public hospital in Pakistan.

In general, the results of our study suggest that an educational intervention can produce a valuable improvement in KAP. Our results are similar to the previous studies, which also concluded positive outcomes after the educational intervention administered by pharmacists (Tahoon et al., 2020; Saleh, Abu Farha and Alefishat, 2021). A systematic review by Roque et al. (2014) concluded that educational intervention applied to antimicrobial use practices could produce an improved outcome.

Regarding the pre-intervention knowledge of HWs, 84.7% agreed/strongly agreed that inappropriate antibiotic use leads to resistance, like the pre-intervention response rate of other studies (Tegagn et al., 2017; Tahoon et al., 2020). In Florida, 98% of nurse practitioners agreed that inappropriate antibiotic use causes resistance (Abbo et al., 2012). A total of 93.6% of HWs agreed/strongly agreed that inappropriate antibiotic use renders treatment ineffective, similar to a study conducted in Egypt (Tahoon et al., 2020). A total of 70% of our respondents agreed that misusing antibiotics could cause harm. A Floridian study (Abbo et al., 2012) reported 96% agreement, while an Ethiopian study (Tegagn et al., 2017) reported 57.9%. This large discrepancy may be due to the developed nature of the Floridian study setting. A total of 50.8% agreed that inappropriate use increases patients' costs (Tegagn et al., 2017).

As the educational level of different professionals are hugely varied, a statistically significant difference exists for the variable "profession" in both pre- and post-intervention stage between doctors, nurses, and dispensers regarding the knowledge of HWs. A similar trend was observed in a study conducted in South Africa (Balliram et al., 2021). For other independent variables, a statistically significant difference was found between the age category (20–29 and 40–49) and experience category (<5 and >10) in the pre-intervention stage, while in the post-intervention stage, differences across these categories were found to be non-significant. This could be because of the intervention applied and the learning effect achieved via intervention in HWs.

Before the conduction of the educational intervention, only 28.2% of the HWs were familiar with the term antimicrobial resistance, which is quite different from studies conducted in Ethiopia (Tegagn et al., 2017) and Egypt (Tahoon et al., 2020). However, another study conducted in Pakistan's tertiary hospitals reported that physicians were highly familiar with antimicrobial resistance (Hayat, Rosenthal, Gillani, et al., 2019). This difference can be due to the inclusion of different cadres of HWs in our study. Only 5.6% of the HWs were familiar with the ASP. This finding is in line with various other studies from Nigeria (Babatola et al., 2021), Saudi Arabia (Baraka et al., 2019), Ethiopia (Tegagn et al., 2017), Egypt (Tahoon et al., 2020), and Pakistan (Hayat, Rosenthal, Zhu, et al., 2019). The possible reason could be the lack of implementation of the ASP and awareness campaigns regarding the importance of the ASP in the healthcare system. Contrary to these findings, studies from Australia (Cotta et al., 2014) and South Africa (Burger et al., 2016) showed high familiarity with the ASP. However, the familiarity rate improved to 56.5% after

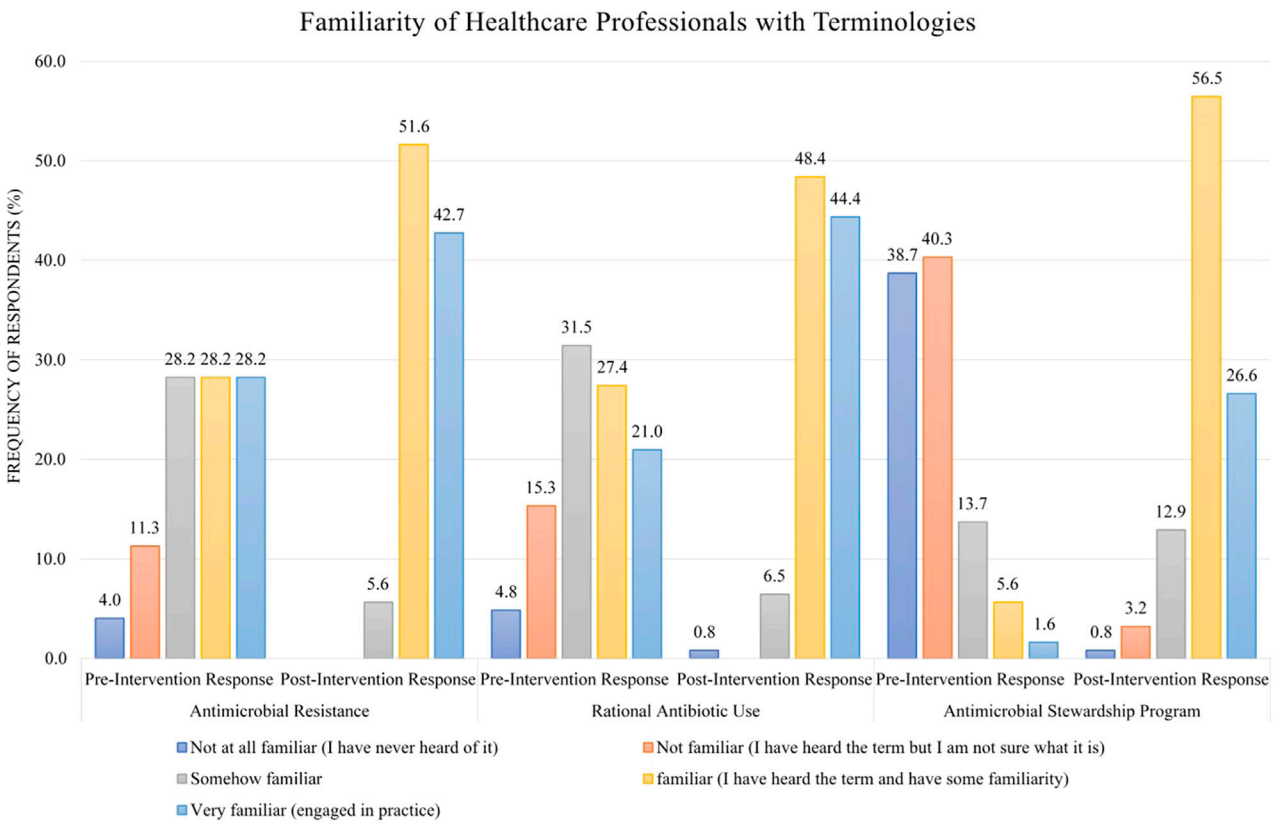


FIGURE 2
Comparison of pre- and post-intervention responses regarding the familiarity of healthcare workers with terminologies.

the intervention, indicating that the educational intervention proved beneficial in acquainting HWs with the ASP. This high awareness among developed nations is probably because of the regulatory compulsion regarding implementing the ASP in hospital settings (Australian Commission, 2011; CDC, 2019).

Like most of the studies (Tegagn et al., 2017; Baraka et al., 2019; Hayat, Rosenthal, Zhu, et al., 2019; Tahoon et al., 2020), respondents showed a positive attitude toward antimicrobial use and resistance; educational intervention only made it better. Before the intervention, almost a similar proportion of respondents agreed and disagreed (40.3% and 37.1%, respectively) regarding overusing antimicrobials at their hospital. Almost similar results were reported by other researchers as well (Abbo et al., 2012; Tegagn et al., 2017). Most of the respondents of this study agreed and strongly agreed (53.2% and 37.1%, respectively) that resistance is a serious public health issue faced worldwide, which is a similar finding to various studies reported where most respondents agreed that antimicrobial is a global problem, 95.1% (Baraka et al., 2019), 96.6% (Babatola et al., 2021), and 93.37% (Balliram et al., 2021). Only 43.5% of the respondents from our study considered antimicrobial resistance to be a problem at their hospital, which is relatively low, whereas a similar finding was reported by studies where only few respondents agreed that antimicrobial resistance was a problem at their hospital (Abera et al., 2014; Cotta et al., 2014; Hayat, Rosenthal, Zhu, et al., 2019; Balliram et al., 2021). The matter is of grave concern. Awareness campaigns regarding this falsely perceived notion of HWs and rational antibiotic use must be arranged nationally and locally. Most of the study respondents preferred education regarding correct antibiotic use, which aligns with previous studies (Abbo et al., 2012; Kalungia et al., 2019; Balliram et al., 2021).

As with the practices of HWs other than doctors, most respondents disagreed with dispensing or administering antimicrobials without prescription and for a longer duration than the physician prescribes on a patient's request. In public healthcare institutions, it is likely that due to regular internal audits and for record-keeping sake, the practice of without-prescription dispensation or administration is avoided to the maximum extent. Instead, it is more of a community problem where dispensing antimicrobials is frequently done without a prescription. Many studies confirm this finding; a study concluded that 59.9% and 59.4% of community pharmacists dispense antimicrobials without prescription and for longer than the prescribed duration, respectively (Erku, 2016). Another study reported that 74% of pharmacists dispense antimicrobials without a prescription, mainly due to business interests (Poyongo and Sangeda, 2020). In comparison to a study where the practices of community pharmacists were deemed poor (Sarwar et al., 2018), our study concluded a good practice of HWs.

Regarding the prescribing practices of doctors, most of our study participants agreed that IV antibiotics should be stepped into oral ones, which is a similar finding reported by Tegagn et al.

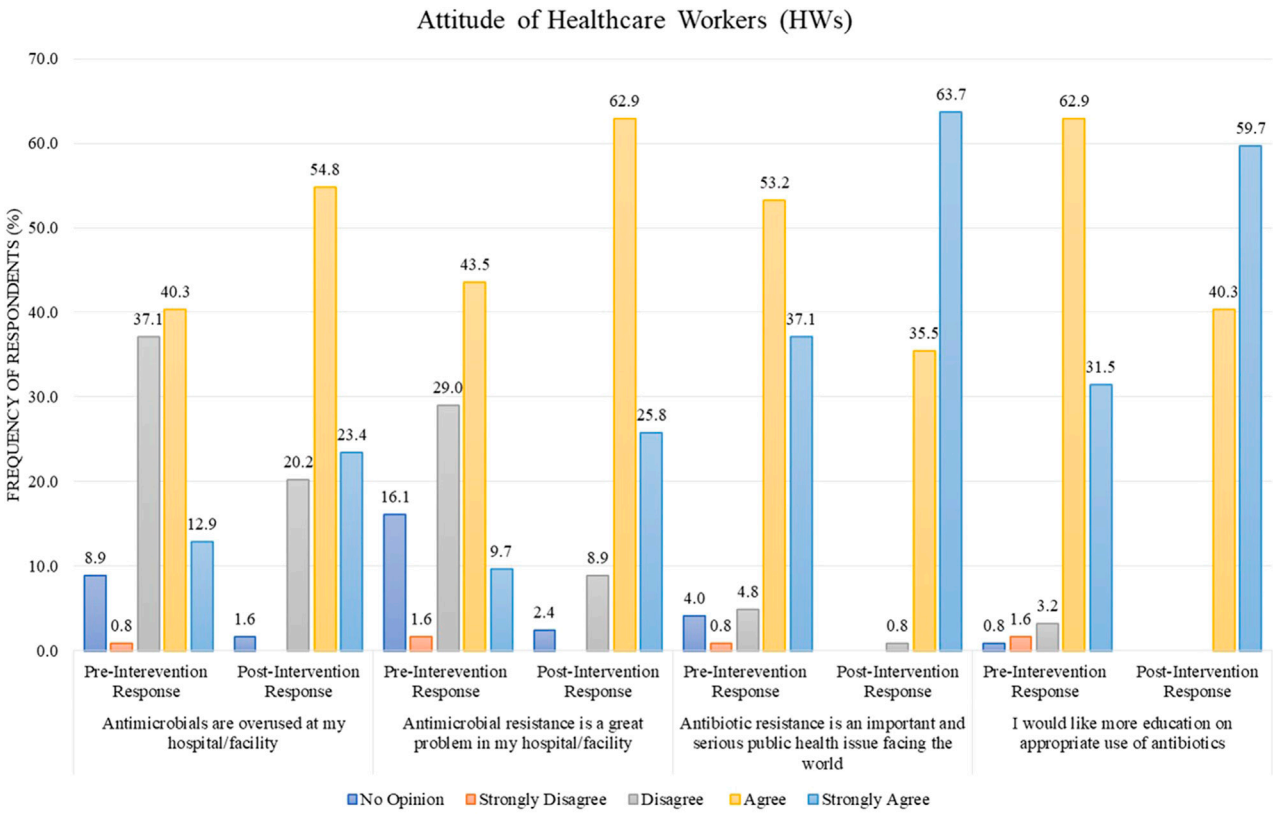


FIGURE 3
Comparison of pre- and post-intervention responses regarding the attitude of healthcare workers.

(2017). In contrast, the results of our study differ from those of Tegagn et al. regarding the statement, "broad-spectrum antibiotics should be used in place of narrow-spectrum antibiotics to reduce resistance." A relatively mixed response regarding this statement was noted before the intervention, which contradicts the results reported by these studies (Abera et al., 2014; Baraka et al., 2019). However, after the intervention, most prescribers strongly disagreed with the statement, which aligns with the results reported in this study (Saleh, Abu Farha and Alefishat, 2021).

## 4.1 Challenges and future recommendations

In Punjab's secondary care health system, there is no notified antibiotic policy or guidelines from the administrative side. Prescribing is considered the sole prerogative of physicians, with almost negligible inputs from other professional cadres, mainly pharmacists. In such circumstances, administering an educational intervention by a pharmacist is of utmost importance. Moreover, due to the lack of an established ASP in hospital settings, the custom of collaborative teamwork among doctors, nurses, and pharmacists concerning antibiotic rationalization is almost negligible, posing a serious challenge for pharmacists in devising an intervention. To conduct educational programs, the substantive support of local hospital administration and acceptance of the clinical role of pharmacists at the hospital level are imperative.

Efforts to educate HWs must continue to ensure the best patient care practices. Future studies should focus on conducting educational programs targeting the specific cadre of professionals, as per their job description and area of lacking. The efficacy of educational programs is short term (Apisarnthanarak et al., 2006; Barlam et al., 2016). A time series analysis can be beneficial in determining the efficacy of the educational intervention.

## 4.2 Strengths and limitations

This study provides the necessary confidence to the pharmacist community working in hospitals that a pharmacist-led effort regarding the implementation of the rational use of antibiotics produces beneficial outcomes. As this was a single-site study, the results obtained from this study cannot be generalized to all hospitals. Participants were enrolled via convenience sampling, so the characteristics of the clinicians who could not participate or chose not to participate are unknown. Time constraint was a limiting factor in determining sample size for data collection. Finally, the data were collected via a self-administered questionnaire, so there is a potential for response bias in the data.

This study has a few limitations. Participants were enrolled via convenience sampling, so the characteristics of the clinicians who

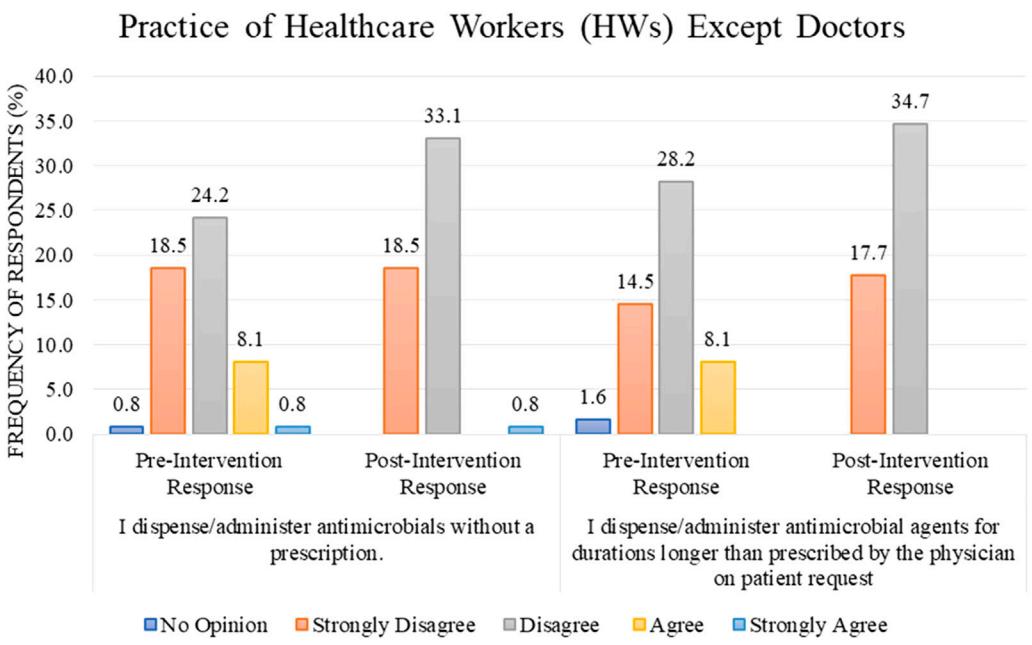


FIGURE 4
Comparison of pre- and post-intervention responses regarding the practice of healthcare workers except doctors.

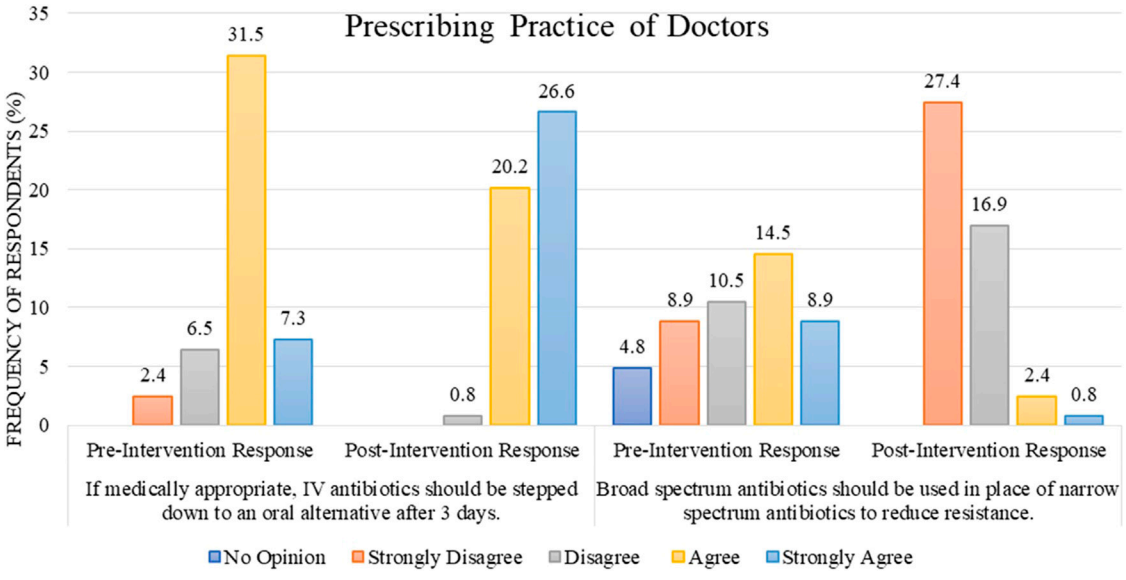


FIGURE 5
Comparison of pre- and post-intervention responses regarding the prescribing practice of doctors.

could not participate or chose not to participate are unknown. Finally, the data were collected via a self-administered questionnaire, so there is a potential for response bias in the data.

This study has few limitations. Firstly, as this was a single-site study, the results obtained from this study cannot be generalized to all hospitals. Secondly, participants were enrolled via convenience sampling, so the characteristics of the clinicians who could not participate or chose not to participate are unknown. Thirdly, time constraint was a limiting factor in determining sample size for data collection. Finally, the data were collected via a self-administered questionnaire, so there is a potential for response bias in the data.

## 5 Conclusion

The study findings conclude that the educational intervention proved to be beneficial in improving the knowledge, attitude, and practice of healthcare workers in this hospital facility regarding rational antibiotic use. Considering educational programs as a backbone of the ASP, it is imperative to sustain efforts in ongoing educational programs of HWs to foster high awareness and adherence to the ASP among HWs.

## Data availability statement

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

## Author contributions

SA: formal analysis, investigation, resources, and writing–original draft. FK: conceptualization, data curation, formal analysis, software, and writing–review and editing. MTA: conceptualization, supervision, validation, visualization, and writing–review and editing. MU: conceptualization, data curation, formal analysis, investigation, software, and writing–review and editing. MB: investigation, methodology, visualization, and writing–review and editing. MaA: conceptualization, validation, visualization, and writing–review and editing. MM: conceptualization, methodology, project administration, validation, and writing–review and editing.

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## Conflict of interest

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

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# Esketamine combined with sufentanil *versus* sufentanil in patient-controlled intravenous analgesia: a meta-analysis

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**Objective:** Patient-controlled intravenous analgesia (PCIA) can alleviate pain to some extent, and several randomized controlled trials (RCTs) have examined the efficacy of esketamine-assisted sufentanil in postoperative PCIA. In this research, we conducted a meta-analysis of relevant RCTs to compare the effect and safety of esketamine-sufentanil *versus* sufentanil alone for postoperative PCIA.

**Methods:** We systematically searched the Cochrane Library, PubMed, Embase, Web of Science, CNKI, and other libraries up to December 2023 to screen out RCTs examining the use of esketamine combined with sufentanil for PCIA. We analysed analgesia scores, sedation scores, adverse drug reactions and *postpartum* depression scores as outcome indicators.

**Results:** This meta-analysis included 32 RCTs. The results of the meta-analysis were as follows. 1) Visual Analog Scale: The VAS scores at 6, 12, 24, and 48 h were lower in the esketamine-sufentanil group than in the sufentanil alone group, and significant differences were found at all time points ($p < 0.05$). 2) Ramsay Sedation Scale: The sedation score of the esketamine-sufentanil group at 48 h after surgery was higher than that of the sufentanil group alone [mean difference (MD) = −0.09 points, confidence interval (*CI*): (−0.26, −0.07), $p = 0.27$], but this difference was not significant ($p > 0.05$). 3) Safety: Compared with sufentanil alone, the incidence rates of postoperative nausea-vomiting, dizziness-headache, skin pruritus and respiratory depression were significantly lower in the esketamine-sufentanil group. 4) *Postartum* depression: The reduction in *postpartum* depression scores were significantly greater in the esketamine-sufentanil group than in the sufentanil alone group at 3 days [MD = −1.35 points, *CI*: (−1.89, −0.81), $p < 0.00001$] and 7 days [MD = −1.29 points, *CI*: (−2.42, −0.16), $p = 0.03$].

**Conclusion:** The meta-analysis showed that the use of esketamine combined with sufentanil for postoperative PCIA could improve postoperative analgesia, alleviate *postpartum* depression and reduce the rate of postoperative adverse reactions, but there was no significant difference in sedation.

KEYWORDS

**patient-controlled intravenous analgesia, sufentanil, esketamine, postoperative pain, meta-analysis**

# 1 Introduction

Postoperative pain is a reaction to tissue damage in patients undergoing surgery. Effective postoperative analgesia can not only reduce patients' pain but also decrease postoperative complications and enhance patients' recovery, which are intrinsic requirements for rapid postoperative recovery (Barratt et al., 2021). Patient-controlled intravenous analgesia (PCIA) is a widely recognized method of postoperative analgesia that combines two or more analgesic drugs to produce a synergistic effect by acting on different targets. It not only reduces the dosage of analgesic drugs but also enhances their analgesic effect. Among the various drugs used for postoperative pain, opioids are commonly used as analgesics, as they can effectively control pain. (Shanthanna et al., 2021). However, the use of opioids may cause adverse reactions, including postoperative nausea and vomiting (PONV), respiratory depression, intestinal obstruction, delirium, and pain sensitivity, thereby significantly increasing patient pain and prolonging hospital stays (Bicket et al., 2017). Therefore, some clinical guidelines recommend combinations of analgesic drugs for PCIA to provide effective pain relief while reducing opioid-induced adverse reactions and related risks (Li et al., 2020).

Esketamine, which is the S (+) isomer of ketamine, acts on the N-methyl-D-aspartic acid (NMDA) receptor and plays an anaesthetic role (Zanos et al., 2018a). Its drugging effect is nearly twice as great as that of (R,S)-ketamine and three times greater than that of (R)-ketamine (Wang et al., 2019). Research has shown that a low dose of esketamine can reduce the incidence of anaesthesia-related side effects and has good analgesic effects, fewer adverse reactions, a short recovery time, and antidepressant effects (Hamp et al., 2018; Shoib et al., 2022). Therefore, esketamine is widely used in clinical practice. Sufentanil, which is a derivative of fentanyl, is a powerful μ-opioid receptor agonist that has the advantages of rapid onset, stable haemodynamics, and few side effects. It is currently an ideal postoperative analgesic drug (Qu and Wu, 2022). In recent years, sufentanil has become popular in clinical practice for PCIA. Thus, we performed a meta-analysis of randomized controlled trials (RCTs) on sufentanil and esketamine to quantify treatment with esketamine as the adjuvant for PCIA after sufentanil surgery.

# 2 Methods

The data in this study were collected and analysed in accordance with the guidelines published by the Cochrane Society and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). Ethics approval and informed consent were not required because this meta-analysis was a summary of prior research.

## 2.1 Search strategy

In this review, two researchers independently searched the PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang and VIP databases from inception to December 2023, to retrieve potentially relevant literature. The search was conducted by combining free words with subject words, and the search terms included "esketamine," "sufentanil," "s-ketamine," "esketamine hydrochloride," "sufentanil citrate," "intravenous" and "analgesia" using the Boolean operators "AND or OR". RCTs examining the use if esketamine and sufentanil or the use of sufentanil alone for postoperative PCIA were considered for potential inclusion. To prevent the omission of literature, additional relevant references were manually searched. Then, two authors, Manman Yao and Baoxia Fang, independently searched the literature and extracted the data. Disagreements regarding study inclusion were resolved by discussion or by consulting a third party.

## 2.2 Study inclusion and exclusion criteria

The inclusion criteria were as follows: 1) Study design: RCTs; 2) Subjects: adult surgical patients who used intravenous PCIA after surgery; 3) Intervention: esketamine combined with sufentanil for PCIA; 4) Comparison: sufentanil alone for PCIA; 5) Outcome measures: at least one of the following outcomes: VAS score, RSS score, postoperative adverse reactions (nausea, vomiting, dizziness, headache, pruritus, and respiratory depression) and postpartum depression score.

The exclusion criteria were as follows: 1) non-RCTs; 2) patients with single medication or combined medication but no PCIA after surgery; 3) studies of postoperative dural self-controlled analgesia combined with medication; 4) studies with no control group or without sufentanil; 5) studies without the original text, studies with incomplete data, or duplicate studies.

## 2.3 Data extraction

The literature was screened independently by two authors, and the data were extracted and cross-checked. Disagreements were resolved by discussion or by consulting a third party. First, the titles were screened, followed by reading the abstracts and full texts to exclude clearly unrelated references. If necessary, the reviewers contacted the authors of the original study by email or phone to obtain additional information that not extracted from the publication. The following data were extracted: 1) essential information about the study, including the title of the study, primary author, journal of delivery, etc. 2) baseline characteristics of participants and interventions, including sample size, type of surgery, drug use, etc. 3) critical information for evaluating the risk of bias; and 4) outcome indicators and outcome measures.

## 2.4 Quality assessment

After collecting relevant literature that met the eligibility criteria, the two authors independently analysed the included studies. The risk of bias of each included study was evaluated across seven domains using the Cochrane Risk of Bias Tool (Higgins et al., 2011). For each study, the domains were categorized as high risk of bias, unclear risk of bias, or low risk of bias. Disagreements between the two reviewers were resolved by discussion or by consulting a third party.

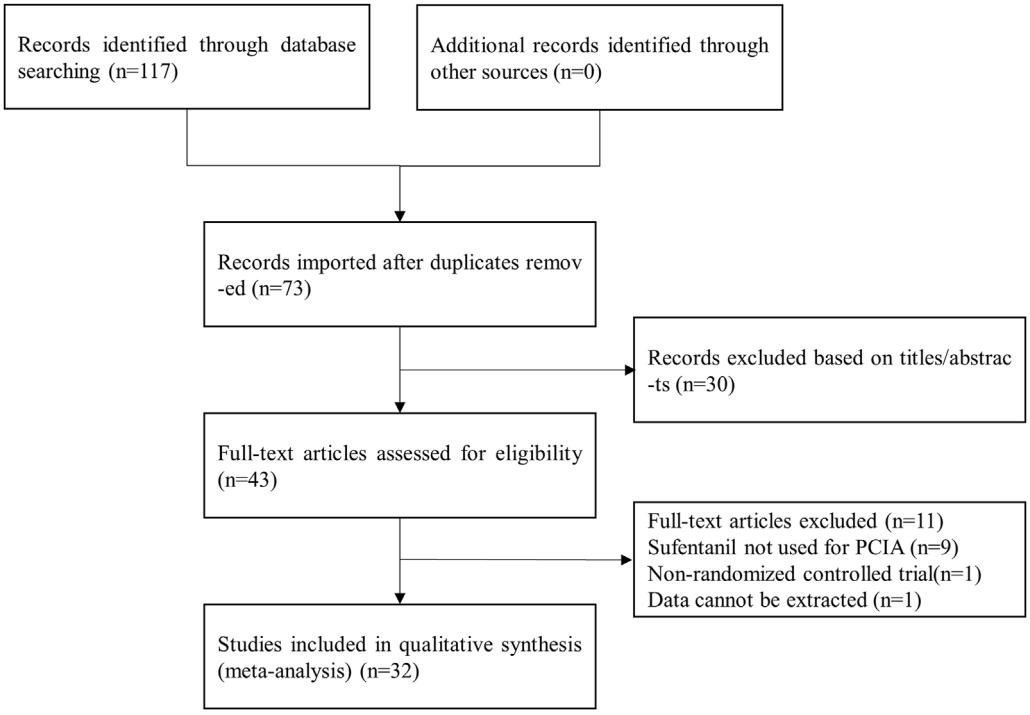


FIGURE 1
Study flow chart.

## 2.5 Statistical analysis

Quantitative analysis of the included data was performed using Review Manager 5.4. The mean difference (MD) of measurement data was used as the statistic of effect analysis, and the risk difference (RD) or odds ratio (OR) of dichotomous variables was the effect size measure (combined with the corresponding 95% *CIs*). Heterogeneity between the included studies was evaluated using the $\chi^2$ test and $I^2$ statistic. $p > 0.1$ and $I^2 < 50\%$ indicated low heterogeneity, and in such cases, a fixed effects model was used. $p < 0.1$ and $I^2 > 50\%$ indicated high heterogeneity, and in such cases, a random effects model was used.

A sufficient number of studies were included in this study (n > 10), so a publication bias analysis was conducted. If necessary, sensitivity analyses were performed to determine the source of heterogeneity by excluding studies one at a time. $p < 0.05$ indicated statistically significant differences. In the included studies, esketamine was widely used in caesarean sections. Through comprehensive analysis and expert advice, the study analysed the effects of esketamine on depression after caesarean delivery.

# 3 Results

## 3.1 Study selection and characteristics of studies

In this paper, 117 relevant studies were initially retrieved after using the keywords to search the databases. Then, 44 duplicate publications were excluded, and 73 studies remained for preliminary screening. After further reading the titles and abstracts of the remaining articles, 30 studies that did not meet the standards were excluded, and the remaining 43 studies were subjected to full-text screening. A total of 9 papers that examined PCIA without sufentanil were excluded, 1 nonrandomized controlled trial was excluded, and 1 study with incomplete data was excluded. Ultimately, 32 valid studies were included in this meta-analysis, including 3,709 patients (Guo et al., 2021; Li, 2021; Lyu et al., 2021; Yan, 2021; Wang JF. et al., 2022; Wang N. et al., 2022; Cai et al., 2022; Chi et al., 2022; Wang Y. et al., 2022; Wang W. et al., 2022; Han et al., 2022; He et al., 2022; Jiang et al., 2022; Li et al., 2022; Liang, 2022; Luo et al., 2022; Peng et al., 2022; Qiu et al., 2022; Qiu and Wang, 2022; Wang, 2022; Xu and Li, 2022; Zhang et al., 2022; Zheng et al., 2022; Zhou et al., 2022; Yang B. et al., 2023; Zhang et al., 2023a; Yang SQ. et al., 2023; Gui et al., 2023; Han et al., 2023; Su et al., 2023; Wang et al., 2023; Xie et al., 2023) (Figure 1).

## 3.2 Study characteristics

This meta-analysis included 32 RCTs, and the included studies were published between 2016 and 2023. The characteristics of the included studies are shown in Table 1.

## 3.3 Risk of bias assessment

All 32 studies (Guo et al., 2021; Li, 2021; Lyu et al., 2021; Yan, 2021; Wang JF. et al., 2022; Wang N. et al., 2022; Cai et al., 2022; Chi et al., 2022; Wang Y. et al., 2022; Wang W. et al., 2022; Han et al.,

TABLE 1 Characteristics of included trials.

| Trials (year) | Country | Age | Group | Drug concentration (PCIA) | | Sugery | Time (h) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | Sufentanil | ESK | | | |
| HL Liang 2022 | China | 21–37 | Control ($n$ = 38) | 3 μg/kg | 2 mg/kg | Caesarean section | 48 | 1,4 |
| | | | ESK + sufentanil ($n$ = 38) | 2 μg/kg | | | | |
| HY Jiang 2022 | China | 24–31 | Control ($n$ = 30) | 2 μg/kg | 2 mg/kg | Caesarean section | 48 | 1,2,4 |
| | | | ESK + sufentanil ($n$ = 30) | 2 μg/kg | | | | |
| XW Chi 2022 | China | 24–45 | Control (n = 56) | 3 μg/kg | 2 mg/kg | Caesarean section | 48 | 1,2,3 |
| | | | ESK + sufentanil (n = 56) | 2 μg/kg | | | | |
| L Cai 2022 | China | 18–65 | Control ($n$ = 43) | 2.5 μg/kg | 2 mg/kg | Hip replacement | 72 | 1,2,4 |
| | | | ESK + sufentanil ($n$ = 43) | 1.25 μg/kg | | | | |
| SG Wang 2022 | China | 21□37 | Control ($n$ = 200) | 3 μg/kg | 2 mg/kg | Caesarean section | 48 | 1,2,3,4 |
| | | | ESK + sufentanil ($n$ = 200) | 2 μg/kg | | | | |
| JF Wang 2022 | China | 18–65 | Control ($n$ = 60) | 2 μg/kg | 1.5 mg/kg | thoracic surgery | 48 | 4 |
| | | | ESK + sufentanil ($n$ = 60) | 1 μg/kg | | | | |
| XY Zhang 2022 | China | 25–40 | Control ($n$ = 60) | 1.5 μg/kg | 1.5 mg/kg | Mixed hemorrhoids | 72 | 1 |
| | | | ESK + sufentanil ($n$ = 61) | 1.5 μg/kg | | | | |
| SG Ly 2022 | China | 64–72 | Control ($n$ = 50) | 1.5 μg/kg | 1.44 mg/kg | abdominal operation | 48 | 1,2,4 |
| | | | ESK + sufentanil ($n$ = 50) | 1.05 μg/kg | | | | |
| Y Su 2023 | China | 39–80 | Control (n = 34) | 1.5 μg/kg | 1.2 mg/kg | thoracic surgery | 48 | 1,2,4 |
| | | | ESK + sufentanil (n = 33) | 1 μg/kg | | | | |
| F Xie 2023 | China | 41–69 | Control ($n$ = 52) | 2 μg/kg | 1 mg/kg | abdominal operation | 48 | 1,4 |
| | | | ESK + sufentanil ($n$ = 52) | 1.5 μg/kg | | | | |
| N Wang 2022 | China | 66–80 | Control ($n$ = 40) | 100 μg | 1 mg/kg | Esophageal cancer radical surgery | 48 | 1,2 |
| | | | ESK + sufentanil ($n$ = 40) | 50 μg | | | | |
| F Qiu 2022 | China | 50–75 | Control (n = 30) | 2 μg/kg | 1 mg/kg | spinal fusion | 48 | 1,2,4 |
| | | | ESK + sufentanil (n = 30) | 1.5 μg/kg | | | | |
| WF Gui 2023 | China | 18–70 | Control ($n$ = 32) | 2 μg/kg | 0.5 mg/kg | thoracic surgery | 48 | 4 |
| | | | ESK + sufentanil ($n$ = 34) | 2 μg/kg | | | | |
| J Li 2022 | China | 34–67 | Control ($n$ = 45) | 2 μg/kg | 0.5 mg/kg | radical mastectomy w | 48 | 1 |
| | | | ESK + sufentanil ($n$ = 45) | 2 μg/kg | | | | |

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included trials.

| Trials (year) | Country | Age | Group | Drug concentration (PCIA) | | Sugery | Time (h) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | Sufentanil | ESK | | | |
| JG Zheng 2022 | China | 18–45 | Control (*n* = 70) | 1 μg/kg | 0.5 mg/kg | Caesarean section | 48 | 1 |
| | | | ESK + sufentanil (*n* = 70) | 1 μg/kg | | | | |
| YQ Han 2022 | China | 18–45 | Control (n = 153) | 2 μg/kg | 0.5 mg/kg | Caesarean section | 48 | 4 |
| | | | ESK + sufentanil (n = 122) | 2 μg/kg | | | | |
| Y Wang 2022 | China | 25–35 | Control (*n* = 132) | 50 μg | 0.2–0.5 mg/kg | Caesarean section | 48 | 4 |
| | | | ESK + sufentanil (*n* = 108) | 50 μg | | | | |
| PL Li 2021 | China | 20–40 | Control (*n* = 153) | 2 μg/kg | 0.5 mg/kg | Caesarean section | 48 | 1,2,3 |
| | | | ESK + sufentanil (*n* = 122) | 2 μg/kg | | | | |
| B Yang 2023 | China | 44–57 | Control (*n* = 40) | 2 μg/kg | 0.36 mg/kg | abdominal operation | 48 | 1,4 |
| | | | ESK + sufentanil (*n* = 40) | 2 μg/kg | | | | |
| JM Yan 2016 | China | 20–24 | Control (n = 50) | 1 μg/kg | 0.36 mg/kg | Caesarean section | 48 | 1,3,4 |
| | | | ESK + sufentanil (n = 50) | 0.5 μg/kg | | | | |
| Y Peng 2022 | China | 18–64 | Control (*n* = 18) | 2 μg/kg | 0.25 mg/kg | Spinal orthopedics | 72 | 2,4 |
| | | | ESK + sufentanil (*n* = 18) | 1.5 μg/kg | | | | |
| W Wang 2022 | China | 22–35 | Control (n = 39) | 1.5 μg/kg | 0.2 mg/kg | Caesarean section | 48 | 4 |
| | | | ESK + sufentanil (n = 40) | 1.5 μg/kg | | | | |
| P Zhou 2022 | China | 65–82 | Control (*n* = 30) | 200 μg | 100 mg | Hip replacement | 48 | 1,2 |
| | | | ESK + sufentanil (*n* = 30) | 100 μg | | | | |
| QM Qiu 2022 | China | 35–62 | Control (*n* = 30) | 3 μg/kg | 50 mg | general anesthesia | 48 | 1,2,4 |
| | | | ESK + sufentanil (*n* = 30) | 3 μg/kg | | | | |
| J Guo 2021 | China | 20–35 | Control (*n* = 56) | 100 μg | 50 mg | Caesarean section | 24 | 1,2,3 |
| | | | ESK + sufentanil (*n* = 56) | 100 μg | | | | |
| R He 2022 | China | >18 | Control (n = 41) | 100 μg | 45 mg | Caesarean section | 48 | 3 |
| | | | ESK + sufentanil (n = 41) | 50 μg | | | | |
| YF Luo 2022 | China | 50–69 | Control (*n* = 30) | 2 μg/kg | 0.03 mg/kg/h | thoracic surgery | 48 | 1,4 |
| | | | ESK + sufentanil (*n* = 30) | 2 μg/kg | | | | |
| N Xu 2022 | China | 18–70 | Control (*n* = 30) | 0.03 μg/kg/h | 25 μg/kg/h | Open reduction of fracture | 48 | 1,4 |
| | | | ESK + sufentanil (*n* = 30) | 0.02 μg/kg/h | | | | |

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included trials.

| Trials (year) | Country | Age | Group | Drug concentration (PCIA) | | Sugery | Time (h) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | Sufentanil | ESK | | | |
| M Wang 2023 | China | 18–80 | Control ($n$ = 43) | 100 μg | 1.25 mg/kg | breast cancer surgery | 48 | 3 |
| | | | ESK + sufentanil ($n$ = 43) | 100 μg | | | | |
| TP Zhang 2023 | China | 18–65 | Control ($n$ = 42) | 2 μg/kg | 50 mg | abdominal surgery | 48 | 1,3 |
| | | | ESK + sufentanil ($n$ = 44) | 2 μg/kg | | | | |
| T Han 2023 | China | 27–37 | Control ($n$ = 70) | 150 μg | 0.5 mg/kg | Caesarean section | 48 | 1,3 |
| | | | ESK + sufentanil ($n$ = 70) | 150 μg | | | | |
| SQ Yang 2023 | China | 18–80 | Control ($n$ = 97) | 2.2 μg/kg | 2 mg/kg | Caesarean section | 48 | 1,3 |
| | | | ESK + sufentanil ($n$ = 99) | 2.2 μg/kg | | | | |

[1]Postoperative VAS, pain score.
[2]Postoperative RSS, sedation score.
[3]The incidence of postoperative adverse reactions.
[4]Postoperative EPDS, score; ESK = esketamine.

2022; He et al., 2022; Jiang et al., 2022; Li et al., 2022; Liang, 2022; Luo et al., 2022; Peng et al., 2022; Qiu et al., 2022; Qiu and Wang, 2022; Wang, 2022; Xu and Li, 2022; Zhang et al., 2022; Zheng et al., 2022; Zhou et al., 2022; Yang B. et al., 2023; Zhang et al., 2023a; Yang SQ. et al., 2023; Gui et al., 2023; Han et al., 2023; Su et al., 2023; Wang et al., 2023; Xie et al., 2023) described the details of random sequence generation. Twelve studies (Li, 2021; Yan, 2021; Chi et al., 2022; Wang W. et al., 2022; Han et al., 2022; Luo et al., 2022; Qiu and Wang, 2022; Zheng et al., 2022; Zhang et al., 2023a; Yang SQ. et al., 2023; Han et al., 2023; Wang et al., 2023) described the blinding method of participants and people and were thus considered to have a low risk of bias for this domain, while the remaining 20 studies did not describe the blinding methods and were considered to have an unclear risk of bias. Ten studies (Li, 2021; Chi et al., 2022; Wang W. et al., 2022; Han et al., 2022; Qiu and Wang, 2022; Zheng et al., 2022; Zhang et al., 2023a; Yang SQ. et al., 2023; Han et al., 2023; Wang et al., 2023) described the methods of assigning concealment. Detailed information on the methodological quality of the included studies is shown in Figure 2.

## 3.4 Results of meta-analysis

### 3.4.1 Postoperative VAS score

Eighteen studies reported VAS scores for esketamine combined with sufentanil and sufentanil alone at 6, 12, 24, and 48 h after surgery (Figure 3). The random effects model was used to analyse the pooled data. The outcomes indicated that the VAS scores for esketamine combined with sufentanil were significantly lower than those of sufentanil alone at 6, 12, 24, 48 h [$MD_6$ = −0.37 points, *CI*: (−0.54, −0.20), $p < 0.0001$]; [$MD_{12}$ = −0.31 points, *CI*: (−0.49, −0.12), $p = 0.001$]; [$MD_{24}$ = −0.45 points, *CI*: (−0.69, −0.20), $p = 0.0003$]; [$MD_{48}$ = −0.40 points, *CI*: (−0.60, −0.20), $p < 0.0001$]. Therefore, the clinical effect of the combination of the two drugs for postoperative self-controlled intravenous analgesia at 6, 12, 24, and 48 h was significantly better than that of sufentanil alone. Sensitivity analysis showed that when study by SG Wang et al. was deleted, the heterogeneity decreased from 93% to 78% at 12 h, but the heterogeneity is still high in other time periods.

### 3.4.2 Postoperative RSS score

Eleven studies reported RSS scores for esketamine combined with sufentanil and sufentanil alone at 6, 12, 24, and 48 h after surgery. There was obvious heterogeneity among different studies ($p < 0.01$); this heterogeneity was potentially related to many factors, such as surgical methods, patients' own differences, PCIA administration plans, and compatible doses. Therefore, the random effects model was used to analyse the pooled data. The results of the meta-analysis showed that the use of esketamine and sufentanil led to nonsignificantly higher RSS scores at 6, 12, 24, and 48 h after surgery than the use of sufentanil alone ($p > 0.05$). This finding indicates that esketamine combined with sufentanil had no significant effect on enhancing postoperative sedation, as shown in Figure 4. Sensitivity analysis was conducted and the results remained stable, while heterogeneity is still high.

### 3.4.3 Postoperative adverse reaction rate

Twenty-four studies reported the incidence of postoperative adverse events (Figure 5). The results showed that compared with patients treated with sufentanil alone, patients treated with esketamine-sufentanil combination therapy had lower incidence rates of PONV [OR = 0.60, *CI*: (0.40, 0.89), $p = 0.01$], dizziness-headache [OR = 0.66, *CI*: (0.46, 0.94), $p = 0.02$], pruritus [OR = 0.23, *CI*: (0.12, 0.44), $p < 0.0001$], and respiratory depression [OR = 0.18,


FIGURE 2
Risk of bias of the included studies, based on the Cochrane Risk of Bias tool.

*CI*: (0.05, 0.62), $p = 0.007$]. All outcomes showed significant differences between treatment groups. These findings indicate that the combination of esketamine and sufentanil significantly reduces the incidence of postoperative adverse reactions.

### 3.4.4 Postoperative postpartum depression score

The study analysis found that esketamine was widely used for caesarean section, so we performed subgroup analysis and collected the Edinburgh postpartum depression scores at 3 days and 7 days postpartum. We found that the differences between groups were statistically significant (Figure 6). The reduction in postpartum depression scores were greater in the esketamine-sufentanil group than in the sufentanil alone group at 3 days [MD = −1.35, *CI*: (−1.89, −0.81), $p < 0.00001$] and 7 days [MD = −1.29, *CI*: (−2.42, −0.16), $p = 0.03$]. These results show that esketamine-sufentanil can effectively reduce the incidence of postpartum depression.

### 3.4.5 Publication bias

For the 32 included studies, we analysed the publication bias for the outcome of dizziness and headache by constructing a funnel plot. The results are shown in Figure 7, with the OR value as the centre, indicating that all sample points are scattered. This suggests that there was some publication bias, indicating that the literature may have a higher degree of clinical heterogeneity and publication bias.

## 4 Discussion

Postoperative pain is one of the most common complications in patients who undergo surgery, and effective postoperative analgesia is a requirement for patients to recover quickly after surgery. At present, PCIA is widely used clinically for postoperative analgesia, and the use of two or more kinds of analgesic drugs for PCIA can achieve good analgesic effects while reducing the drug dosage (Albrecht et al., 2016). Sufentanil, which is a derivative of fentanyl, is the most common postoperative analgesic drug in clinical practice at present. However, an increase in the dosage is associated with increases in nausea, vomiting and other adverse reactions (Choi et al., 2014). Esketamine, which is the S (+) isomer of ketamine, has a bioavailability of up to 100% when injected intravenously. Esketamine has 3–4 times the affinity of ketamine for NMDA receptors (Jelen et al., 2021) and 2–3 times the affinity of ketamine for opioid receptors (Zanos et al., 2018b). Although the incidence of dissociation symptoms and other psychotic adverse reactions caused by esketamine is higher than that of ketamine at the same dose and is dose dependent, the side effects caused by ketamine are somewhat related to the dose of ketamine. Furthermore, the dosage of esketamine is half of that of ketamine with the same analgesic effect. Therefore, the use of esketamine during anaesthesia produces a less irritating response to the patient's heart, and the analgesic effect is better. Additionally, esketamine is helpful for alleviating the patient's bad mood and can meet the analgesic requirements at a lower dose.

Chen et al. (2017) found that compared with the sufentanil group, the use of ketamine-sufentanil for PCIA not only reduced the analgesic effect but also reduced the incidence of PONV and other adverse reactions. Riddell et al. (2019) have also found that low-dose

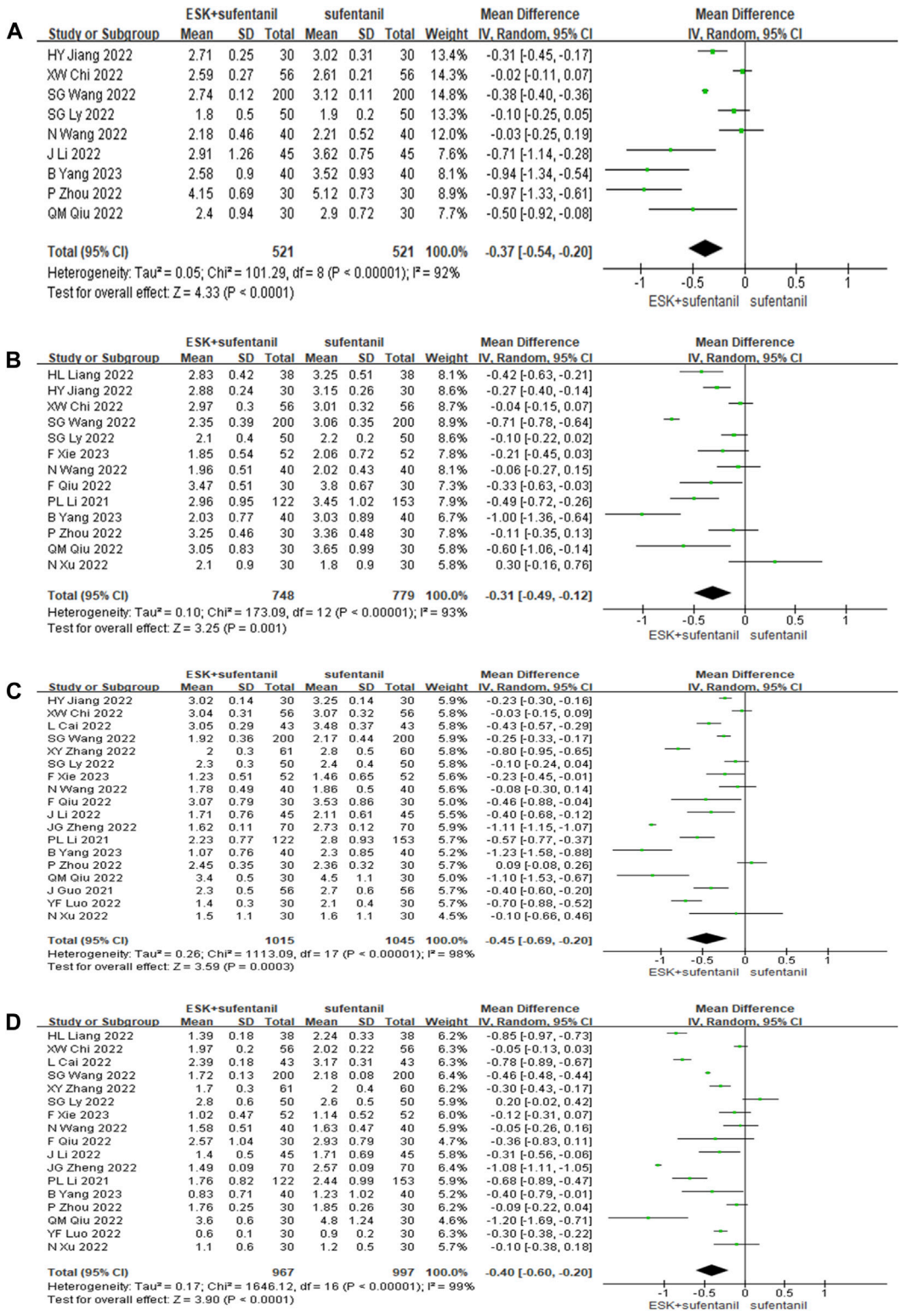


FIGURE 3
Forest plot of VAS scores at 6 h **(A)**, 12 h **(B)**, 24 h **(C)**, and 48 h **(D)** postoperatively. ESK = esketamine; VAS = visual analogue scale.

ketamine is an effective adjuvant to reduce pain and opioid demand during painful orthopaedic surgery, especially in the first 24 h after surgery. However, although the structure of esketamine is similar to that of ketamine, their pharmacokinetics and pharmacodynamics are different. Further analyses are needed to determine whether the combination of esketamine and sufentanil will have the same effect.

In this study, we analysed the role of esketamine as a sufentanil adjuvant in the treatment of PCIA and found that esketamine has a

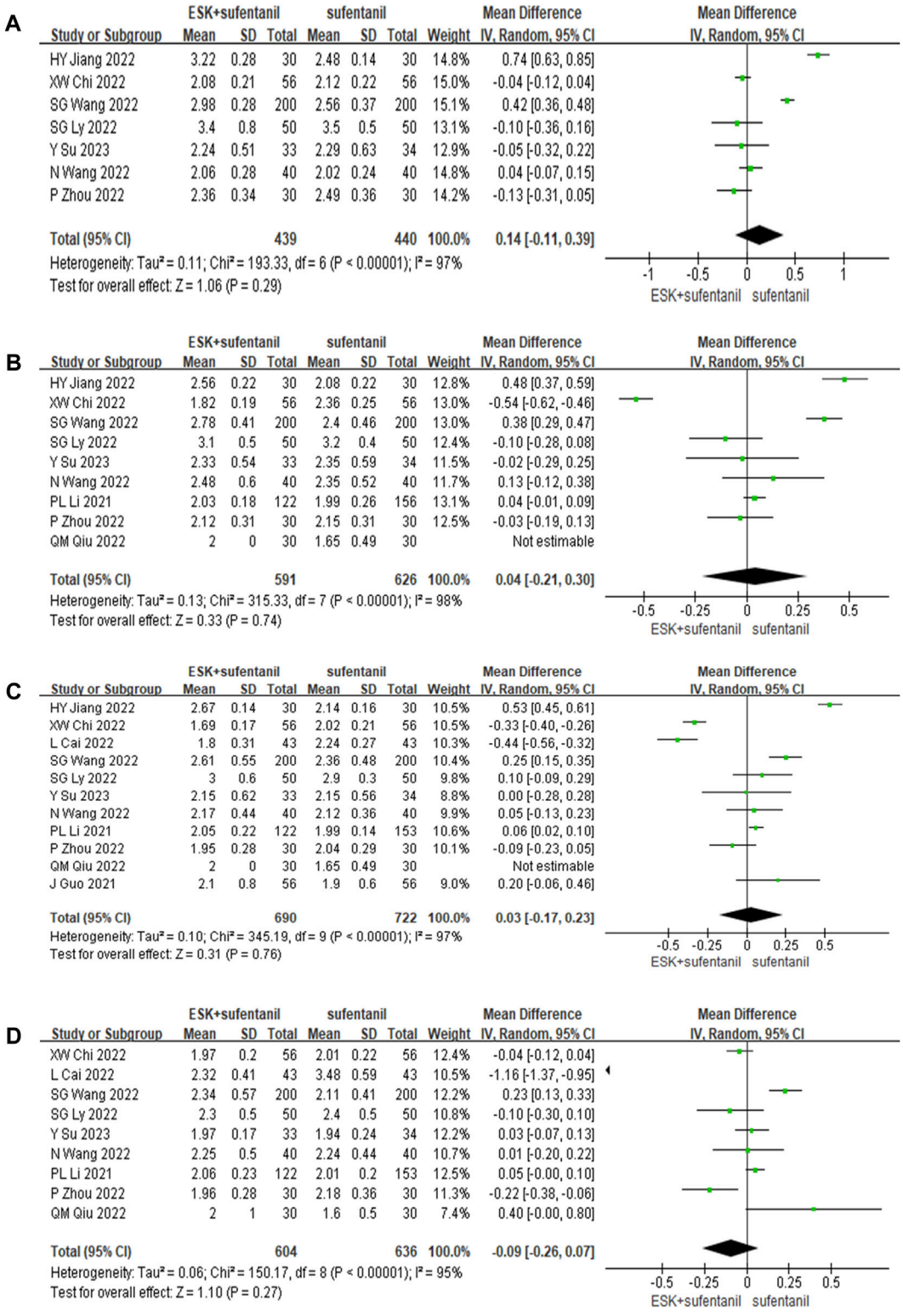


FIGURE 4
Forest plot of RSS scores at 6 h **(A)**, 12 h **(B)**, 24 h **(C)**, and 48 h **(D)** postoperatively. RSS = Ramsay Sedation Scale.

significant role in postoperative analgesia. In addition, the incidence of side effects related to sufentanil (such as nausea-vomiting, dizziness-headache, skin pruritus and respiratory depression) were reduced in the esketamine-sufentanil group. The combination of esketamine and sufentanil was also effective in reducing the incidence of postpartum depression.

Compared with the sufentanil group, the rate of complications in the esketamine-sufentanil group were significantly lower, and the

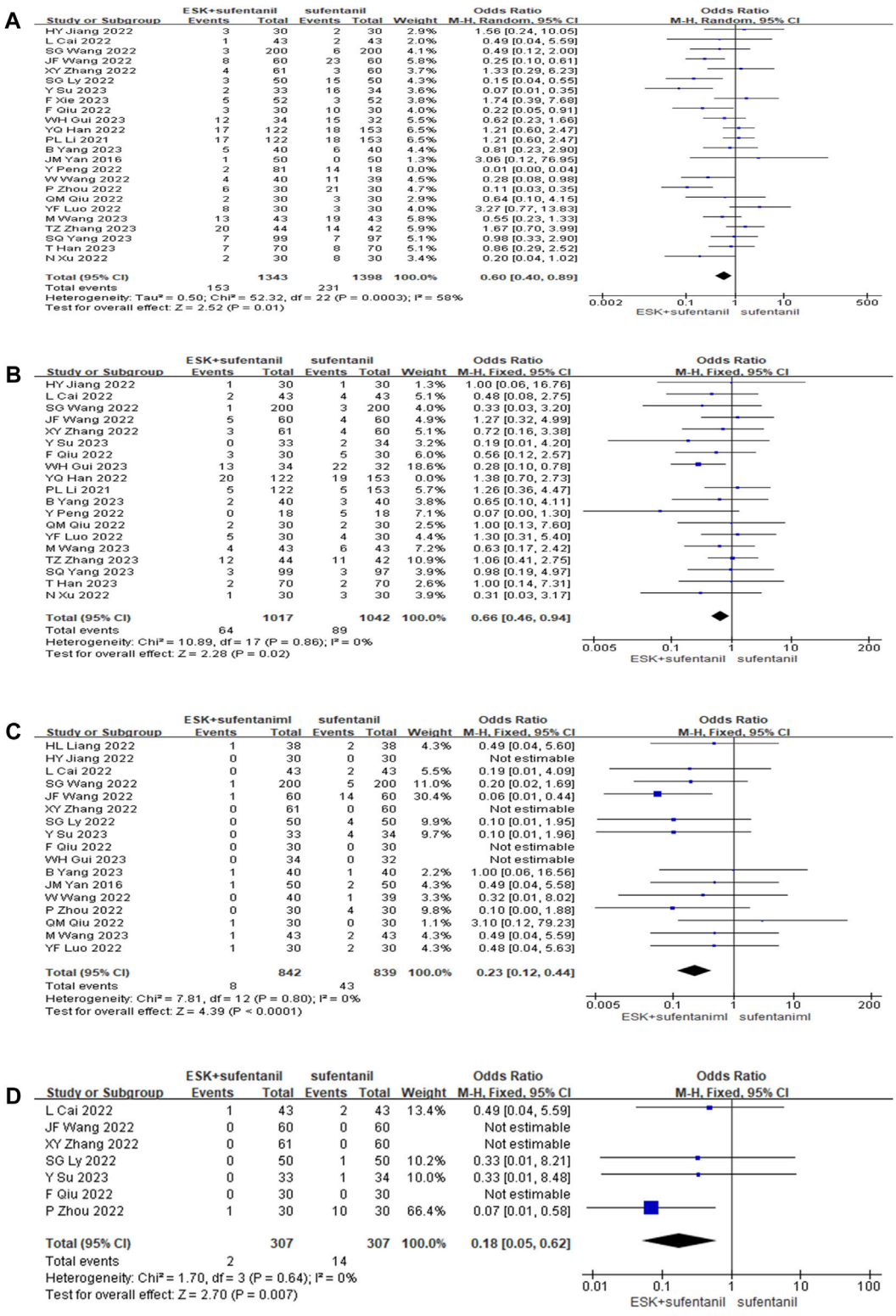


FIGURE 5
Forest plot of postoperative nausea, vomiting **(A)**; dizziness, headache **(B)**; itchy skin **(C)**; respiratory depression **(D)**.

sedation scores of patients were lower. The potential reasons for these phenomena are as follows. 1) The combination of the two drugs can reduce the use of sufentanil compared with a single-drug treatment. 2) There is a certain connection between the NMDA receptor and the opioid receptor on which esketamine acts. Animal studies have shown that NMDA receptor antagonists can reduce the incidence of adverse reactions such as nausea-vomiting by inhibiting the release of opioids (Patierno et al., 2005).

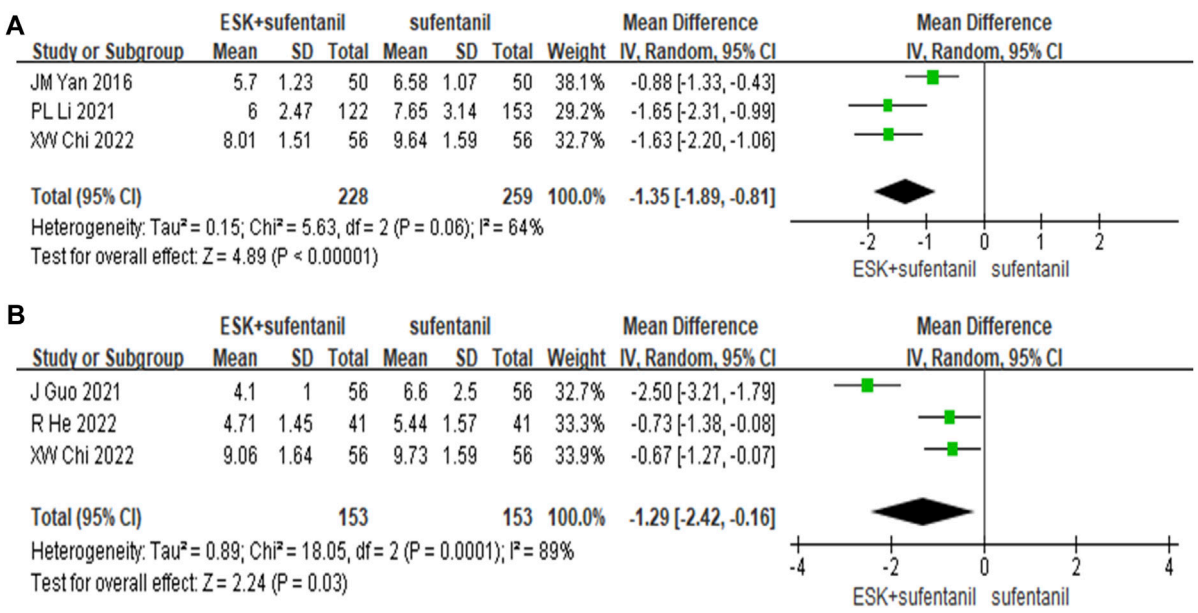


FIGURE 6
Forest plot of EPDS scores at 3 days **(A)** and 7 days **(B)** postoperatively. EPDS = Edinburgh postnatal depression scale.

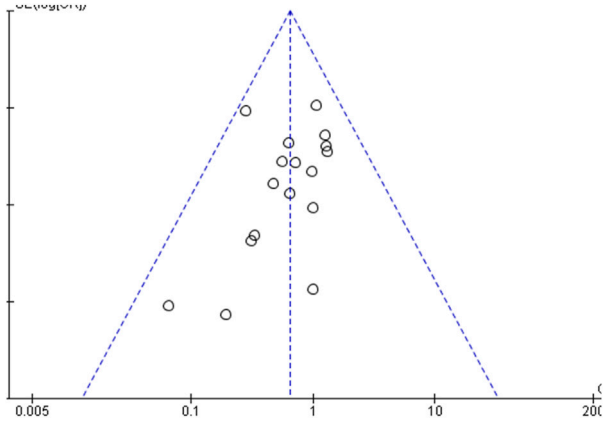


FIGURE 7
Funnel plot for publication bias assessment.

Zhang et al. (2023b) found that the esketamine-sufentanil combination for PCIA was highly effective in reducing postoperative pain at 24 h and significantly reduced the incidence of PONV compared with sufentanil alone. The results of the current study are consistent, thus providing a rationale for the administration of esketamine after 24 h. Previous meta-analyses usually analysed opioids (such as sufentanil, fentanyl, or morphine). Esketamine, as a new analgesic drug, has been widely used in the clinic in recent years. There are many studies on the commercial efficacy of esketamine in the treatment of PCIA in combination with sufentanil, but there is a lack of evidence-based medicine on the effects and safety. In this study, we integrated studies on the use of esketamine, with 28 publications in the last 7 years.

Our research revealed an article by YQ Han (Han et al., 2022). We contacted the author but did not receive any response, so we only included data on postoperative adverse reactions. This meta-analysis has some limitations. 1) Although the number of studies is large, most of them are of low methodological quality, and blinding methods were not implemented, leading to a high risk of bias and potentially affecting the results. 2) All of the included studies investigated Chinese adult patients, and even though they were published in English, it is unclear at present that our study results can be generalized to other racial groups. 3) The type of surgery, perioperative anaesthesia regimen, and drug doses varied across studies; thus, there was a high degree of heterogeneity. 4) This research did not evaluate the impact of various doses, and more randomized controlled trials are required to determine the best doses of esketamine and sufentanil for the various procedures.

Finally, in the preparation process of analgesic solutions, when two or more drugs are mixed together, visible physical reactions such as precipitation, discolouration, turbidity and gas production may occur due to the different physical and chemical properties of drugs or invisible chemical reactions such as hydrolysis, redox and titre reduction. Few studies have examined the stability compatibility of analgesic drugs in analgesic pumps. Therefore, it is necessary to strengthen the investigation and evaluation of the stability compatibility of esketamine and sufentanil in analgesic pumps to ensure the safety of clinical medication and reduce the occurrence of drug injury events.

## 5 Conclusion

Compared with sufentanil alone, the combination of esketamine and sufentanil for intravenous PCIA was more effective in terms of relieving pain, reducing the incidence of adverse effects, and decreasing the rate of postpartum depression, but there was no significant difference in sedation.

## Author contributions

MY, BF, and FC conceived this review. MY, BF, JY, and PC conducted retrieval, data filtering and extraction. MY and PC analyzed the included data. MY and PC finished the first draft. JY and FC changed the first draft. 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



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# Impacts of national volume-based drug procurement policy on the utilization and costs of antihypertensive drugs in a Chinese medicine hospital: an interrupted time series analysis of 5138 patients

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**Objectives:** The study aimed to estimate the effects of National Volume-based Drug Procurement (NVBP) policy on drug utilization and medical expenditures of hypertension patients in public medical institutions in mainland China.

**Methods:** This study used patient-level data based on electronic health records retrieved from the hospital information system of Nanjing Hospital of Chinese Medicine. Data on patients with hypertension who received care at this institution between 2016 and 2021 was used for analysis. Segmented linear regression models incorporating Interrupted Time Series (ITS) analysis were adopted to examine the effects of NVBP policy on drug utilization and health expenditures of eligible patients. Drug utilization volume and health expenditures were the primary outcomes used to assess the policy effects, and were measured using the prescription proportion of each drug class and the overall per-encounter treatment costs.

**Results:** After the implementation of NVBP policy, the volume of non-winning drugs decreased from 54.42% to 36.25% for outpatient care and from 35.62% to 15.65% for inpatient care. The ITS analysis showed that the volume of bid-winning drugs in outpatient and inpatient settings increased by 9.55% ($p < 0.001$) and 6.31% ($p < 0.001$), respectively. The volume changes in non-volume based purchased (non-VBP) drugs differed between outpatients and inpatients. The proportion of non-VBP drugs immediately increased by 5.34% ($p = 0.002$) overall, and showed an upward trend in the outpatient setting specially ($p < 0.001$) during the post-intervention period. However, no significant differences were observed in the proportion of non-VBP drugs in inpatient setting ($p > 0.05$) in term of level

change ($p > 0.05$) or trend change ($p > 0.05$). The average per-visit expenditures of outpatients across all drug groups exhibited an upward trend ($p < 0.05$) post policy intervention. In addition, a similar increase in the overall costs for chemical drugs were observed in inpatient settings (coefficient = 2,599.54, $p = 0.036$), with no statistically significant differences in the regression slope and level ($p = 0.814$).

**Conclusion:** The usage proportion of bid-winning drugs increased significantly post policy intervention, indicating greater use of bid-winning drugs and the corresponding substitution of non-winning hypertensive drugs. Drug expenditures for outpatients and health expenditures per visit for inpatients also exhibited an upward trend, suggesting the importance of enhanced drug use management in Traditional Chinese Medicine hospital settings.

KEYWORDS

**antihypertensive drugs, healthcare expenditures, interrupted time series, national centralized drug procurement, volume-based procurement antihypertensive drugs, national volume-based drug procurement**

# 1 Introduction

China has been actively controlling the rapidly growing medical costs and alleviating the financial burdens of medical care for patients. However, drug expenditures continue to increase year on year (Tao et al., 2020). According to China Health Statistical Yearbook 2021, China' total health expenditure has grown rapidly from 458.4 billion Chinese Yuan (CNY) in 2000–7,217.5 billion CNY in 2020 in China (Ma et al., 2021). Over the past 20 years, this total has grown by 15.7 times the starting amount, with an annual growth rate being higher than GDP growth rate per year. Although the proportion of drug expenditure has declined in recent years, total drug expenditures were 223.8 billion CNY in China over this period, accounting for 31.0% of overall health expenditure, which is far higher than the average level of 17% in the Organization for Economic Cooperation and Development (OECD) countries (Papanicolas et al., 2018; Wang et al., 2021a). Drug expenditures are subject to both unit drug prices and drug utilization volume, which correspond to the pharmacoeconomic supply and demand sides, respectively (Han et al., 2015). Thus, preventing rising drug prices is a much-noted potential solution to reducing medical expenditures (Wen et al., 2021).

To ensure a patient's choice of treatment options while mitigating price hikes on essential medications for chronic conditions, Chinese government issued a National Centralized Drug Procurement (NVBP) policy in January 2019 (The people's Republic of China, 2019). The NVBP policy represents the first attempt at nationwide volume-based drug procurement in mainland China, aiming to provide patients with high-quality drugs at lower prices through economies of scale. Four municipalities and seven sub-provincial cities in mainland China were selected as pilot cities for the first round of the NVBP policy's implementation, with this pilot policy introduction subsequently becoming known as the "4 + 7" policy (Li and Bai, 2019).

To date, seven rounds of NVBP pilots have been conducted and implemented in all tertiary level-A hospitals nationwide. The current drug list for NVBP pilots has expanded and continued to be implemented in more regions. Unlike provincial-based drug procurement pilots, NVBP policy is organized by the central government's procurement division. Under supervision of the State Council, the Joint Procurement Office (JPO) was established as an alliance formed by representatives of local drug procurement agencies. Thus, NVBP policy received an unprecedented level of political commitment (Yuan et al., 2021).

The primary strength of the NVBP policy lay in its "volume-based procurement", which encompassed several unique policy measures. First, volume-price linkage of procured drugs was achieved (Qu et al., 2021). Pharmaceutical enterprises offered maximum discounts on drug prices to obtain a larger market. Second, all generic drugs became obligated to pass a Generic Consistency Evaluation (GCE) before being listed for procurement. This ensured that generic drugs were adequately screened for consistency in quality and efficacy in line with those of their corresponding brand name drug equivalents (The people's Republic of China, 2016). Third, the NVBP policy guaranteed utilization of bid-winning drugs, improved the drug supply chain efficiency, and reduced capital and marketing costs (Yuan et al., 2021).

Previous studies have reported that after the implementation of the NVBP policy, non-winning generic drugs were substituted with bid-winning original and generic drugs (Lu et al., 2022a). The daily cost of bid-winning original and generic drugs decreased significantly, as did that of non-winning drugs (Yang et al., 2022). After the NVBP policy, the utilization of generic cardiovascular drugs was increasing, and the drug expenditure had been reduced by 61% (Wang et al., 2020a). A national survey revealed that average medication affordability improved from 8.2 days' wages to 2.8 days' wages, and that all the bid-winning cardiovascular drugs became affordable following the NVBP policy (Yuan et al., 2021). Relevant studies have also reported that NVBP policy played a positive role in reducing the overall drug costs and improving the average medication affordability (Li et al., 2019; Chen et al., 2020; Zhang et al., 2022). However, some researchers indicated that while total medical expenditures and drug costs decreased by 11.4% and 13.8%, respectively, other expenditures increased by 16.3% (Li et al., 2021). A similar finding was found that drug expenditures were effectively reduced while, overall health expenditures increased over time (Shen et al., 2021). In other words, Price cuts alone may be insufficient to reduce the overall healthcare burdens of patients

(Kwon et al., 2019). Other studies have clarified that price reduction alone did not necessarily lead to a decrease in overall healthcare economic burden (Zhen et al., 2018; Yang et al., 2021a).

Many existing research conclusions primarily rely on drug purchase data from regional or institutional sources of comprehensive hospitals, rather than more detailed individual prescription data. This could limit the generalizability of findings concerning the effects of policies. Furthermore, several aspects of the NVBP policy's impact remain ambiguous. For instance, drug usage and healthcare costs could vary in different pilot cities. Mainly because the baseline drug use structure varied in cities and insufficient payment capacity of local health insurance funds. Similarly, the policy effectiveness might vary in different healthcare environments. In China, healthcare facilities range from comprehensive hospitals emphasizing Western medicine to Traditional Chinese Medicine (TCM) hospitals. Unlike Western-oriented hospitals, TCM hospitals offer patients both traditional Chinese medicinal treatments and non-pharmacological TCM therapies like acupuncture and massage. The zero-markup policy has varied effects across these healthcare settings. Specifically, the impact of the policy appears more pronounced in Western medicine hospitals compared to TCM hospitals (Jiang et al., 2020). Due to the above reasons and further in depth analysis by using real-world data, we conducted a quantitative study examining the shifts in the use of hypertensive medications and the medical expenses of patients. The selection of hypertensive patient was primarily based on the fact that centralized procurement involved many category of antihypertensive drugs on the list. Another reason was that a high prevalence of hypertension, which made it easier to obtain sufficient number of research subjects. So, this analysis was based on individual patient data from a TCM hospital, comparing periods before and after the introduction of the NVBP policy.

# 2 Materials and methods

## 2.1 Data sources and collection

Real-world prescription and expenditure data for hypertension patients was sourced from the Hospital Information System (HIS) of a Chinese Medicine Hospital in Nanjing. Nanjing, the capital city of Jiangsu Province, is a megacity in South China. Nanjing consists of 11 districts, with a total administrative area of 6,587.04 $km^2$ and a total population of 9.49 million in 2022. By the end of 2021, Nanjing has 3,451 medical institutions, of which 277 are hospitals. In Nanjing, the overall clinical visits are 84.72 million in 2021, the medical costs per time per patient in outpatient and inpatient are 360.78 CNY and 17,550.41CNY, respectively. This Chinese Medicine Hospital is a prominent tertiary-grade level-A Chinese Medicine hospital, housing about 1,500 regular beds. The study targeted patients diagnosed with hypertension who had medication records spanning from 1 January 2016, to 30 April 2021.

Exclusion criteria were set to filter out specific patients.

1. Those with secondary or refractory hypertension, hypertension accompanied by valvar heart disease, or hypertension coexisting with severe, debilitating chronic illnesses like cancer or liver diseases.
2. Primary hypertension patients missing essential demographic or clinical details.

The extracted data covered a wide range, encompassing diagnostic details, demographic information, patient visit logs, prescription records, hospitalization details, imaging, consultations, lab tests, and expenditure. Specifically, the medication data incorporated drug names, specifications, dosage forms, quantities purchased, and manufacturing details.

Till 30 April 2021, the four rounds of NVBP have been implemented. To gauge the impact of the NVBP policy on various hypertension medications, drugs derived from HIS were segmented into NVBP policy-related drugs and non-volume based purchased (non-VBP) drugs. The NVBP policy-related drugs were sorted into bid-winning drugs and non-winning drugs based on the bidding results of four rounds of NVBP, otherwise they were deemed to non-winning drugs. Specific timing had been set for the bid-winning drugs involved in the four rounds of NVBP within the research period. The antihypertensive drugs, which were not included in the list of the four batches of NVBP, were defined as non-VBP drugs. Expenditure data encapsulated total healthcare costs, drug-related costs, consultation fees, and other expenses. This "other" category consisted of services, materials, treatment operations, and surgeries. Furthermore, participants were bifurcated based on whether they were outpatients or inpatients.

Adopting a retrospective methodology, the study took on the lens of a healthcare provider when analyzing costs. The study secured approval from the Research Ethics Committee of Nanjing Hospital of Chinese Medicine, under the code KY2021091. Electronic health records (EHR) data from HIS has recently received increasing recognition as a rich real-world research resource for studying healthcare issues (Huser and cimino, 2013; Chalmers et al., 2016; Cowie et al., 2017). EHR data were subsequently used in this study to gain a more well-rounded understanding of the real-world drug utilization and medical expenditures of patients with hypertension before and after the implementation of the NVBP policy.

## 2.2 Outcome variable

This study evaluated the impact of NVBP policy on drug utilization and expenditures of hypertension patients. So, the primary outcomes were the drug use volume and expenditures. The drug use volume was measured by the prescription proportion of drugs, which was calculated as the total number of prescriptions with the same category as a proportion of the summed prescriptions for enrolled hypertension patients in the month. To evaluate the effect on policy-related drugs, the chemical antihypertensive drugs were divided into three categories: winning, non-winning drugs, and non-VBP drugs. The prescription proportion was opted to be used because the aim was not only to observe changes in the volume at patient-level, but also to examine alterations in medication structure of outpatients and inpatients during the observation period. Expenditure data was measured by CNY. The average health expenditure per visit was calculated as the overall healthcare expenditures in accordance with the number of patient visits in a given month. The average monthly drug expenditures, consultation

expenditures and other expenditures were calculated in the same manner. Hypertension patients' average monthly health expenditures were calculated using the following formula:

Whereas $b_i$ represents the specific kind of expenditure incurred by outpatients/inpatients each time, n represents the total numbers of outpatient/inpatient visits in a given month, and N represents total number of outpatients/inpatients in the month.

## 2.3 Statistical analysis

Descriptive statistics were used to quantify the change in drug use volume of each category and expenditures of hypertension patients before and after the implementation of NVBP policy. Graphical displays of the use volume of each drug category and the expenditure variables were created to visualize the monthly changes in drug use volume and patient burden over the period covering from January 2016 to April 2021.

A single-group interrupted time series (ITS) was designed to assess the policy effects on drug use volume and expenditures of patients diagnosed with hypertension. ITS is a commonly used approach to evaluate the longitudinal effects of interventions that occur at a fixed point in time (Wagner et al., 2002). The time unit was set to 1 month and the intervention time was set to January 2020, which time was the policy implemented in the hospital. Therefore, a monthly time series was constructed involving 64 time points between January 2016 and April 2021, including 48 points pre-intervention and 16 points post-intervention. Owing to the lack of data available prior to 2019, the monthly time series of outpatients was obtained at 28 different points between January 2019 and April 2021, including 12 pre-intervention and 16 post-intervention points. Segmented regression models were used that controlled for baseline trends to estimate changes in the levels and trends of each outcome variable after the implementation of the NVBP policy. The following segmented linear regression model was developed:

$Y_t$ refers to the outcome variable (volume or expenditures) in month *t*, and time is a continuous variable indicating time in months at time t from the start of the observation period; intervention is an indicator for time t occurring before (intervention = 0) and after (intervention = 1) NVBP policy; time after intervention indicates months passed since the intervention (time prior to the intervention is coded 0). In this model, $\beta_0$ represents the baseline level of outcome variable at the beginning of the observation period. $\beta_1$ estimates the linear trend during the pre-intervention period. $\beta_2$ estimates the change in level immediately following policy intervention. β3 estimates the differences between pre- and post-intervention slopes. $\varepsilon_t$ is an estimate of the random error at time t. Durbin–Watson test was performed to test the presence of first-order auto-correlation, a Durbin–Watson value obtained of around 2 indicates no sign of auto-correlation. R version 4.2.1 was used to perform the ITS analysis.

A sensitivity analysis was carried out to validate the robustness of the results. During the observation period, four rounds of VBP batches had been implenmented, we appropriately specified the implementation time of different rounds during the policy promotion period to 1 January 2020, which was the first implementation time of NVBP policy in the hospital, and conducted ITS analysis. Furthermore, the absolute prescription volume was chosen an the indicator to investigate the volume change after policy intervention.

# 3 Results

## 3.1 Descriptive analysis

5,138 hypertension patients covering the period from January 2016 to April 2021, met the relevant inclusion criteria, and were subsequently included in this study, involving 2076 outpatients and 3,062 inpatients. The inclusion and exclusion criteria were shown in Figure 1. As shown in Table 1, no significant difference in socio-demographic characteristics of hypertension patients enrolled the research was observed before and after the policy, whether in the outpatients or inpatients settings.

A total of 32 antihypertensive drugs related to the NVBP policy between January 2020 and April 2021 were included in this study. Among them, 11 were bid-winning drugs and 21 were non-winning drugs (Supplementary Table S1). Monthly trend charts of the use proportion of bid-winning, non-winning and non-VBP drugs among outpatients and inpatients are shown in Figure 2 and Figure 3. The proportion of bid-winning antihypertensive drugs increased remarkably, while the non-winning drugs prominently decreased after the implementation of NVBP policy. As shown in Table 2, the volume proportion of bid-winning drugs increased by 11.29% for outpatients and rose from 0.01% to 9.04% for inpatients before intervention period and after intervention period, whereas downward trends were observed for non-winning drugs. The volume proportion of non-VBP drugs increased by 15.24% in outpatients and 18.53% in inpatients after the policy implementation, respectively.

Figure 4 and Figure 5 visualized trends in monthly expenditures among outpatients and inpatients per visit before and after the implementation of NVBP policy, the drug expenditures of outpatients with hypertension increased, as well as the health expenditures in inpatient setting. As shown in Table 3, after policy implementation, the average expenditures for total drugs, non-winning drugs and non-VBP drugs per visit increased by 48.03%, 5.23% and 123.10%, respectively, in the outpatient setting. The expenditure on bid-winning drugs was only 1.53 yuan for outpatients with hypertension. Overall healthcare, all drugs, western medicines, consultations and other associated expenditures increased by 48.62%, 14.69%, 46.58% and 109.51%, respectively. The out-of-pocket expenditures and TCM expenditures decreased by 2.17% and 21.41% (see Table 4). The length of hospital stay increased from 15.58 days to 19.02 days for hypertension patients before and after implementation of the NVBP policy.

## 3.2 ITS analysis for the changes of volume

AS shown in Table 5. The prescription proportion of bid-winning drugs increased by 9.55 and 6.31 per month ($p < 0.001$) in the outpatient and inpatient settings after policy intervention, respectively. The trend change was not statistically significant

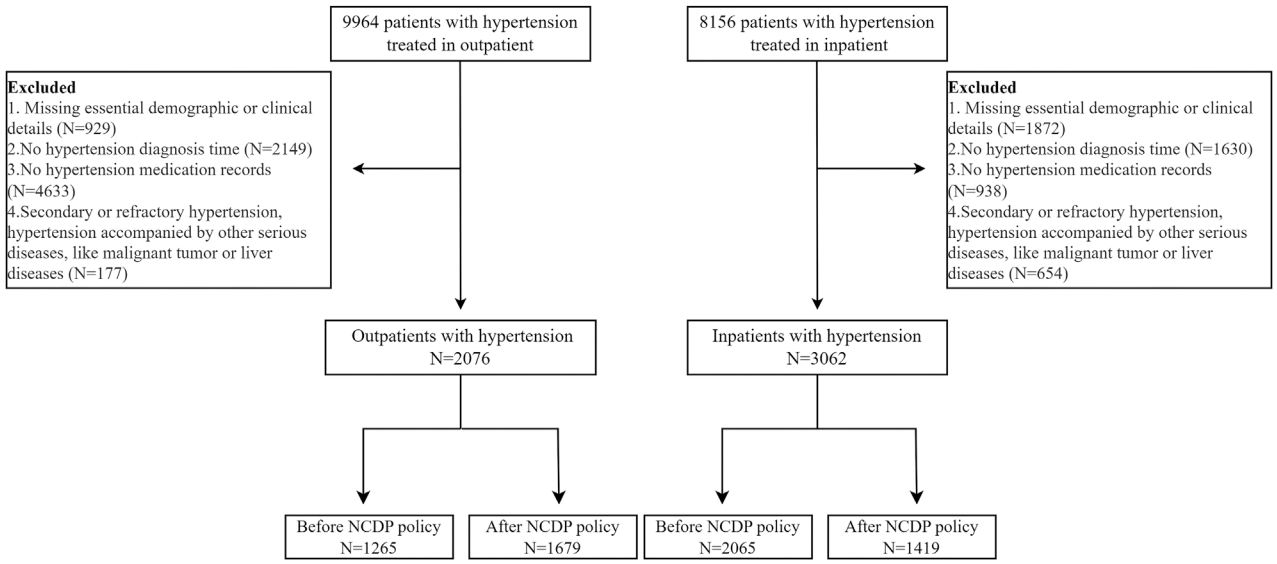


FIGURE 1
Patients enrolment into the study.

($p = 0.459$) among outpatients, whereas there was an upward trend (coefficient = 0.36, $p < 0.001$) among inpatients after intervention. A significant decline (−0.91 per month, 95%CI = −1.33 to −0.49, $p < 0.001$) was observed in the utilization of non-winning drugs among outpatients were found before and after implementation of the NVBP policy. The proportion of non-winning drugs decreased by 11.27% immediately post intervention ($p = 0.013$) in inpatient setting, though no statistically difference was found in the trend change ($p = 0.459$). For non-VBP drugs, the level and trend change showed an increase in terms of the prescription proportion for outpatients ($p = 0.002$ and $p < 0.001$, respectively), while no significant differences were observed in the volume changes ($p > 0.05$) for inpatients. The changes in TCM use were also analyzed post policy intervention. No significant changes were observed in the level or trend (both $p > 0.05$) of TCM in either outpatients or inpatients. There is no statistical difference in the volume use of TCM following the implementation of NVBP policy.

## 3.3 ITS analysis for the changes of expenditures

The results of the ITS analysis for expenditure changes in outpatients with hypertension are shown in Table 6. The per visit total drug expenditures of outpatients increased by 31.11 yuan ($p = 0.003$). There were abrupt increases in expenditures for bid-winning drugs, non-winning drugs and non-VBP drugs. Expenditures on bid-winning products increased by 1.31 yuan ($p < 0.001$) after the intervention, following by an increasing trend (coefficient = 0.04, $p = 0.049$). The non-winning products increased by11.30 yuan ($p = 0.010$), but exhibited a downward trend (coefficient = −1.06, $p = 0.046$). Meanwhile, no significant change was observed for the trend of non-VBP drugs ($p = 0.702$). Among hypertension patients treated in inpatient setting, as shown in Table 7, the expenditures of total healthcare, overall western medicines, consultations and other associated expenditures immediately increased ($p = 0.024$, $p = 0.036$, $p = 0.008$ and $p = 0.004$, respectively) when NVBP policy was implemented. However, the slope changes in expenditures showed no statistically differences. Meanwhile, no significant changes were observed in the level ($p = 0.119$) or trend of all drug expenditures ($p = 0.572$). After the implementation of NVBP policy, the length of hospital stay showed an upward trend (coefficient = 2.37, $p = 0.011$), whereas the change trend before and after the implementation of NVBP policy was not apparent (coefficient = 0.04, $p = 0.675$).

## 3.4 Sensitivity analysis

After the execution time of all bid-winning drugs was unified to 1 January 2020, which was the first implementation time of NVBP policy in the hospital. The volume propertion of bid-winning drugs increased and the proportion of non-winning drugs decreased both in the outpatient and inpatient settings (Supplementary Table S2). The changes of non-VBP were different in the outpatients and inpatients. The findings were consistent with those obtained using specific bidding times. In terms of absolute prescription volume, the ITS results showed that NVBP policy promoted the consumption of bid-winning antihypertensive drugs and suppressed the utilization of non-winning drugs. The immediate and long-term trends of non-VBP drugs were stable, with no change in the trends among inpatients before and after the NVBP policy implementation. However, the usage volume of non-VBP drugs increased after the policy implemented (Supplementary Table S3). The results were consistent with the findings using the prescription proportion of drugs. The sensitivity analysis proved the robustness of the research findings.

TABLE 1 Clinical characteristics of outpatients and inpatients before and after the implementation of NVBP policy.

| Characteristics | Outpatients | | | Inpatients | | |
|---|---|---|---|---|---|---|
| | Before (n = 1,265) | After (n = 1,679) | | Before (n = 2,065) | After (n = 1,419) | |
| | n (%) | n (%) | *p* | n (%) | n (%) | *p* |
| Male | 659 (52.1) | 880 (52.4) | 0.865 | 1,027 (49.7) | 731 (51.5) | 0.301 |
| Age(y) | | | 0.876 | | | 0.423 |
| <60 | 135 (10.7) | 181 (10.8) | | 19 (0.9) | 15 (1.6) | |
| 60~ | 687 (54.3) | 949 (56.5) | | 646 (31.3) | 431 (30.4) | |
| 70~ | 213 (16.8) | 285 (17.0) | | 713 (34.5) | 463 (32.6) | |
| ≥80 | 230 (18.2) | 264 (15.7) | | 687 (33.3) | 510 (35.9) | |
| Insurance | | | 0.593 | | | 0.005 |
| UEBMI | 693 (54.8) | 902 (53.7) | | 1,696 (82.1) | 1,217 (85.8) | |
| Other insurance | 572 (45.2) | 777 (46.3) | | 369 (17.9) | 202 (14.2) | |
| Comorbidity | | | | | | |
| MI | 7 (0.6) | 10 (0.6) | 0.881 | 26 (1.3) | 22 (1.6) | 0.469 |
| Apoplexy | 2 (0.2) | 1 (0.1) | 0.407 | 4 (0.2) | 13 (0.9) | 0.003 |
| Dyslipidemia | 101 (8.0) | 136 (8.1) | 0.909 | 83 (4.0) | 86 (6.1) | 0.006 |
| Diabetes mellitus | 394 (31.1) | 519 (30.9) | 0.891 | 793 (38.4) | 567 (40.0) | 0.355 |
| CKD | 121 (9.6) | 149 (8.9) | 0.520 | 210 (10.2) | 92 (6.5) | <0.001 |
| Class of antihypertensive drugs | | | | | | |
| CCB | 820 (64.9) | 1,019 (60.7) | 0.022 | 1,427 (69.1) | 989 (69.7) | 0.709 |
| ACEI | 130 (10.3) | 161 (9.6) | 0.536 | 386 (18.7) | 252 (17.8) | 0.484 |
| ARB | 490 (38.8) | 581 (34.6) | 0.021 | 720 (34.9) | 466 (32.8) | 0.215 |
| Diuretic | 175 (13.8) | 233 (13.9) | 0.973 | 551 (26.7) | 474 (33.4) | <0.001 |
| β-blocker | 399 (31.5) | 492 (29.3) | 0.191 | 584 (28.3) | 473 (33.3) | 0.001 |
| α-blocker | 23 (1.8) | 29 (1.7) | 0.853 | 122 (5.9) | 129 (9.1) | <0.001 |
| Compound preparation | | | | | | |
| ARB + Diuretic | 328 (25.9) | 381 (22.7) | 0.042 | 382 (18.5) | 209 (14.7) | 0.004 |
| ARB + CCB | 302 (23.9) | 356 (21.2) | 0.085 | 317 (15.4) | 199 (14.0) | 0.279 |
| ARB + other drug | 13 (1.0) | 27 (1.6) | 0.178 | 19 (0.1) | 28 (2.0) | 0.008 |
| ACEI + Diuretic | 88 (7.0) | 93 (5.6) | 0.113 | 43 (2.1) | 10 (0.7) | 0.001 |
| ACEI + CCB | 63 (5.0) | 120 (7.1) | 0.016 | 24 (1.2) | 50 (3.5) | <0.001 |
| TCM | 731 (57.8) | 933 (55.6) | 0.023 | 1823 (88.3) | 1,216 (85.7) | 0.025 |

Abbreviations: UEBMI, urban employee basic medical insurance; MI, miocardial infarction; CKD, chronic kidney disease; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

# 4 Discussion

To the best of the authors' knowledge, this is the first study patient-level data in the real world have been used to evaluate the impact of NVBP policy on the associated drug use and expenditure relating to hypertension patients. Considering the differences in the treatment setting, we selected hypertension patients treated in outpatient and inpatient departments as the population for data collection to investigate the policy impact from different dimensions.

Overall, this study found that the NVBP policy promoted the consumption of bid-winning antihypertensive drugs and suppressed the utilization of non-winning drugs, indicated significant changes in drug utilization of policy-related drugs. In the long run, the policy will promote the overall improvement of drug quality at patient level. However, the NVBP policy was not associated with the

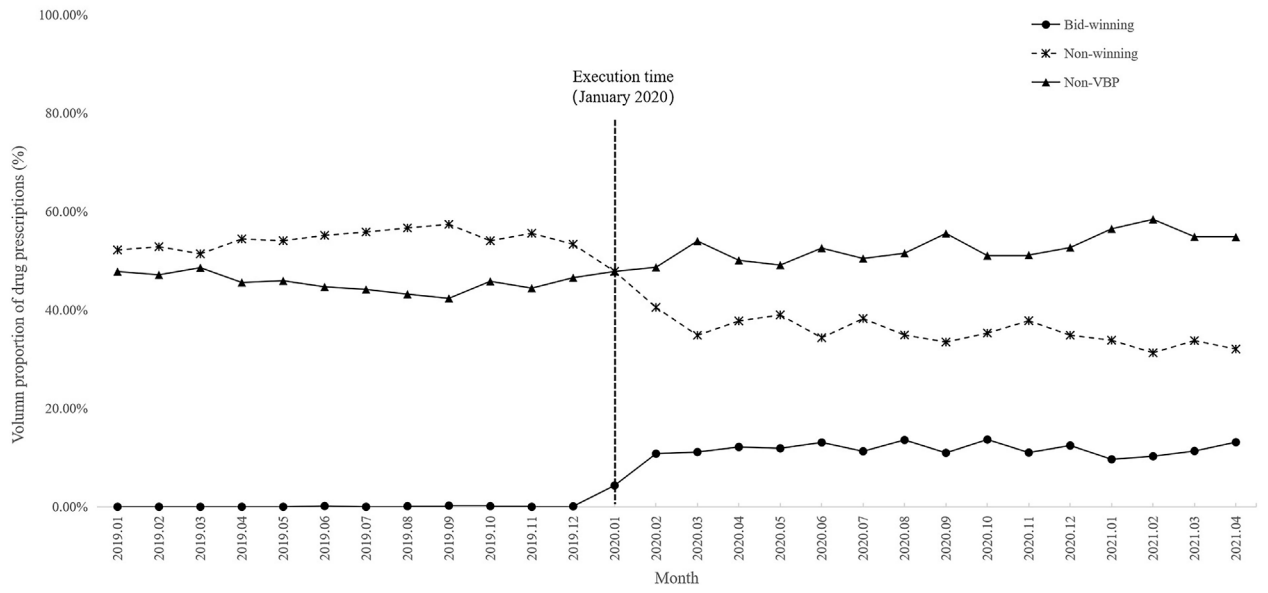


FIGURE 2
Trends in monthly volume proportion of bid-winning, non-winning and non-VBP antihypertensive drugs in outpatient setting from January 2019 to April 2021.

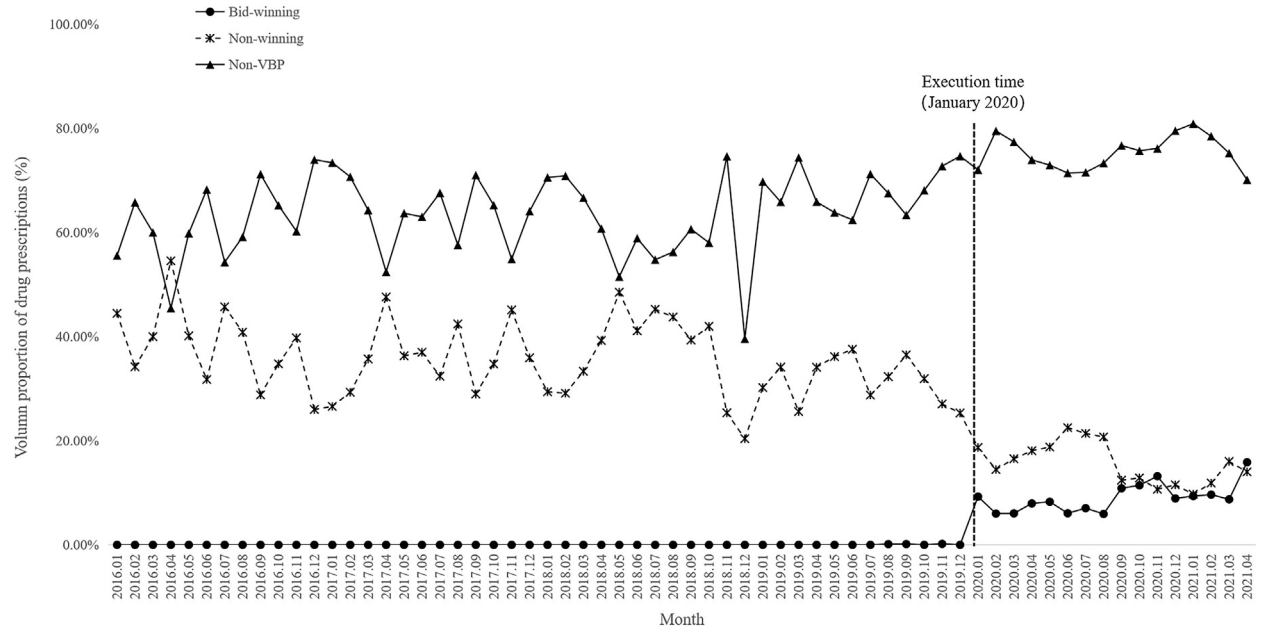


FIGURE 3
Trends in monthly volume proportion of bid-winning, non-winning and non-VBP antihypertensive drugs in inpatient setting from January 2016 to April 2021.

decrease in the drug expenses and the healthcare burden of hypertension patients in the sample TCM hospital, which indicated deviation of policy implementation effects in the different medicine institutions.

The present study found that the utilization of bid-winning antihypertensive drugs remarkably increased in both outpatient and inpatient settings. Significant statistical increasing was observed in the ITS analysis of volume proportion for bid-winning drugs. As a consequence, the proportions of non-winning drug utilization dropped by 33.38% and 56.07% among patients treated in outpatient and inpatient settings, respectively. These results are consistent with those obtained in previous studies, the national policy steer changes in prescribing behaviour and contributes to the substitution use of bid-winning products (Chen et al., 2020; Yu,

TABLE 2 Changes of volume proportion of bid-winning, non-winning and non-VBP drugs before and after implementation of NVBP policy.

| Categories | Outpatient department | | | Inpatient department | | |
|---|---|---|---|---|---|---|
| | Before | After | Growth rate (%) | Before | After | Growth rate (%) |
| Bid-winning drugs | 0.06 | 11.29 | 18,579.41 | 0.01 | 9.04 | 90,340.71 |
| Non-winning drugs | 54.42 | 36.25 | −33.38 | 35.62 | 15.65 | −56.07 |
| Non-VBP drugs | 45.52 | 52.46 | 15.24 | 63.54 | 75.31 | 18.53 |

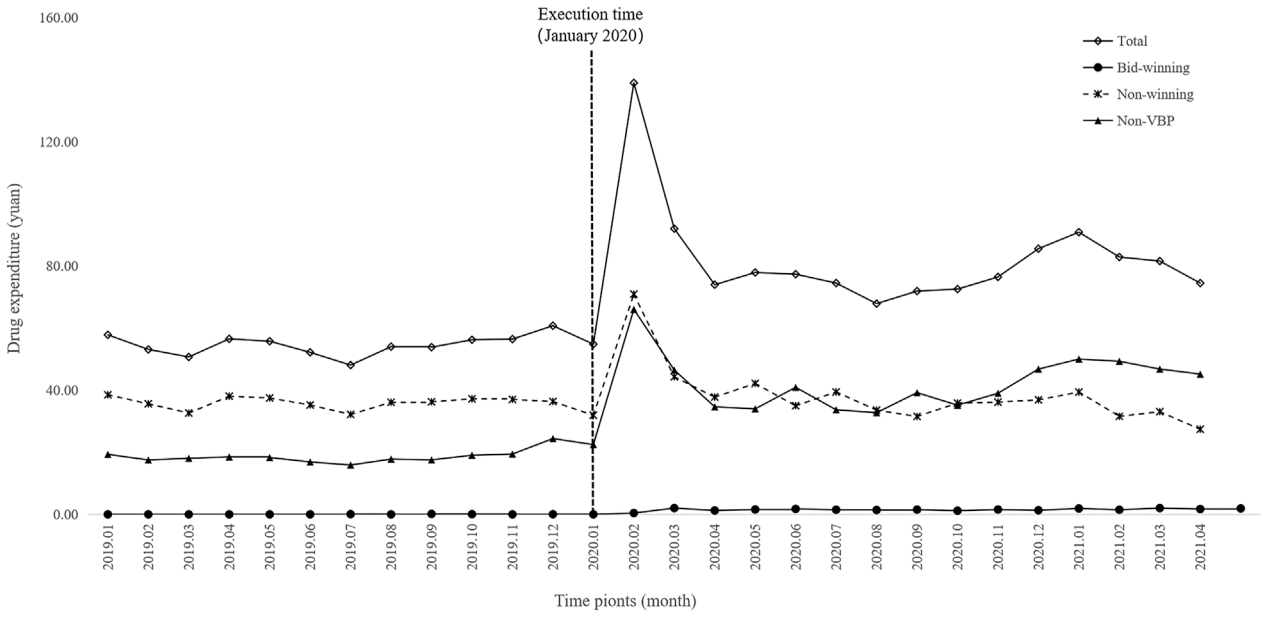


FIGURE 4
Trends in monthly drug expenditures of outpatients per visit from January 2019 to April 2021.

2020; Wang et al., 2021b). The tread of changes in number of patients using bid-winning and non-winning consistent with the changes in volume proportion of the two categories (Supplementary Appendix SA1). At the patient level, the proportion of bid-winning prescriptions and the number of patients increased, meanwhile the proportion of hypertensive patients using bid-winng antihypertensive drugs also rose. The increased use of bid-winning drugs may be related to the significant price reduction that occurred after the implementation of the NVBP policy, and thus implied that the affordability of antihypertensive drugs increased significantly and released some unmet medication demands after drug price reduction (Wang et al., 2020b). Besides, to ensure the completion of the relevant policy assessment target, healthcare institutions have launched a series of incentives for doctors to prioritize recommending the bid-winning antihypertensive drugs (Liu et al., 2021; Lu et al., 2022b). As is well known, only generic drugs which have passed consistency evaluation are deemed eligible to participate in National Volume-based Procurement. With the continuous implementation of NVBP policy, the drug use of hypertension patients will increasingly focus on bid-winning drugs, which will significantly improve the overall quality of drug used at the population level (Hu, 2019; Liu, 2020). Meanwhile, the advance of policy will promote pharmaceutical enterprises to pay more attention to drug quality and innovation (Lu et al., 2022a). Research had found that the average price cut of the centralized Volume-Based drugs was about 52%, with a maximum decrease of 98%, which complies with the policy intention of improving drug accessibility.

It is widely recognized that the high expenditures of antihypertensive drugs is one of the important factors influenced the effective control of hypertension in China (Li et al., 2019). Wang et al.'s found that the monthly drug expenditure of hypertension patients accounted for 16.38% of the total expenditure in Gansu Province, so family drug burden for those living with hypertension are the key challenges (Wang et al., 2020a). Prior to the implementation of the NVBP policy, only a very small amount of bid-winning drugs were obtained from enrolled hypertension patients in the HIS, with an average proportion of 0.06% in outpatient settings. After the policy implementation, the usage of the bid-winning antihypertensive drugs increased rapidly. The bid-winning drug expenditures averaging of 1.53 yuan per visit remained affordable although the significant level and trend change of bid-winning drug expenditures in outpatient setting after the policy were observed, and which indicated the policy effect of relieve the drug

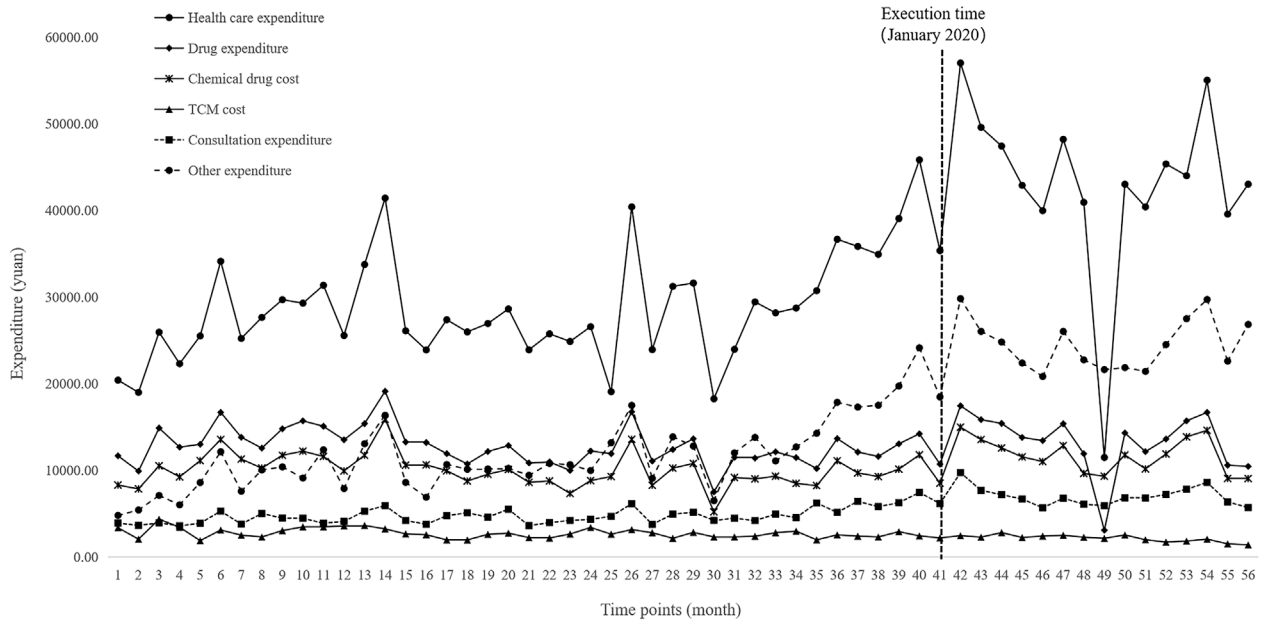


FIGURE 5
Trends in monthly healthcare expenditures of inpatients per visit from January 2016 to April 2021.

TABLE 3 Changes of expenditures of hypertension patients in outpatient setting before and after implementation of NVBP policy.

| Categories | Before (yuan) | After (yuan) | Growth rate (%) |
|---|---|---|---|
| Total drugs | 54.63 | 80.86 | 48.03 |
| Bid-winning drugs | 0.02 | 1.53 | 6,343.48 |
| Non-winning drugs | 36.05 | 37.93 | 5.23 |
| Non-VBP drugs | 18.56 | 41.40 | 123.10 |

TABLE 4 Changes of expenditures of hypertension patients in inpatient setting before and after implementation of NVBP policy.

| Categories | Before | After | Growth rate (%) |
|---|---|---|---|
| Overall healthcare (yuan) | 28,735.91 | 42,708.13 | 48.62 |
| Drug expenditures (yuan) | 12,800.87 | 13,166.63 | 2.86 |
| Medical drug expenditures (yuan) | 10,059.29 | 11,537.07 | 14.69 |
| TCM expenditures (yuan) | 2,741.58 | 2,154.47 | −21.41 |
| Consultation expenditures (yuan) | 4,750.95 | 6,963.96 | 46.58 |
| Other expenditures (yuan) | 11,553.23 | 24,205.45 | 109.51 |
| Out of pocket expenditures (yuan) | 6,872.88 | 6,723.87 | −2.17 |
| Hospital days (day) | 15.58 | 19.02 | 22.06 |

burden of hypertensive patients. However, some patients and doctors still had doubts about the safety and efficacy of the bid-winning drugs. It is necessary to explore more systematic approaches to boosting public confidence in bid-winning generic drugs and enhance physicians' acceptability of them (Zhu et al., 2023).

Different changes were also found in the usage volume of non-VBP drugs in different healthcare settings. The ITS results showed that the immediate and long-term trends were stable, with no change in the trends among inpatients before and after the NVBP policy implementation. However, the usage proportion of non-VBP drugs increased by 5.34% after the NVBP policy was

TABLE 5 ITS results of volume proportion of bid-winning, non-winning, non-VBP and TCM antihypertensive drugs.

| Categories | Outpatients | | Inpatients | |
|---|---|---|---|---|
| | Coef | 95% CI | Coef | 95% CI |
| Bid-winning | | | | |
| Level change,β2 | 9.55 | (6.87, 12.23)*** | 6.31 | (5.10, 7.52)*** |
| Trend change,β3 | 0.14 | (-0.22, 0.49) | 0.36 | (0.24, 0.48)*** |
| Durbin-Watson,d | 1.86 | | 1.76 | |
| Non-winning | | | | |
| Level change,β2 | −15.84 | (-19.19, −12.50)*** | −11.27 | (-19.84, −2.69)* |
| Trend change,β3 | −0.91 | (-1.33, −0.49)*** | −0.33 | (-1.20, 0.54) |
| Durbin-Watson,d | 2.15 | | 1.89 | |
| Non-VBP | | | | |
| Level change,β2 | 5.34 | (2.41, 8.28)** | 7.82 | (-0.02, 15.66) |
| Trend change,β3 | 0.75 | (0.38, 1.13)*** | −0.01 | (-0.78, 0.77) |
| Durbin-Watson,d | 1.99 | | 1.90 | |
| TCM | | | | |
| Level change,β2 | 0.19 | (-32.08, 32.46) | −2.89 | (-39.21, 33.44) |
| Trend change,β3 | −2.75 | (-7.70, 2.21) | −0.80 | (-4.42, 2.82) |
| Durbin-Watson,d | 1.94 | | 1.97 | |

Abbreviations: Coef., coefficient; SE, standard error; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 6 ITS results for drug expenditures in outpatient setting.

| Categories | Coef | 95% CI | *p* |
|---|---|---|---|
| Total drug expenditures | | | |
| Level change,β2 | 31.11 | (12.45, 49.76) | 0.003** |
| Trend change,β3 | −0.74 | (-3.07, 1.60) | 0.541 |
| Durbin-Watson,d | 2.03 | | |
| Bid-winning drug expenditures | | | |
| Level change,β2 | 1.31 | (1.03, 1.59) | <0.001*** |
| Trend change,β3 | 0.04 | (0.00, 0.07) | 0.049* |
| Durbin-Watson,d | 1.94 | | |
| Non-winning drug expenditures | | | |
| Level change,β2 | 11.30 | (3.34, 19.27) | 0.010* |
| Trend change,β3 | −1.06 | (-2.05, −0.07) | 0.046* |
| Durbin-Watson,d | 2.10 | | |
| Non-VBP drug expenditures | | | |
| Level change,β2 | 18.13 | (7.02, 29.25) | 0.004** |
| Trend change,β3 | 0.28 | (-1.13, 1.68) | 0.702 |
| Durbin-Watson,d | 2.00 | | |

Abbreviations: Coef., coefficient; SE, standard error; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

implemented, and with an upward trend observed among outpatients. The number of patients using non-VBP drugs both in outpatient and inpatient settings had no significant difference, with an observed upward tread before and after the policy (Supplementary Appendix SA1). Besides, the present study revealed that the average drug expenditures of hypertension patients in outpatient setting increased by 48.03% per visit, with non-VBP drug expenditure specifically increasing by a significant 123.10%. The expenditure of reduced-price drugs declined, but the use of non-VBP drugs increased significantly, which led to an increase in the drug expenditures and an increase in the medical burden of hypertension outpatients. The authors of this study have previously hypothesized that this increased in overall drug expenditure may be related to unreasonable prescription behaviors, such as increasing daily doses of antihypertensive drugs (Yang et al., 2021b). The increase in the proportional volume of non-VBP drugs was a so-called "side-effect" that is very commonly observed in relation to pharmaceutical policies (Kwon et al., 2019). Although the NVBP policy had promoted efficiency and eliminated the presence of gray profit in drug supply chain, service charges of medical institutions and physicians' compensation systems did not change substantially (Fu et al., 2015). Therefore, compared with inpatient department, physicians operating in outpatient setting were more likely to change their prescription behavior by increasing the number of prescriptions to generate higher salaries. Compared to outpatients, inpatients might have a high degree of compliance with drug brands due to more severity of disease, and it is difficult for inpatients to change their medication habits to switch to bid-winning generic drugs (Wang et al., 2023). These considerations could also be some of the reasons for the differences in drug utilization between the outpatient and inpatient departments. Thus, further monitoring of clinical rational drug use and standardization of the prescription behavior of physicians are suggested after implementation of the policy.

In this study, it was found that the implementation of the NVBP policy improved the healthcare expenditures of hypertensive patients in inpatient setting. Notably, increments in expenditure were more prominent among consultations and other associated expenditures. Patients experienced an immediate and significant of 10,140.00 yuan in healthcare expenditure ($p = 0.024$), 1,490.40 yuan in consultation expenditure ($p = 0.008$) and 5,753.79 yuan in other associated expenditures ($p = 0.004$) after the implementation of NVBP policy. However, slope changes in all of the above expenditures were not obvious, indicating that the immediate effects of NVBP policy were noticeable, and the long-term trends were steady. Some studies have also reported that drug prices decreased after the implementation of centralized bidding system, whereas other non-drug expenditures continued to increase. Healthy institutions and physicians may provide patients with additional services, by overusing laboratory tests or unnecessary services to increase other non-drug expenditures such as service charges and operating costs (Li et al., 2021; Shen et al., 2021). These findings are generally in line with the results obtained in this study suggesting that price cuts alone cannot effectively lessen the burden on hypertensive patients. Drug price, drug volume, drug use

TABLE 7 ITS results for healthcare expenditures in inpatient setting.

| Categories | Coef | 95% CI | *p* |
|---|---|---|---|
| Overall healthcare expenditures | | | |
| Level change,β2 | 10,140.00 | (1,609.10, 18,670.90) | 0.024* |
| Trend change,β3 | −364.40 | (-1,194.66, 465.86) | 0.394 |
| Durbin-Watson,d | 2.00 | | |
| Drug expenditures | | | |
| Level change,β2 | 2,462.74 | (-579.45, 5,504.93) | 0.119 |
| Trend change,β3 | −86.03 | (-382.50, 210.44) | 0.572 |
| Durbin-Watson,d | 1.97 | | |
| Chemical drug cost | | | |
| Level change,β2 | 2,599.54 | (236.25, 4,962.83) | 0.036* |
| Trend change,β3 | −27.87 | (-258.62, 202.88) | 0.814 |
| Durbin-Watson,d | 1.95 | | |
| TCM cost | | | |
| Level change,β2 | 210.68 | (-364.93, 786.29) | 0.476 |
| Trend change,β3 | −43.52 | (-99.66, 12.62) | 0.135 |
| Durbin-Watson,d | 1.98 | | |
| Consultation expenditures | | | |
| Level change,β2 | 1,490.40 | (437.29, 2,543.51) | 0.008** |
| Trend change,β3 | −79.86 | (-182.56, 22.84) | 0.134 |
| Durbin-Watson,d | 2.00 | | |
| Other expenditures | | | |
| Level change,β2 | 5,753.79 | (2012.48, 9,495.10) | 0.004** |
| Trend change,β3 | −72.51 | (-438.01, 292.99) | 0.700 |
| Durbin-Watson,d | 2.00 | | |
| Out of pocket expenditures | | | |
| Level change,β2 | −45.78 | (-2,696.37, 2,604.81) | 0.973 |
| Trend change,β3 | 145.86 | (-115.11, 406.83) | 0.278 |
| Durbin-Watson,d | 1.97 | | |
| Hospital days | | | |
| Level change,β2 | 2.37 | (0.61, 4.14) | 0.011* |
| Trend change,β3 | 0.04 | (-0.13, 0.21) | 0.675 |
| Durbin-Watson,d | 1.99 | | |

Abbreviations: Coef., coefficient; SE, standard error; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

structure and treatment mode affect the medical burden of patients. Therefore, it is recommended that relevant real-world investigations are necessary to generate a deeper understanding of the true effects of the NVBP policy. Moreover, medical supervision should be strengthened to reduce the increasing costs incurred by non-pharmaceutical companies.

In this research, using separate or unified policy initiation time yielded similar results. These reasons could be explained as follows. Firstly, the time interval between the first and last drugs affected by the policy is relatively short (approximately 1 year). Secondly, the policy could have a spill-over effect, causing all drugs to be affected due to substitution between anti-dyslipidemia products. Lastly, most of the drugs with a large volume were already affected in the first wave of NVBP, as the intended policy targets.

This study has several limitations. The primary limitation of this study is its reliance on data from a singular hospital, potentially constraining the generalizability of its findings. Notwithstanding this concern, the hospital in question ranks among the top three TCM institutions in Nanjing. This provides a measure of assurance that the results offer a representative evaluation of the NVBP policy's impact on drug utilization and medical expenditure within hypertensive patients in pilot cities. Another limitation pertains to the quality of EHR data, where the authenticity of the results might be affected by non-standard data records. A specific concern emerged with missing outpatient data prior to 2019. To address this, we utilized prescription proportions across drug groups to probe volume changes in outpatient drug utilization due to the NVBP policy. This approach seeks to provide a clear representation of drug use changes pre and post NVBP policy enactment. Additionally, the nationwide implementation of the NVBP policy in public medical institutions complicates the establishment of an unaffected control group. This could introduce confounding variables affecting the research outcomes. As a countermeasure, we employed a single-group Interrupted Time Series (ITS), which could not exclude other factors that may affect the policy effects in this study. In spite of this, recognized as a robust quasi-experimental design, ITS is particularly effective and widely recognized method to access the policy effect when randomized controlled trials are infeasible. This method evaluates policy effects at a collective level (patient group) instead of an individual one. Additionally, the extended durations preceding and following the intervention ensure stability in estimates and diminished variability in the time series analysis. Thus, despite potential drawbacks, our results remain notably credible, grounding their foundation in the ITS analysis. Lastly, the study's focus was primarily centered on drug utilization and expenditures of real-world hypertension patients. This means areas like the NVBP policy's influence on the quality of bid-winning generic drugs, patient health outcomes, and patient adherence were not explored in depth. Future studies might delve into these aspects to comprehend the policy's broader, long-term impacts on clinical outcomes.

## 5 Conclusion

The study addresses a significant gap in the literature, moving beyond the confines of purchase data to evaluate the real-world clinical implications of the NVBP policy within a Chinese medical institution. Post-policy intervention, a noticeable shift was observed in outpatient drug utilization, with an increase in the use of bid-winning and non-VBP drugs and a decrease in non-winning drugs. Interestingly, patterns in inpatient drug utilization differed from outpatient trends. Additionally, while the policy enhanced the preference for bid-winning drugs over non-winning counterparts,

it coincided with an uptick in medical expenditures. This underlines the need for robust clinical use monitoring and integrated reforms across medical insurance, health institutions, and drug distribution systems to alleviate the financial strain on patients.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by the Research Ethics Committee of Nanjing Hospital of Chinese Medicine, under the code KY2021091. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

LS: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. YCheng: Investigation, Methodology, Writing–original draft. JZ: Supervision, Writing–review and editing, Project administration. YB: Data curation, Writing–original draft. DK: Project administration, Writing–original draft. RH: Data curation, Writing–original draft. YChen: Data curation, Writing–original draft. HW: Writing–original draft. NG: Supervision, Writing–review and editing. AM: Supervision, Writing–review and editing.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1302154/full#supplementary-material

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# Assessment of the implementation of accelerated drug marketing registration procedures for antineoplastic and immunomodulating agents in China: based on 2016–2022 review data

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**Objective:** Since 2016, China has successively implemented Accelerated Drug Marketing Registration Procedures (ADMRPs) for drugs, including Breakthrough Therapy Drug (BTD), Conditional Approval (CA), and Priority Review and Approval (PRA), which have played an important role in promoting the development and review of clinically urgently needed drugs. In this study, we focused on the antineoplastic and immunomodulating agents approved for marketing through ADMRPs, to provide a reference for promoting the formation of a stable and mature regulatory system for the review and approval of antineoplastic drugs and immunomodulating agents in China.

**Methods:** Reviewed the National Medical Products Administration (NMPA) drug review reports for the years 2016–2022 and screened the antineoplastic and immunomodulating agents approved through ADMRPs. Then, with the help of the NMPA website and the Yaozhi Database, two researchers independently queried and entered the detailed information of the selected drugs, and checked with each other. The attribute classification and main characteristics of the drugs were then analyzed with descriptive statistics to obtain the trend of drug types, drug review and approval status, and timeliness.

**Results:** A total of 206 antineoplastic and immunomodulating agents were approved for marketing through five accelerated marketing registration procedures (or procedure combinations), with the average review time shortened by about 81 days. Among them, imported drugs accounted for a larger proportion, the most drugs for treating non-small cell lung cancer and lymphoma, and the largest number of PD-1/PDL-1 inhibitors, but pediatric drugs and rare disease drugs accounted for a smaller proportion.

**Conclusion:** ADMRPs can promote the accessibility of antineoplastic and immunomodulating agents in China and safeguard the life and health rights of

more patients. Nevertheless, it is necessary to pay attention to the expansion of the types of indications for medicines and to increase the development of drugs that are urgently needed by a small number of patients.

KEYWORDS

**antineoplastic and immunomodulating agents, accelerated drug marketing registration procedures, drug review and approval, breakthrough therapy drug, conditional approval, priority review and approval, China**

# 1 Introduction

As early as 1996, the World Health Organization (WHO) included antineoplastic and immunomodulating agents into the same category in the Anatomical Therapeutic Chemical (ATC) system for management based on the anatomical classification of cancer and immune diseases and the pathogenesis of the diseases (Furlow, 2021; Mikhael et al., 2021). Since then, the development of antineoplastic and immunologic drugs has attracted the attention of the global pharmaceutical industry. In recent years, with the aging of the population and changes in the disease spectrum, there has been a trend towards an increased burden of cancer and immunization diseases globally, especially in developing countries. 19.29 million new cancer cases occurred globally in 2020, and it is expected that the burden of cancer will increase by 50 percent by 2040 when the number of new cancer cases worldwide will reach nearly 30 million (Bray et al., 2021; Sung et al., 2021). In addition, according to a research study, the prevalence of immune diseases increased rapidly from 7.7% in 2000–2002 to 11.0% in 2017–2019 (Conrad et al., 2023). China has a large population base with 1.41 billion people. In 2020, China had 4.57 million new cancer cases, accounting for 23.7% of the world's total, with the number of new cancer cases far exceeding that of the rest of the world, and the prevalence of immune diseases also showed an increasing trend (Xia et al., 2022; Chen et al., 2023). In 2006, the WHO explicitly classified oncological diseases and some immune diseases as chronic diseases, and many countries subsequently formulated relevant measures to deal with these diseases (Yabroff et al., 2011; Luengo-Fernandez et al., 2013; Ward et al., 2021; Cao et al., 2022). In recent years, as tumor treatment has moved from the era of cytotoxic drug therapy to the era of targeted therapy and immunotherapy based on cytogenetics, molecular biology, and immunology, and the quality of patients' lives has been effectively improved, the development of antineoplastic drugs and immunological drugs has become an important area of development for cross-fusion (Emens et al., 2017; Caini et al., 2022; Li et al., 2022; Pasetto and Lu, 2023; Swain et al., 2023). It has become a global consensus to accelerate the research and development (R&D) and approval of antineoplastic and immunomodulating agents to meet the demand for drugs for clinical use in related diseases (Fu et al., 2022; Zhang et al., 2022).

China is the second largest prescription drug market in the world, and with the rising incidence of oncology and immune diseases, the demand for antineoplastic and immunomodulating agents is growing (Huang et al., 2021; Zhong et al., 2021; Shang et al., 2023). To this end, China's National Medical Products Administration (NMPA) has carried out a series of reforms to the drug review and approval system since 2015, as shown in Supplementary Table S1, which has had a huge impact on the R&D, approval, and clinical application of antineoplastic and immunomodulating agents. In particular, the successive implementation of the four Accelerated Drug Marketing Registration Procedures (ADMRPs), namely the Priority Review and Approval (PRA), the Conditional Approval (CA), the Breakthrough Therapy Drug (BTD), and the Special Approval (SA) has led to the accelerated approval and marketing of more clinically urgently needed drugs (National Medical Products Administration, 2020). The scope of application and application procedures for the four ADMRPs are shown in Supplementary Table S2. In addition, the "Healthy China Action - Cancer Prevention and Control Implementation Plan (2019–2022)" was jointly formulated by the National Health Commission and other agencies in 2019, encouraged the R&D and accelerated approval of antineoplastic and immunomodulating agents within the country, and facilitated the simultaneous marketing of new drugs from abroad in China, to achieve the enhancement of the accessibility of antineoplastic and immunomodulating agents. (National Health Commission, 2019).

In this paper, we analyzed the trend of approved drug types, drug review, and approval situation, and timeliness based on the data of the annual review report of the Center for Drug Evaluation (CDE) of NMPA for the period of 2016–2022, combing the information related to antineoplastic and immunomodulating agents approved through ADMRPs, including the drug name, incorporation procedures, source (domestic or imported), drug mechanism of action, target and indication, etc., to provide references to promote the review and approval of China's antineoplastic and immunomodulating agents to form a stable and mature regulatory system.

# 2 Materials and methods

In the pre-study period, we learned that the CDE released the 2022 Annual Drug Review Report on 6 September 2023. Meanwhile, considering that China has successively implemented the ADMRPs since 2016, we selected the 2016–2022 Annual Drug Review Report as the main reference for obtaining the drugs approved for marketing through the ADMRPs. Then, the NMPA public data (https://www.nmpa.gov.cn/) and the Yaozhi Database (https://db.yaozh.com/) were used as the main data sources to obtain more drug attributes and review information, including acceptance number, the manufacturer, the accelerated marketing registration procedures including, the ATC classification, the indication, the target, the date of filing, the date of approval, and other information, which were entered into EXCEL 2022. This data entry process was initiated on 1 October 2023, and was completed independently and cross-checked by two researchers, with the research team members consulting together if they encountered disagreements. In the

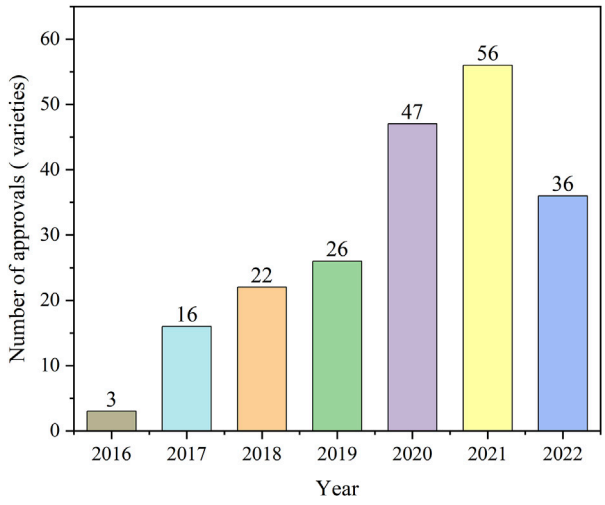


FIGURE 1
Number of antineoplastic and immunomodulating agents approved through the accelerated marketing registration procedures in 2016–2022.

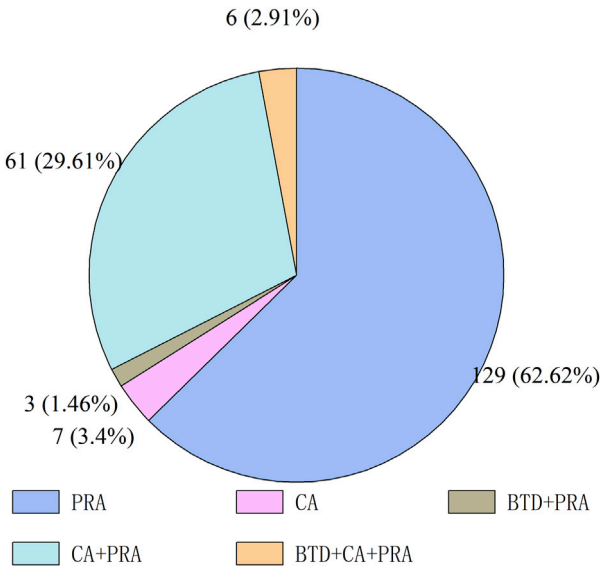


FIGURE 2
Accelerated drug marketing registration procedures adopted for approved marketed antineoplastic and immunomodulating agents.

process, we found some drugs with different acceptance numbers because they had different specifications. However, according to the relevant descriptions in the Drug Review Reports issued by CDE and the practice in several literature, the same drug with different specifications declared by the same company at the same time was recognized as one (Chen et al., 2022; Luo et al., 2023; Su et al., 2023). Therefore, in this paper, the statistics were also conducted in this way.

After 2 weeks, all the data were entered and checked for accuracy, and antineoplastic and immunomodulating agents were screened according to the ATC classification. Then the data included in the study were analyzed by descriptive statistics using EXCEL 2022 and graphing using Origin 2019b to derive the trend of drug classes, drug review and approval, and timeliness of antineoplastic and immunomodulating agents approved for marketing by adopting the ADMRPs.

# 3 Results

## 3.1 Analysis of the number of approvals and inclusion procedures

Figure 1 shows the number of antineoplastic and immunomodulating agents approved through ADMRPs from 2016 to 2022. As can be seen from the figure, in recent years, the Chinese government increased its attention to the review and approval of antineoplastic and immunomodulatory drugs, and the number of drugs approved for marketing increased year by year, with the largest number of approvals in 2021 at 56. The number in 2022 decreased, which was mainly attributed to the phenomenon of market saturation of some antineoplastic and immunomodulating agents, as well as the impact of the COVID-19 epidemic on the development review and approval of drugs (Su et al., 2020), but still more than the number before the epidemic (in

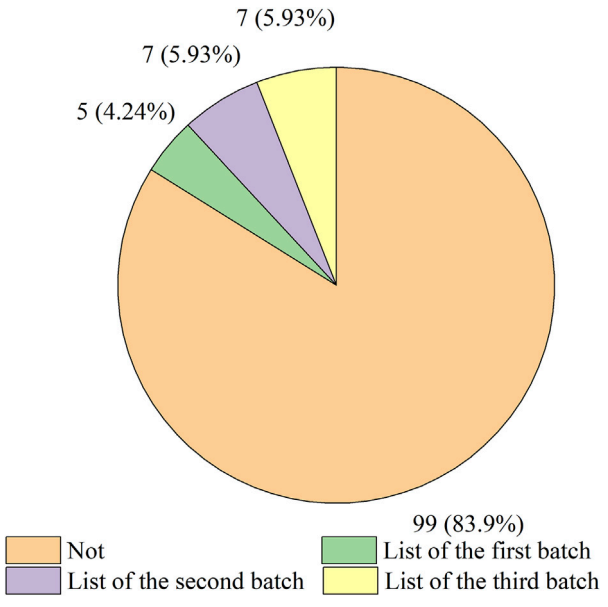


FIGURE 3
Distribution of the number of overseas antineoplastic and immunomodulating agents in urgent clinical need.

2019). Among the 206 approved drugs, five main procedures (or procedure combinations) were adopted, as shown in Figure 2. PRA procedures were adopted most, with 129 products, accounting for 62.62%; followed by the combination of CA + PRA procedures, with 61 products, accounting for 29.61%. The other three were CA (3.4%), BTD + PRA (1.46%), and BTD + CA + PRA (2.91%). The reason for the combination of two or three procedures is that, for varieties included in the BTD, the applicant may apply for CA

TABLE 1 Distribution of the number of drugs for rare diseases and children among antineoplastic and immunomodulating agents.

| | Yes | Not |
|---|---|---|
| Drugs for rare diseases | 10 (4.85%) | 196 (95.15%) |
| Drugs for children | 11 (5.34%) | 195 (94.66%) |

and an application for PRA when applying for marketing authorization for the drug if the applicant is assessed to comply with the relevant conditions; the applicant may also apply for the adoption of a PRA for the drug included in the CA.

## 3.2 Quantitative analysis of drugs imported

Of all the drugs, 116 antineoplastic and immunomodulating agents from overseas had been approved to be marketed in China through ADMRPs, accounting for 57.14%, while domestically produced drugs accounted for only 42.86%. Some of the imported drugs had also benefited from the preferential policies promulgated by the Chinese government to enter the Chinese market through the List of Overseas New Drugs Urgently Needed in Clinical Settings. In November 2018, the CDE released the List of the First Batch of Overseas New Drugs Urgently Needed in Clinical Settings, and as of November 2022, three batches of the list had been released, with a cumulative total of 73 drugs included (Center for Drug Evaluation, 2018; Center for Drug Evaluation, 2019; Center for Drug Evaluation, 2020). According to Figure 3, a total of 19 varieties were included in the list of 116 imported drugs counted. Among them, five varieties were included in the "List of the First Batch of Overseas New Drugs Urgently Needed in Clinical Settings", namely: Secukinumab Injection, Pembrolizumab Injection (2), Olaparib, Dinutuximab beta Injection. Seven varieties were included in the "List of the Second Batch of Overseas New Drugs Urgently Needed in Clinical Settings", namely: Adalimumab Injection (3), Apalutamide, Olaparib, and Pembrolizumab Injection (2). Another seven varieties were included in the "List of the Third Batch of Overseas New Drugs Urgently Needed in Clinical Settings", namely: Teriflunomide, Palbociclib Capsules, Olaparib, Alectinib Hydrochloride Capsules, Pembrolizumab Injection, Dimethyl Fumarate Enteric Capsules, and Giritinib Fumarate Tablets. The above drugs included in the list were included by CDE in PRA to accelerate the review, which to a certain extent solved the dilemma of drugs available outside but not available within China, and fulfilled the clinical drug needs of some patients.

## 3.3 Distribution of rare disease drugs and pediatric drugs

Unlike the United States, which has an Orphan Drug Act specifically for rare diseases, China has not yet introduced a bill on rare disease certification. As to what constitutes a rare disease, it is mainly based on the Rare Disease Catalog issued by the National Health Commission as the basis for identification. As of October 2023, the National Health Commission had released two batches of Rare Disease Catalogs, including 207 diseases (National Health Commission, 2018; National Health Commission, 2023). The Second Batch of the Rare Disease Catalog was released in September 2023, which was outside the timeframe of our research data. Therefore, only the First Batch of Rare Disease Catalog was used as a reference. As can be seen from Table 1, among these antineoplastic and immunomodulating agents, there were only 10 drugs belonging to the same category of rare disease drugs, accounting for 4.85%. Accordingly, China still has a long way to go in strengthening the management of rare diseases, guaranteeing the accessibility of medicines for patients with rare diseases, and accelerating the development and approval of antineoplastic and immunomodulatory drugs for rare diseases.

In addition, as shown in Table 1, only 11 antineoplastic and immunomodulating agents for children, accounted for 5.34% of the medicines included in the analysis. Although the proportion of children suffering from cancer or immune diseases is not as high as that of adults, the demand for children's antineoplastic and immunomodulatory drugs in China is higher than that of other countries. At present, there are few types of medicines for children on the market and a single dosage form, so it is also necessary to pay attention to the development and approval of antineoplastic and immunomodulatory drugs used by children, to improve the accessibility of medicines for children.

## 3.4 Distribution of indications and targets of drugs

According to the data feedback, the 206 indications of antineoplastic and immunomodulating agents that were included contained 44 diseases, and the top ten indications in terms of the number were summarized and counted as shown in Figure 4, and all the indications and the corresponding number of drugs are detailed in the Supplementary Table S3. Of all the drugs, the number of anticancer drugs was predominant, with non-small cell lung cancer and lymphoma having the highest number at 33. Lung cancer is one of the malignant tumors with high morbidity and mortality rates worldwide. Lung cancer ranked first among all new cases of malignant tumors in China in 2022, accounting for 18.06%, and the number of deaths due to lung cancer accounted for 23.9% of the total number of deaths due to malignant tumors in China, which likewise ranked first. The analysis of the data on approved drug indications and the current distribution of cancer in the Chinese population showed that the R&D and approval of antitumor drugs in China were matched with the situation of cancer patients.

Further, according to the mechanism of action and type of target of the drugs, the classification and quantity statistics were made, and the contents shown in Table 2 were obtained. According to the action type of drugs, they can be divided into four major categories: antitumor drugs, immune-promoting drugs, immune-suppressive drugs, and endocrine therapies, among which antitumor drugs were the most numerous. In terms of drug mechanism of action, the largest number of monoclonal antibodies and antibody-drug couplings was found; while in terms of target type, the largest number of Programmed Cell Death Protein-1/Programmed Cell

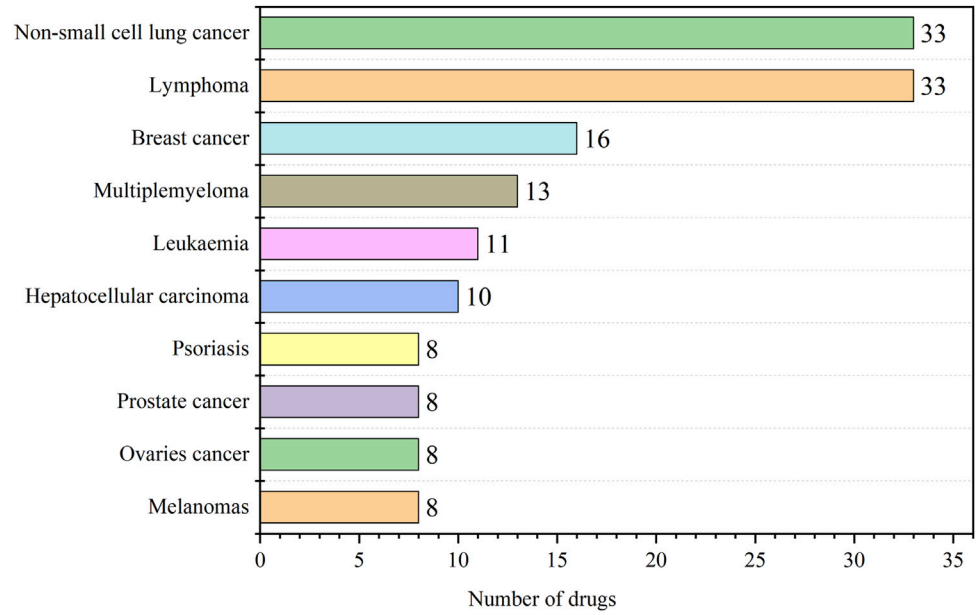


FIGURE 4
Distribution of indications for antineoplastic and immunomodulating agents (top 10).

Death Protein Ligand-1 (PD-1/PDL-1) inhibitors was found, with 31.

## 3.5 Statistics on the length of time for drug approval

According to a previous study, since the reform of the drug review and approval system in 2015, the average review time for new drug applications on the market was 483 days (Su et al., 2020). We calculated the evaluation time of antineoplastic and immunomodulating agents that adopted ADMRPs. The average evaluation time was about 402 days, which was 81 days shorter, and this was still in the case of the COVID-19 epidemic that had obstructed the review and approval of drugs. It can be seen that ADMRPs significantly shortened the review time of drugs and achieved the effects foreseen in the policy formulation.

In addition, we paid special attention to two hot areas in antitumor drugs: PD-1/PDL-1 inhibitors, as well as Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs). These two classes of antitumor drugs were not only hot areas of development in recent years, but also drugs with high clinical demand. As shown in Figure 5, the average review cycle for PD-1/PDL-1 inhibitors was about 295 days, which was 107 days shorter than the average review cycle for all drugs ($p < 0.01$);. In comparison, the average review cycle for EGFR-TKIs was 366 days, which was 36 days shorter ($p < 0.01$). This indicated that in the actual evaluation work, the CDE promoted the review and approval of drugs through comprehensive consideration oriented to the clinical needs and value of antitumor drugs, as well as the data reported by pharmaceutical companies, to meet the needs of a greater number of patients for therapeutic drugs.

# 4 Discussion

## 4.1 Opportunities for clinical use of antineoplastic and immunomodulating agents due to accelerated drug marketing registration procedures

The above results showed that more and more antineoplastic and immunomodulating agents were approved for marketing through ADMRPs. On the one hand, ADMRPs can prioritize the allocation of review resources. By meeting the needs of enterprises to communicate with drug regulatory authorities and shortening the review timeframe to accelerate the listing of drugs, it stimulated the enthusiasm of enterprises to carry out the research and development of antineoplastic and immunomodulating agents and improved the quality of the creation of products. On the other hand, some of the clinically needed antineoplastic drugs and immunomodulating agents can be put into clinical application more quickly to increase the choice of treatments and safeguard the public's accessibility to medicines.

At the same time, this also required the applicant to conduct more rigorously designed post-marketing clinical research with more clinically valuable outcomes, to confirm the long-term clinical benefits and long-term safety outcomes of the drug for patients, and to improve the clinical data chain. In the case of CA, there were 68 drugs approved for marketing through CA (or CA process combinations). It should be emphasized that CA is based on alternative endpoints, intermediate clinical endpoints, or early clinical trial data, and applies to accelerating the listing of urgently needed drugs with outstanding clinical value in the form of "approval before validation" when complete clinical studies have not yet been completed, aiming to shorten the time of clinical research and development of the drug, and to

TABLE 2 Classification statistics of antineoplastic and immunomodulating agents by mechanism of action and target type.

| Type of action | Drug mechanism | Target type | Number (types) |
|---|---|---|---|
| Antitumor drugs | Antimetabolite | Pyrimidine homologs | 2 |
| | | Folate congeners | 3 |
| | Monoclonal antibodies and antibody-drug conjugates | CD20 inhibitors | 3 |
| | | CD22 inhibitors | 1 |
| | | CD38 inhibitors | 3 |
| | | HER2 inhibitors | 4 |
| | | PD-1/PDL-1 inhibitors | 31 |
| | | Trop-2 inhibitors | 1 |
| | | VEGF/VEGFR inhibitors | 3 |
| | | Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) | 19 |
| | | Other monoclonal antibodies and antibody-drug conjugates | 13 |
| | Protein kinase inhibitor | B-Raf serine-threonine kinase (BRAF) inhibitor | 4 |
| | | Bruton tyrosine kinase (BTK) inhibitor | 6 |
| | | Anaplastic lymphoma kinase (ALK) inhibitors | 4 |
| | | Phosphatidylinositol-3-kinase (Pi3K) inhibitor | 2 |
| | | Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors | 3 |
| | | Cyclin-dependent kinase (CDK) inhibitors | 3 |
| | | Other protein kinase inhibitors | 20 |
| | Other antitumor drugs | Hedgehog pathway inhibitors | 2 |
| | | Proteasome inhibitors | 3 |
| | | Poly (ADP-ribose) polymerase (PARP) inhibitors | 8 |
| | | Tyrosine-protein kinase inhibitor | 2 |
| | | Other antitumor drugs | 11 |
| | Alkylating agents | nitrogen mustard | 5 |
| | Cytotoxic antibiotics and related drugs | Anthracycline antibiotics and related drugs | 1 |
| | | Other cytotoxic antibiotics | 1 |
| | Plant alkaloids and other natural medicines | Paclitaxel alkaloids | 4 |
| Immune-promoting drugs | immune-promoting drug | interferon drugs | 1 |
| | | Other immune enhancers | 2 |
| Immune-suppressive drugs | immunosuppressant | Interleukin Inhibitors | 5 |
| | | Calcium-modulated phosphatase inhibitor | 1 |
| | | Selective immunosuppression | 11 |
| | | Tumor necrosis factor-alpha (TNF-α) inhibitors | 8 |
| | | Other immunosuppressants | 7 |
| Endocrine therapy | Hormonal antagonists and related drugs | Aromatase inhibitors | 1 |
| | | Antiestrogenic drugs | 1 |
| | | Antiandrogenic drugs | 6 |
| | | Other hormone antagonists and related drugs | 1 |

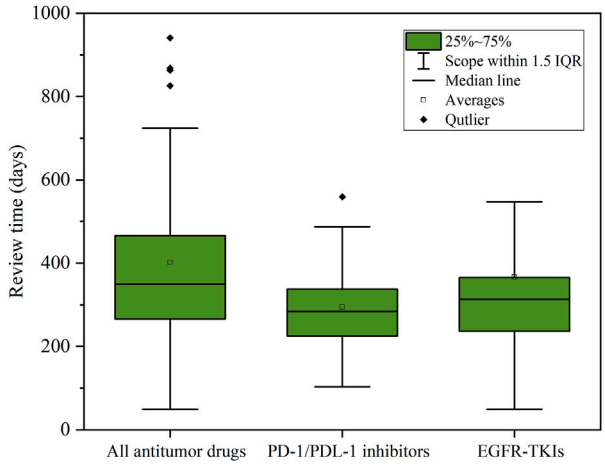


FIGURE 5
Statistics on the length of drug review.

bring advantageous products to the market as soon as possible with the "conditions". Therefore, from the point of view of ensuring the safety of patients, the applicant must formulate a complete post-marketing risk management plan, to clarify the existing or identified risks and potential risks, and strengthen the post-marketing safety monitoring and risk control of the drug according to the plan (Nicolo et al., 2022).

## 4.2 Expansion of indications and scenarios for drugs approved for marketing through accelerated drug marketing registration procedures

From the number of approved drugs and indications, it was found that the currently approved indications of anticancer drugs were mainly focused on lung cancer, lymphoma, and breast cancer. Still, the data also revealed that fewer drugs had been approved in the fields of gastric cancer, esophageal cancer, uroepithelial cancer, metastatic colorectal cancer, cervical cancer, renal cell carcinoma, and other disease areas. These data reflected that the current development and review of antitumor drugs in China as a whole was in line with the order of the number of cancer cases in China, and more and more cancer patients had drugs available. However, China has a huge population base, and some of the cancer conditions with a small number of patients also have more than ten thousand people. For example, in 2022, the number of renal cell carcinoma patients in China was nearly 73,700 (Han et al., 2024), yet only one drug for the treatment of renal cell carcinoma had been approved for marketing through the Priority Review and Approval, which was unable to meet the patients' demand for medication. Thus, enterprises need to make full use of ADMRPs to promote the development and declaration of anticancer drugs, and pay attention to the development of drugs for cancer diseases with fewer patients and the expansion of drug indications; government departments also need to publicize the convenience of ADMRPs through the feedback of the review data and provide technical guidance and support to eligible enterprises.

In addition, among the antineoplastic and immunomodulating agents approved through ADMRPs, the number of drugs for rare diseases or children was very small, at around 5%. Although PRA specified that new varieties, new dosage forms, and new specifications of medicines that meet the requirements of medicines for rare diseases or children with physiological characteristics of children could apply for the use of PRA, the effect of the policy's actual operation was not very obvious. On the one hand, it was related to the fact that China paid less attention to children's drugs and drugs for rare diseases in antineoplastic and immunomodulating agents, resulting in fewer approved, and on the other hand, it was also related to the fact that it was difficult to obtain subjects for clinical trials of children's drugs and drugs for rare diseases. However, with the increased attention paid by the Chinese government to the use of drugs for children and rare diseases in recent years, coupled with the development of real-world research, more attention and support will be given to children's antitumor drugs and rare diseases in ADMRPs in the future.

## 4.3 Strengthening post-marketing surveillance of drugs and establishing a multidimensional evaluation system for the value of antineoplastic and immunomodulating agents

For antineoplastic and immunomodulating agents approved for marketing through ADMRPs, strengthening post-marketing surveillance is an indispensable task to ensure the safety of medicines for patients. From the analysis of the review reports of the 68 drugs that adopted CA in this study, 84% completed phase II clinical trials, and a small number completed phase III clinical trials. Due to the limitations of clinical research is a challenge for the regulatory authorities to weigh the evaluation standards and control the risk-benefit, for drugs approved for marketing by adopting ADMRPs, to protect the urgent clinical needs and shorten the time to market of the drug at the same time, it should be better to do a good job of post-marketing supervision, and to consolidate the closed-loop management. CDE drafted the "Working Procedures for Approval of Application for Conditional Approval for Marketing of Drugs (for Trial Implementation) (Revised Draft for Public Comments)" in August 2023, which explicitly proposed the need for companies to submit clinical research progress reports annually, to quickly grasp the clinical benefits and risks of the drugs after their marketing and indirectly promote the research process (General Department of NMPA, 2023).

From the analysis results, it can be seen that the current developed and approved antitumor drugs were mainly concentrated in the field of higher economic value of the market, focusing on the phenomenon of popular targets was obvious, and there was a general phenomenon of homogenization of innovation, with PD1/PDL-1 being the most prominent. However, value-based health decision-making is influenced by multiple factors, and evaluating the value of

antitumor drugs solely from an economic perspective to guide drug development and review is often one-sided. In addition to their high clinical value, antineoplastic drugs also have higher innovation value and social value than ordinary drugs, so it is particularly important to build a multidimensional drug value evaluation system to achieve a comprehensive evaluation of drugs. In 2021, the National Health Commission issued the Management Guidelines for Comprehensive Clinical Evaluation of Drugs, which had more important guiding significance for developing and clinical use guidance of antineoplastic and immunomodulating agents (National Health Commission, 2021). In the future, the idea of Multi-Criteria Decision Analysis (MCDA) can be used to develop a value evaluation system for antineoplastic and immunomodulating agents suitable for China and applied to the reform of the marketing approval system to clarify the screening criteria for accelerating the approval process for innovative drugs such as new antineoplastic and immunomodulating agents, providing a basis for accelerating the marketing of new antineoplastic and immunomodulating agents.

## 5 Conclusion

ADMRPs can significantly reduce the review time of antineoplastic and immunomodulating agents, promote the accessibility of these drugs in China, and promote the listing of clinically needed domestic or imported drugs in China, safeguarding patients' rights and interests in life and health. However, in the future, it is also necessary to increase attention to the use of drugs for rare diseases and children in antineoplastic and immunomodulating agents and pay attention to the expansion of drug indications. In addition, it is necessary to explore establishing a system for evaluating the value of antineoplastic and immunomodulating agents, to provide a basis for accelerating the marketing of new 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

YL: Conceptualization, Data curation, Formal Analysis, Methodology, Writing–original draft, Writing–review and editing. XL: Formal Analysis, Methodology, Writing–original draft. JY: Data curation, Formal Analysis, Writing–review and editing. LW: Data curation, Formal Analysis, Writing–review and editing. LS: Supervision, Validation, Writing–review and editing. ZH: Conceptualization, Project administration, Supervision, Writing–review and editing.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1345672/full#supplementary-material

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