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Pharmaceutical policy, impact and health outcomes

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Pharmaceutical policy, impact and health outcomes

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Table of contents

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Editorial: Pharmaceutical policy, impact and health outcomes

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Editorial on the Research Topic
Pharmaceutical policy, impact and health outcomes

Pharmaceutical policy is essential given increasing expenditure on medicines and only finite resources, with global expenditure on medicines estimated to reach US$1.5 trillion by the end of 2023 (IQVIA, 2019). This represents an annual compounded growth rate of 3–6% a year in recent years, driven by increasing prevalence of non-communicable chronic diseases (NCDs) with ageing populations and resultant increase in medicine use alongside the increasing costs of new medicines especially for orphan diseases and cancer (Godman et al., 2018; Luzzatto et al., 2018; Godman et al., 2021a; Godman et al., 2021b). The cost of cancer care is a particular Research Topic with world-wide sales of oncology medicines expected to reach $237 billion by 2024, and continue growing (Godman et al., 2021b). This increase is driven by the increasing prevalence rates of patients with cancer alongside the increasing costs of new oncology medicines, with requested prices per life year gained for new oncology medicines rising four-fold or more during the past years after adjusting for inflation (Godman et al., 2021b). This increase is exacerbated by the emotive nature of the disease area (Haycox, 2016). These growth rates though are unsustainable leading to greater scrutiny over the cost and value of new oncology medicines, which will continue (Godman et al., 2021b).

Alongside this, there needs to be greater scrutiny over the costs and use of existing medicines to ensure maximum value, with more than half of all medicines prescribed or dispensed inappropriately (Godman et al., 2021a). In addition, health authorities may not always realise the full potential for available savings. This happens when there are limited demand- and supply-side measures to encourage the preferential prescribing of low cost multiple-sourced medicines or biosimilars as seen in South Korea compared with Western European countries including Sweden and the UK (Kwon and Godman, 2017; Kim et al., 2020; Godman et al., 2021a). The ideal is that patients receive medicines appropriate to their clinical needs, in doses and duration cognisant of their requirements, and at the lowest cost to them and the health service. However, this is not always the case. Alongside this, we are aware there are concerns with rising rates of antimicrobial resistance (AMR), increasing morbidity, mortality, and costs (Godman et al., 2021c). This results from excessive use of antibiotics especially for self-limiting conditions alongside patients with tuberculosis not fully complying with their course of treatment (Ali et al., 2019; Godman et al., 2021c). Both areas need addressing going forward to reduce rising AMR. Similarly, polypharmacy can

increase healthcare expenditure alongside increase adverse outcomes in patients; consequently, potential patients need careful management once the size of the problem has been calculated (Cho et al.; Kwak et al., 2022). In their study, Cho et al. demonstrated in South Korea that the rate of polypharmacy remained high in the elderly during the past 10 years with the rate of hyper-polypharmacy (currently prescribed 10 or more medicines) had increased, which needs actively addressing (Cho et al.).

In view of these multiple Research Topic, this Research Topic sought to examine the strengths and weaknesses of pharmaceutical policy across countries, and its impact on medicine use and health outcomes to provide future guidance. Overall, 22 papers were published as part of this Research Topic across a wide-variety of areas and countries.

Increasing access to medicines, and enhancing their rational use, are extremely important to countries, especially low- and middle-income countries (LMICs) where there are concerns with the current management of patients (Baumgart et al., 2019; Al-Ziftawi et al., 2021). In their study, Lu et al. discuss the impact of the recent Chinese centralised drug procurement policy, called the '4 + 7' policy, on drug utilisation patterns among public medical institutions (Lu et al.). Lu et al. found that the policy had an appreciable impact with the utilisation of bid-winning medicines increasing from 17.03% to 73.61% of procured medicines. Alongside this, the utilisation of multiple-sourced medicines increased by 67.53% and originators decreased by 26.88% as a result of the policy (Lu et al.). The use-proportion of quality-guaranteed medicines also increased from 56.69% to 93.61% of procured medicines (Lu et al.). Long et al. showed similar findings; however, there were no significant price changes in medicines that were not part of this policy (Long et al.). This mirrors the findings from studies conducted across Europe where the introduction of multiple demand- and supply-side measures can enhance the prescribing of target medicines whilst appreciably reducing expenditure without compromising care (Godman et al., 2021a). The same is not true in countries with limited supply- and demand-side measures (Godman et al., 2021a). In the case of selective serotonin re-uptake inhibitors (SSRIs), Wen et al. showed that the '4 + 7' policy resulted in an appreciable increase in their utilisation (76.7%) alongside decreasing expenditure (3.39%) benefitting patients (Wen et al.). The same has been seen for instance in Scotland where multiple measures resulted in a 73.7% reduction in overall SSRI expenditure between 2001 and 2017 despite their utilization increasing 2.34-fold during this period (Godman et al., 2019).

There have also been similar benefits among hospitals in China as part of a national stewardship policy. Under this policy, key medicines of concern, i.e., those which currently have high prices and utilisation but unconfirmed or limited therapeutic effects, have been subject to close scrutiny with the help of clinical pharmacists (Li et al.). Prior to implementation, there was typically increasing usage and spend on these medicines. However, after implementation in one tertiary hospital with 1,300 beds, Li et al. demonstrated 430 fewer DDDs (defined daily doses) per month in 20 medicines under scrutiny alongside a reduction in overall expenditure of US$4,682 per month in the 19 months post implementation (p = 0.003). However in their study, Galimberti et al. failed to show that multiple demand-side measures including feedback reports and online courses failed to appreciably improve GP prescribing in Italy (Galimberti et al.). This contrasts with Sweden where the prescribing of an agreed list of medicines appreciably improved through education and monitoring of prescribing, with a similar situation seen in Sweden and the UK when multiple sourced proton pump inhibitors (PPIs) and statins first became available (Godman et al., 2021a). The differences in findings may be a result of differences in intensity, dissemination and follow-up of the various demand-side measures (Godman et al., 2021a).

There are also concerns with access to medicines and their affordability within the Brazilian healthcare system as it strives to provide universal access (Barbosa et al., 2021; Rocha et al., 2021). In their study, Luz et al. assessed the impact of the ERAF (Estratégia de Regionalização da Assistência Farmacêutica) policy to promote technical cooperation between the State and municipal governments with the aim of improving medicine procurement and distribution. The rationale is to promote the purchasing of high-quality products with reliable suppliers at the lowest-possible prices and transaction costs (Luz et al.). We have seen such procurement activities obtain very low prices for medicines among European countries (Woerkom et al., 2012). However, Luz et al. had concerns that the ERAF policy did not fulfil its goals, with the need to introduce a more sustainable long-term policy to achieve lower prices for medicines as demand grows (Luz et al.). There are similar concerns with the availability of essential medicines within the State of Minas Gerais in Brazil with a need to strengthen funding and public purchasing processes to continue to provide universal healthcare alongside growing demands on available resources (Luz et al.).

On the other hand, the instigation of the Korean Pharmaceutical Information Service (KPIS) to increase transparency in the pharmaceutical supply chain, including the prevention of recalled medicines as well as a decrease in inventory and disposal of out-of-date medicines, resulted in appreciable savings (Kim et al.). Kim et al. calculated the net benefit of the introduction of KPIS at US$571.6 million over 12 years, justifying its introduction (Kim et al.). Such systems can also help monitor possible medicine shortages, which are an increasing concern globally (Acosta et al., 2019). Shortages are more likely to occur with multiple-sourced medicines and older parental medicines where Research Topic of profitability can be a concern, especially where the supply of raw materials is concentrated in only a limited number of manufacturers. In addition, where information systems are lacking to track utilisation and where there are delays in payment (Acosta et al., 2019; Modisakeng et al., 2020; Sarnola et al.). These concerns are leading to pro-active measures across countries to address the situation including planning for shortages with antibiotics (Chigome et al., 2019; Miljković et al., 2020).

Not surprisingly given that new cancer medicines dominate the medicines' pipeline with over 500 companies actively pursuing the development of new oncology medicines (Godman et al., 2021b), there were an appreciable number of papers examining the cost-effectiveness of different oncology medicines. Such analyses are particularly important in LMICs where there are already Research Topic of cost-effectiveness with existing oncology medicines to treat patients with breast cancer (Al-Ziftawi et al., 2021). In their paper, Zhu et al. documented that toripalimab combined with gemcitabine and cisplatin had a greater chance of being cost-effective compared to camrelizamub combined with

gemcitabine and cisplatin or gemcitabine and cisplatin combined from a Chinese payer's perspective for first-line treatment of patients with recurrent or metastatic nasopharyngeal carcinoma (Zhu et al.). Similarly in their study, Chen et al. demonstrated that capecitabine and oxaliplatin appeared more cost-effective than gemcitabine and oxaliplatin again from the perspective of the Chinese healthcare system (Chen et al.). In their network meta-analysis, Li et al. also found that sintilimab plus biosimilar bevacizumab was cost-effective compared to sorafenib in patients with unresectable hepatocellular carcinoma again from the perspective of the Chinese healthcare system (Li et al.). However, whilst adding atezolizumab to platinum-based chemotherapy as first-line treatment of patients with metastatic urothelial cancer improved survival times, Liu et al. did not find this combination was cost-effective in the Chinese setting (Liu et al.). There were also mixed findings in the systematic review of Chan et al. regarding Poly ADP-Ribose Polymerase (PARP) inhibitors across a variety of cancers (Chan et al.). The authors concluded that in advanced ovarian cancer, PARP inhibitors should be prioritised for upfront maintenance for patients with BRCA mutation or BRCAness at recurrence in view their cost-effectiveness in this situation (Chan et al.). The same was not seen in recurrent maintenance in patients with advanced ovarian cancer even with genetic stratification (Chan et al.).

Sensitivity analyses are particularly important when reviewing potential reimbursement and funding for new cancer medicines given that an increasing number are being launched early with only limited effectiveness and safety data (Godman et al., 2021b). This aspect is discussed further by Bae et al., who urge caution when using immature data especially if this diverts funding away from proven cost-effective technologies and subsequently wastes valuable resources (Pontes et al., 2020; Bae et al.).

In the case of other NCDs, Oh et al. in their study assessed the appropriateness of using EQ-5D-3L and EQ-5D-5L when assessing the role and value (Oh et al.). Unsurprisingly, the pooled utility of patients with asthma declined with worsening control and severity of asthma. The authors concluded that both these health-related quality-of-life instruments are useful when assessing the value of asthma treatments (Oh et al.). Kim et al. showed that easing the criteria for reimbursing statins among patients with type 2 diabetes reduces CV events and their related costs (Kim et al.). This mirrors other studies, demonstrating the need for multiple demand- and supply-side measures to ensure low prices for statins alongside increased use to benefit both patients and the healthcare system (Collins et al., 2003; Godman et al., 2021a). There were though concerns with the improper use of PPIs for patients undergoing stress ulcer prophylaxis in non-critical patients in the study of (Li et al.). The authors concluded that effective intervention strategies including education executed by clinical pharmacists could help address the situation (Li et al.). Effective interventions are also needed to reduce prescription opioid misuse in South Korea highlighted by Kim et al. in their study (Kim et al.).

AMR is an increasing concern across countries exacerbated by appreciable purchasing of antibiotics without a prescription in LMICs (Godman et al., 2021c). Dispensing of antibiotics without a prescription is exacerbated by patient pressure even for self-limiting conditions such as acute respiratory illnesses (Godman et al., 2021c). Consequently, it was encouraging to see in the study of Arshad et al. that the public in Pakistan appeared to be aware of the problems associated with multidrug-resistant pathogens and their responsibilities in helping to reduce AMR (Arshad et al.). In their study, Pradipta et al. found that strengthening ambulatory care facilities, including adequate resources and personnel, is important to ensure patients with TB are adequately managed and adherent to prescribed therapies (Pradipta et al.). Otherwise, resistance will develop, which needs to be avoided to help eradicate TB.

In conclusion, there were a considerable number of papers covering this Research Topic. This demonstrates considerable interest across countries to develop and implement pharmaceutical policies to enhance the rational use of medicines. This includes improve access as well as procurement of medicines. In addition, ensuring value for money within finite resources. A number of initiatives can act as exemplars for the future, building on existing initiatives.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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ORIGINAL RESEARCH
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The Impact of a National Stewardship Policy on the Usage Patterns of Key Monitoring Drugs in a Tertiary Teaching Hospital: An Interrupted Time Series Analysis

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Background: The management of Key Monitoring Drugs has become one of important aspects to control the growth of pharmaceutical expenditures in China. The first batch of the China National Key Monitoring Drugs (NKMDs) policy was released in July 2019. However, little is known about the impact of the national stewardship on the trends of NKMDs prescribing practice in hospitals, especially in the Northwestern China.

Methods: We collected 8-years of monthly NKMDs usage data from a tertiary hospital between 2014 and 2021. A segmented regression model of interrupted time series (ITS) analysis was used to evaluate the Defined Daily Doses (DDDs) and spending trends of ten NMKDs in the hospital throughout the study period. The pre-implementation period was from January 2014 to November 2019 and the post-implementation period was from December 2019 to June 2021.

Results: Prior to the implementation of the NKMDs policy, there was an increasing trend both in DDDs and spending for 8 of 10 NKMDs. The interventions managed by clinical pharmacists after the implementation of the national stewardship policy led to a significant decreasing trend of DDDs in the 19 months following implementation, of 430 fewer DDDs per month in total, compared to the pre-implementation period ($p < 0.001$). A similar decrease in spending was seen in the post-implementation period, with a trend of $4,682 less total spending on medications in those months compared to the pre-implementation trend ($p = 0.003$). There was a significant decrease in both monthly DDDs and spending for 6 of the 10 medications in the post-implementation period, while there was a significant increased trend both in monthly DDDs and spending on 1 medication in that period.

Conclusion: Using ITS analysis, the total DDDs and spending on 10 NKMDs in this hospital indicated sustained reductions over 19 months after multidimensional interventions under the implementation of the national policy guidance. The national

stewardship policy could therefore be considered an effective strategy. Additional comprehensive policies should be introduced to further improve the rational use of NKMDs.

Keywords: National Key Monitoring Drugs, national stewardship policy, clinical pharmacists, interrupted time series, hospital

INTRODUCTION

Adjuvant Drugs are defined as agents that aid or increase the action of the principal drug, or that impacts the absorption, mechanism of action, metabolism, or excretion of the primary drug in such a way as to enhance its effects (U.S. National Library of Medicine, 1975; Yang J. et al., 2021a). Adjuvant Drugs do not normally play a major role in terms of therapeutic value or economic cost, but unnecessary prescribing of such medications in the hospitals have become a peculiar phenomenon in China (Han et al., 2016). A survey by Han Shuang showed that unreasonable or off-label use of Adjuvant Drugs occurred in 98% of medical institutions in China (Han et al., 2016). The management of Adjuvant Drugs has become an important aspect of the management of rational drug use in China (Yang J. et al., 2021a). Key Monitoring Drugs are a subset of Adjuvant Drugs, which usually have high prices, consumption rates, and unconfirmed therapeutic effects in clinical application. Key Monitoring Drugs cover a broad range of medications, including drugs that enhance tissue metabolism; vitamins; electrolytes; drugs for enteral and parenteral nutrition; neurotrophic drugs; free radical scavenging drugs; traditional Chinese medicines for promoting blood circulation and removing stasis; and drugs for the auxiliary treatment of liver disease, tumors, and other conditions (Yang J. et al., 2021a). The use of Key Monitoring Drugs has grown rapidly in recent years, owing to their wide applications and the commercial promotion of these drugs (Yang J. et al., 2021a). Key Monitoring Drugs have become a major part of clinical drug consumption but are essentially unavailable outside China, nor are they recommended by the guidelines for the treatment of diseases (Han et al., 2016).

Increased spending on drugs is a global concern (Wettermark et al., 2010), and the problem is even more serious in developing countries, including China. Medical expenditures per capita continued to increase at an average annual rate of 16.3% from 2005 to 2014 in China. (National Bureau of Statistics of the People's Republic of China, 2015). The surging costs of health care in China is strongly related to the high expenses in pharmaceutical costs (Hu et al., 2019). Drug expenditures accounted for 48.3% of total outpatient healthcare expenditures and 38.3% of total inpatient healthcare expenditures in 2014, suggesting that drug expenditures have been extremely high (Li and Yu, 2021). These proportions are among the highest in the world, compared to an averages determined by the Organization for Economic Co-operation and Development (OECD) of around 17% (OECD Library, 2013; Zhang et al., 2015). A deficiency of the approval of new drugs by the China Food and Drug Administration and the profit incentives in prescribing have become the main reason for the unreasonable use of adjuvant drugs in China (Zhong et al., 2016; Li et al., 2012; Zhang et al., 2015). The current excessive use of Key Monitoring Drugs not only leads to an increased incidence of adverse drug reactions and health issues, but it can also contribute to serious financial burden for patients, result in a wastage of medical resources, and place significant undue pressure on the medical insurance fund (Yang J. et al., 2021a).

The management of Key Monitoring Drugs has been one of the primary methods implemented in China to control the rapid growth of pharmaceutical expenditures (Liang et al., 2018), and since 2015 the Chinese health administrative authorities have taken a series of actions on the management of Key Monitoring Drugs. In 2015, the National Health and Family Planning Commission of the People's Republic of China indicated that the catalogue of Key Monitoring Drugs must be properly defined, and a tracking and monitoring system of Key Monitoring Drugs and medicines used in an off-label manner must be established in public hospitals (National Health and Family Planning Commission, 2015). In 2016, the Chinese State Council issued a report on the key tasks of deepening the reform of the medical and health system. The report requires that the irrational prescription of Key Monitoring Drugs and nutritional drugs must be monitored to curb the unreasonable increasing growth of pharmaceutical expenditures initially (General Office of the State Council, 2016). Subsequently, many local Health Commissions established the catalogue of Key Monitoring Drugs, and by 2019, Health Commissions of 14 provinces and 9 municipalities have published these catalogues and promulgated relevant policies designed to restrict or supervise the use of Key Monitoring Drugs. However, due to the unclear definition of Key Monitoring Drugs and the different Key Monitoring Drugs catalogues compiled by local Health Commissions, the effectiveness of the above interventions has been insufficient. Since the catalogue of Key Monitoring Drugs has not been established by the Health Commission of Shaanxi Province, the supervision of Key Monitoring Drugs in Xi'an has had little effect. With a 15% price mark-up on prescribed drugs allowed for public Health Care Institutions in China since the 1980s (Eggleston et al., 2008), significant incentives for profit-making activities and the resulting excessive treatment and over prescriptions were recognized as one of the influential factors of the drastic increase in drug expenditures (Mao et al., 2015). Removing the previously allowed 15% profit margin on drugs under the Zero-Mark-Up Drug Policy (ZMDP) severed the link between drug sales and hospital profits. As one of the matching policies of healthcare reform in China, the ZMDP was implemented in Shaanxi province in 2017. However, the ZMDP has not made substantial progress on drug-related

TABLE 1 | The catalogue of National Key Monitoring Drugs.

No.	Name	Strengths
1	Monosialotetrahexosylganglioside Sodium Injection[a]	2 ml: 20 mg
2	Cattle Encephalon Glycoside and Ignotin Injection	2 ml, 10 ml
3	Oxiracetam Injection	5 ml: 1 g
4	Creatine Phosphate Sodium for Injection	0.5g, 1 g
5	Deproteinised Calf Blood Serum Injection[a]	0.4 g: 10 ml, 0.2 g:5 ml
6	Alprostadil Injection[a]	2 ml: 10 ug, 1 ml: 5 ug
7	Troxerutin and Cerebroprotein Hydrolysate Injection	2, 5, and 10 ml
8	Coenzyme Complex for Injection	0.1 mg, 0.2 mg
9	Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection[a]	5 ml
10	Invert Sugar and Electrolytes Injection[a]	500 ml, 250 ml
11	Mouse Nerve Growth Factor for Injection[a]	30 ug, 20 ug
12	Thymopetin for Injection	10 mg
13	Ribonucleic Acid for InjectionII	50 mg, 100 mg
14	Edaravone Injection[a]	30 mg: 20 ml, 10 mg: 5 ml
15	Ossotide Injection	2 ml: 10 mg, 10 ml: 50 mg
16	Cerebroprotein Hydrolysate for Injection[a]	60 mg, 30 mg
17	Ribonucleic Acid for Injection	6 mg, 10 mg
18	Vinpocetine for Injection[a]	5 mg
19	Deproteinized Calf Blood Extractives for Injection[a]	400 mg
20	Cinepazide Maleate Injection	2 ml: 80 mg, 10 ml: 320 mg

[a]*Drugs included in our study.*

expenditures and rational drug use in public hospitals of Shaanxi province (Yan et al., 2020).

To alleviate patients' medical economic burden, future pharmaceutical reform measures must be carried out to control the excessive and unnecessary use of drugs in hospitals (Yan et al., 2020). The first batch of catalogue of National Key Monitoring Drugs (NKMDs) was released by the Medical Administration Bureau of the National Health Commission of the People's Republic of China in July 2019 (General Office of the National Health Commission, 2019), which means special rectification targeted at Key Monitoring Drugs for improvement has been scheduled in a national stewardship campaign, and a total of 20 drugs were included (**Table 1**). Traditionally, the difficulty in management of Key Monitoring Drugs laid mainly in the lack of clear definition of these drugs and the lack of unified supervision methods (Zhong et al., 2016). For the first time, the catalogue of Key Monitoring Drugs were released at the national level, which pointed out the management direction of these drugs. The specific measures recommended in the stewardship policy have become the basis of management. Hence, we derive the testable hypothesis that the consumption of NKMDs will decrease after the implementation of policy interventions.

To the best of our knowledge, the effectiveness of the national stewardship policy on NKMDs consumption has not been characterized in Northwestern China. This study was designed as a retrospective observational study to determine the trends in prescribing practice of NKMDs during the years 2014–2021. We use an Interrupted Time Series (ITS) analysis to quantitatively evaluate the impact of a national stewardship policy and clinical pharmacists' interventions on NKMDs prescribing in a tertiary hospital of Northwestern China, with the goal of providing a basis for future NKMDs stewardship in China.

MATERIALS AND METHODS

Data Source and Study Design

Data were obtained from the Xi'an People's Hospital (Xi'an Fourth Hospital) hospital information system (HIS) monthly for 8 consecutive years, from January 2014 to June 2021. This tertiary hospital is located in Shaanxi Province of Northwestern China and offers comprehensive medical, teaching, and scientific research capacities. The hospital has around 1,300 beds with an average daily admission rate of approximately 4,000 patients and >78,000 inpatient admissions annually.

Collected data included information on the following variables concerning NKMDs: generic names, drug specifications, manufacturers, units, total doses, and unit prices. All the usage of and spending on thirteen NMKDs available in the hospital were collected thoroughly monthly. Once the drugs were prescribed in the hospital, the quantity and spending data were captured and extracted by HIS. Since the consumption and spending of each drug were counted monthly separately. Therefore, there was no recall bias or misclassification bias to contend with. Sample size calculation wasn't required. Three drugs (Oxiracetam Injection, Cinepazide Maleate Injection, Cattle Encephalon Glycoside and Ignotin Injection) were excluded from this study because they were not used continuously or in small quantities.

Drug usage was defined as DDD (defined daily dose), which is the average maintenance dose per day of a drug when used for its major indication in adults. The DDD of the 10 NMKDs studied here were identified according to the instructions provided by the manufacturer (DDD were not available in the Anatomic Treatment and Chemical classification). The instructions of each of the 10 NMKDs in our study were provided as a supplementary file (see **Supplement S1**). To evaluate the effect

of the policy, consumption related indicators were selected as the main indicators in our study. We chose two parameters to reflect the trends and the changing process of 10 NMKDs consumption: DDDs and spending. DDDs of these drugs were used to assess their rate of consumption. Monthly drug spending was recorded in the Chinese currency Renminbi "yuan" (CNY) and then converted into USD (6.44 CNY equals to 1 USD), and is the total amount spent on each drug, for each month. The total DDDs for each month was calculated by summing the individual DDDs for each of the study NKMDs. Similarly, the total monthly expenditure on NKMDs was calculate as the sum of spending on all individual NKMDs each calculated month.

As this was a nationwide stewardship program and randomization with a control group without the intervention was impossible, an ITS analysis was used for this data (Linden, 2015). To evaluate the effect of the NKMDs policy intervention, we conducted an ITS analysis that lasted for 90 months: 66 months before the intervention (pre-implementation, January 2014–June 2019), 5 months lag in the effect of intervention (July 2019–November 2019), implementation completely in December 2019, and 19 months after the intervention (December 2019–June 2021). The ITS regression was performed with Newey-West standard errors (itsa command in Stata) and all models were investigated for autocorrelation using the Cumby-Huizinga test for autocorrelation (Cumby and Huizinga, 1992) using the actest command in Stata version 14, in which all statistical analyses were performed.

To further investigate the differences in total DDDs and expenditure between the pre- and post-policy implementation periods, the pre-policy trend was extrapolated by 19 months (the total number of additional observed months in the post-policy period) using the tsappend function, followed by the extrapolation of the data based on the linear regression trend using the xi:reg function. The difference between the extrapolated data and the observed data was then calculated, in both absolute and relative terms, at 12-months and 19-months post-implementation. This calculation indicates the difference in the observed data compared to what the expected trend in the data would have produced, had no intervention been implemented.

Intervention

The catalogue of Key Monitoring Drugs (the same as the national advisory) was released by the Health Commission of Shaanxi Province in September 2019. Based on the relevant policies to restrict and supervise patterns of NKMDs, the catalogue of NKMDs was published and multidimensional interventions measures were formulated in November 2019 at the study hospital. A scientific management system for NKMDs was established through administrative intervention, educational programs, prescription review and audit, and information management. Medication guidelines were formulated to clearly specify the conditions and principles of clinical application of NKMDs. Several measures were undertaken to ensure that interventions were strictly enforced, including checking the training attendance records, inspecting the prescription audit results, and verifying the bonus and punishment lists. Furthermore, the results of prescription audits were ranked monthly and were closely related to clinicians' performance pay. The management leading group also checked and monitored the progress of the interventions monthly. The detailed interventions are further described in the **Supplement S2**. Multidimensional interventions measures were implemented constantly by clinical pharmacists from December 2019 to June 2021.

RESULTS

Overall, the total combined DDDs for all NKMDs trended downward in the post-intervention period, at a rate of 430.73 DDDs per month ($p < 0.001$), compared to the pre-intervention period. Similarly, the total monthly spending on NKMDs in the post-intervention period was in significant decline at a rate of $4,681.93 USD per month ($p < 0.001$) compared to the pre-intervention period. Based on these results, the policy intervention led to a dramatic 76.23 and 69.70% decrease in total DDDs and spending, respectively, of NMKDs in June 2021 compared with November 2019.

Of the ten NKMDs investigated in this study, six showed a significant ($p < 0.05$) decrease in monthly DDDs following implementation of new national policy, with one (Invert Sugar and Electrolytes Injection) showing a significant increase in monthly DDDs. The remaining three NKMDs (Monosialotetrahexosylganglioside Sodium Injection, Alprostadil Injection and Deproteinized Calf Blood Extractives for Injection) had no significant change in trend of DDDs in the post-implementation months. Similarly, there was a significant decrease in monthly spending on six NKMDs in the post-implementation period, a significant increase in spending for two NKMDs in that period (Invert Sugar and Electrolytes Injection, Deproteinized Calf Blood Extractives for Injection), and two (Monosialotetrahexosylganglioside Sodium Injection and Alprostadil Injection) of which showed no significant change in spending trend in the post-implementation period.

Table 2 shows the results of the ITS analyses for total DDDs and total spending, indicating the original starting value, the trend in values in the pre-implementation period, the value during the month of implementation, and the trend in values in the post-implementation period. Post-trend analyses for both 12 and 19 months post-intervention were completed, and the comparisons between the observed data and those predictions were calculated, which indicated the intervention effect was effective and sustained. **Figure 1** demonstrates the monthly DDDs for all NKMDs combined over time, from January 2014 to June 2021, and indicates the linear trend of DDDs in the pre-intervention period and the post-intervention period. **Figure 2** displays similar data for total combined spending on NKMDs over time. **Supplementary Table S1** and **Supplementary Figure S1** shows individual ITS analyses for DDDs of all ten NKMDs (**Supplementary Table S1** and **Figure 1**), and **Supplementary Table S2** and **Supplementary Figure S2** shows individual ITS analyses for spending on all ten NKMDs (**Supplementary Table S2** and **Figure 2**).

TABLE 2 | Interrupted Time Series analyses for total DDDs and total spending.

	Total DDDs	Total spending
Trend Prior to Policy (95% CI)	155.78	1,855.34
	(117.48–194.08)	(1,564.32–2,146.36)
December 2019 - Immediate Change (95% CI)	−7,674.73	−98,363.65
	(−10,675.96–4,673.50)	(−138,435.20–58,292.15)
Trend December 2019 - June 2021	−430.73	−4,681.93
	(−634.90–226.57)	(−7,721.50–1,642.36)
Constant (95% CI)	7,475.65	114,990.40
	(6,266.81–8,684.48)	(105,431.40–124,549.30)
12 Months Extrapolated Difference[a]	−10,463.71	−114,280.09
12 Months Relative Extrapolated Difference[b]	48.72%	57.51%
19 Months Extrapolated Difference	−18,369.70	−228,073.50
19 Months Relative Extrapolated Difference	21.38%	25.03%

[a]*Difference is calculated as the actual observed value of total DDDs or total spending at 12- or 19-months post-intervention, minus the extrapolated value of total DDDs or total spending at 12- or 19-months post-intervention, following the trend from January 2014 to November 2019.*

[b]*Relative difference is calculated as the actual observed value of total DDD or total spending at 12- or 19-months post-intervention, divided by the extrapolated value of total DDDs or total spending at 12- or 19-months post-intervention, following the trend from total DDDs January 2014 to November 2019 total spending.*

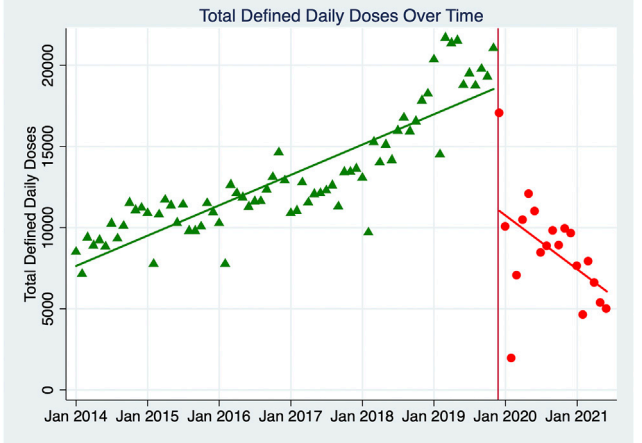

FIGURE 1 | Monthly total Defined Daily Doses of ten NKMDs combined. The monthly DDDs for all NKMDs combined over time was demonstrated, from January 2014 to June 2021. The linear trends of DDDs in the pre-intervention period and the post-intervention period were labeled with different colors, green-pre-intervention period and red-the post-intervention period.

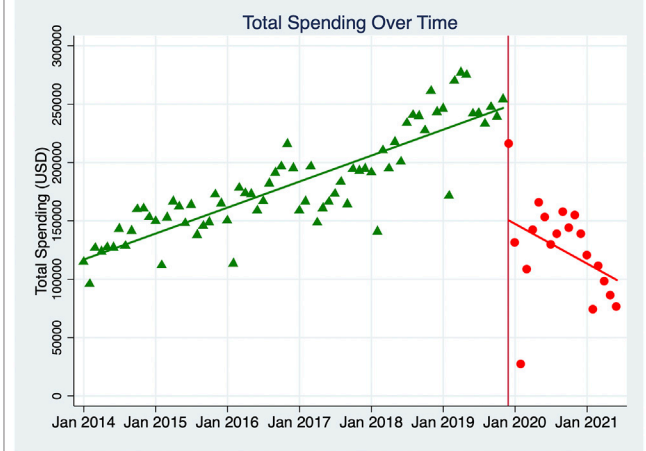

FIGURE 2 | Monthly total spending (USD) of ten NKMDs combined. The monthly spending (USD) for all NKMDs combined over time was demonstrated, from January 2014 to June 2021. The linear trends of spending (USD) in the pre-intervention period and the post-intervention period were labeled with different colors, green-pre-intervention period and red-the post-intervention period.

DISCUSSION

This study evaluated the change in usage of NMKDs, from the perspective of DDDs and spending, after a strict national stewardship policy was implemented. This study revealed that there was an increasing trend in the usage and spending of the ten NKMDs between 2014 and 2019, but that this significantly decreased after the introduction of the multidimensional intervention managed by clinical pharmacists under the implementation of the national stewardship policy. While the overall use pattern of NKMDs within seasons was similar, the intervention led to a dramatic 76.2 and 69.7% decrease in DDDs and spending of NMKD, respectively, in June 2021 compared with November 2019, which reflects the national government-driven policy could be considered an effective strategy. In April 2019, the National Health Commission of the People's Republic of China issued a notice on drug use monitoring and clinical evaluation, which requires a comprehensive evaluation of drug utilization in order to improve local medical support systems and the quality of treatment services (National Health Commission, 2019). Clinicians have an obligation to ensure that the medicines they prescribe do not result in increased harm or cost unless there is at least a reasonable expectation of a benefit to the patient. Thus, the most rational route toward correct use of NKMDs is to prescribe them by strictly adhering to evidence-based guidelines. Therefore, clinical practice guidelines and recommendations for clinical application of NKMDs was published to ensure doctors'

prescribing behavior is suitable to clinical needs. Guidance, education, stewardship, and supervision on rational NKMDs use were addressed as professional strategies together with administrative strategies. At Xi'an People's Hospital, the interventions were managed by clinical pharmacists and supported by the Pharmaceutical Management Professional Committee, with multiple other sectors participating as well. The strict enforcement of the above stewardship campaign also contributed to the decline in drug usage and medication spending. The interventions were found to be effective in facilitating the safe and rational use of drugs for clinical purposes. Several other studies have also indicated the positive effects of this policy on controlling the growing consumption of NKMDs, promoting the clinical rational use of NKMDs and savings in unnecessary drug expenses for patients (Yang J. et al., 2021a; Ke et al., 2021; Zhang W. et al., 2021b; Wang et al., 2020), which was consistent with our study. A recent study which evaluated the effect of the national stewardship on NKMDs prescribing in the secondary and tertiary hospitals of Guangdong province found that spending on NKMDs as the proportion of total expenditure on medication decreased from 4.8% in the first half of 2018 to 2.7% in the second half of 2019, following policy implementation (Ke et al., 2021). A study indicated that the establishment of clinical rational NMKDs use evaluation system based on the multi-disciplinary collaboration model had led to a significant decrease in irrational prescribing of NKMDs, and in addition the dosage and spending of 8 NKMDs decreased significantly (Zhang W. et al., 2021b). Another study indicated that the proportional expenditure on seven NKMDs decreased from 4.4% of total medication spending to 2.8% and a drop of 25.8% in DDDs of the consumption of NKMDs in a teaching hospital after the interventions (Wang et al., 2020). That overall NKMDs use significantly decreased in February 2020 in our study may be explained in part due to the impact of the outbreak of COVID-19, during which the government advocated for people to stay at home. However, by May 2020, the number of patients visiting the hospital had returned to equal to the same period in 2019.

NKMDs included in the first batch of catalogues were mainly drugs involved in the prevention or treatment of cardiovascular, cerebrovascular and nervous system diseases, tumor adjuvant therapy, and nutritional electrolyte preparation. We observed that the gradual increasing trend, both in monthly DDDs and spending, for 6 of the 10 medications during the pre-implementation period turned into a significant downward trend in the post-implementation period. In contrast, we did not observe a significant decreasing trend for prescriptions of Monosialotetrahexosylganglioside Sodium Injection, Deproteinized Calf Blood Extractives for Injection and Alprostadil Injection in the post-implementation period. The driving force for these differential changes in prescribing trends is unclear. A partial explanation may be that the off label prescribing of Deproteinized Calf Blood Extractives for Injection, Alprostadil Injection, and Monosialotetrahexosylganglioside Sodium Injection in ophthalmology has not been significantly changed in our hospital. A previous study found that the proportion of the purchase expenditure of Monosialotetrahexosylganglioside Sodium Injection showed a significant downward trend (Ke et al., 2021), which wasn't consistent with our study. There was a significant increased trend both in monthly DDDs and spending on Invert Sugar and Electrolytes Injection in the post-implementation period. Invert Sugar and Electrolytes Injection was remain widely used in the department of otolaryngology for postoperative nutritional support treatment for patients undergoing surgery of the pharyngeal region, tonsils and thyroid, as well as patients in emergency department in our hospital after the intervention. However, nutritional support treatment with Invert Sugar and Electrolytes Injection should be limited to critically ill patients (for perioperative patients undergoing major operation or complicated procedures, trauma, tumor, infection, burns, shock, etc.) or patients with a history of diabetes or hyperglycemia, while patients undergoing minor operation without abnormal electrolytes or blood glucose during hospitalization was not recommended (Zhu et al., 2017). This phenomenon highlights the potential for further supervision in these medication through targeted intervention.

The proper use of NKMDs is conducive to the rehabilitation of patients, while over prescription and irrational use of NKMDs not only increases the economic burden of patients and the country's medical resources, but also increases the risk of adverse drug reactions due to combinations or unnecessary use of drugs. According to the Pharmaceutical Data Base of China's National Pharmaceutical Industry Information Center, the total sales of the 20 NKMDs covered by the "national policy" exceed $1.55 billion USD in 2018, and the sales of some varieties of NKMDs in hospital exceeded $15.53 million USD (Baidu Research Engines, 2019). In particular, the sales of Oxiracetam Injection totaled nearly $230 million USD, while the sales of Icotinib Hydrochloride Tablets, the first domestic innovative drug in China, was $ 190 million USD which reached a "record high" in 2018 (People's Daily Online, 2019). Previous studies have shown the documented misuse of NKMDs was common in public hospitals of China (Lin et al., 2015; Zhu et al., 2017; Zhang H. et al., 2021a). The rate of irrational usage of Invert Sugar and Electrolytes Injection was 26.6% in a large tertiary teaching hospital in January 2016, which were comprised of unapproved indications, overly long treatment durations, contraindication, and inappropriate drug combinations (Zhu et al., 2017). Another drug-utilization study showed that Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection was used off-label extensively in malignant tumor patients, which accounted for 11.76% of the total 38,126 patients from 24 tertiary hospitals (Zhang H. et al., 2021a). This phenomenon has since led to serious concerns from the public about the safety and quality of health care (Han et al., 2016). To reduce the risk of medication and strengthen drug use monitoring, China's Center for Drug Evaluation of National Medical Products Administration issued a notice on suggestions for revision of the instructions for Invert Sugar Injection and Invert Sugar and Electrolytes Injection in June 2018, which removed the recommended use of these drugs as diluents under the indications, and added adverse drug reactions involving digestive, respiratory, nervous, circulatory, urinary

system diseases, skin and subcutaneous tissue, eye diseases and local reactions (China's Center for Drug Evaluation of National Medical Products Administration, 2018). According to a document issued by China's Center for Drug Reevaluation of National Medical Products Administration (China's Center for Drug Reevaluation of National Medical Products Administration. 2016), the drug instruction of Monosialotetrahexosylganglioside Sodium Injection was revised to include warning words, ADR information, contraindications, and usage in children. China's Center for Drug Reevaluation of National Medical Products Administration issued notice on the revision of the instructions for Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection in September 2019 (China's Center for Drug Reevaluation of National Medical Products Administration, 2019), and ADR information of the risk of severe allergic reactions especially anaphylactic shock, contraindications and warnings were added.

In recent years, implementing health insurance payment methods that encourage the physician to deliver cost-effective health services represent a promising direction in China's new healthcare reform. Policy makers are exploring to expand medical payment systems of Global Budget Payment System (GBPS) and Diagnosis Related Group System (DRGs) to curb the excessive growth of medical expenditure (Huang et al., 2016; Liu et al., 2017). These systems offer a prospective reimbursement to hospitals, with the total expected spending determined ahead of a budget year mainly based on a fee-for-service or grouping of patients according to their diagnosis and other traits. The DRG system is a payment mechanism known as the "ceiling price for a single disease", which forces the control of medical expenditures and promotes the efficient utilization of medical resources in hospitals. The shift from the traditional retrospective cost-based system to prospective DRG-based system led to the containment of medical costs (Liu et al., 2017). One study has indicated that the proportion of expenses on Key Monitoring Drugs of total drugs was significantly decreased, which provided a reference for continuous optimization of the expense management model after management of Key Monitoring Drugs based on DRGs (Yang X. et al., 2021b). In June 2019, National Healthcare Security Administration issued a notice on the requirement of attempted implementation of the medical payment system for DRGs in 30 pilot cities (National Healthcare Security Administration, 2019). DRGs were implemented in four hospitals of Xi'an in July 2021, including Xi'an People's Hospital. In August 2021, the National Health Commission of the People's Republic of China, (2021) issued documents requesting the hospitals to adjust the catalogues of NKMDs. The catalogues of NKMDs were requested to include 30 drugs selected from six categories of drugs (including Adjuvant Drugs, PPIs, antibacterials, etc.) because of abnormally large consumption and the current situation of irrational use in hospitals (National Health Commission. 2021). This means that the subsequent catalogues of NKMDs will continue to be updated, and the dynamic management of NKMDs will be established moving forward. While challenges remain, the Chinese government has focused on the appropriate use of NKMDs and the impact of the catalogue will be sustained.

This study has three main strengths. First, this was the first quantitative study to investigate the impact of the national stewardship on the trends of NKMDs prescribing pattern in hospital of the Northwestern China (DDDs and spending were selected as the main indicators). Second, the availability of longitudinal data from the hospital allowed examination of long-term associations between a stewardship intervention and NMKDs prescribing. There were no significant changes to the organization of the hospital during the study period, which allowed for a stable population over the study period. Furthermore, the analyzed data were captured routinely, meaning the likelihood of missing data is very low. Finally, the ITS analysis used is a robust design for evaluation of real-world interventions which cannot be randomized, and there were adequate time points before and after the intervention in our data series.

Our study has several limitations. First, it was conducted in Xi'an only, which may not represent the general situation in China. Despite social and economic conditions and doctors' prescription behavior differing across regions in China, the NKMDs stewardship program was carried out at the national level. Our study serves as a practical case to illustrate that NKMDs abuse can be effectively controlled through scientific management. Therefore, the multidimensional interventions embedded in our research for reducing NKMDs prescribing are worthy of reference for other hospitals of China. The second limitation is that comparisons based on the spending parameter may sometimes offer reduced value in the evaluation of drug use. The prices of all NKMDs decreased by 15% under the influence of the ZMDP policy implemented in Shaanxi province in April 2017. And the prices of some varieties of NKMDs decreased slightly under the influence of the National Centralized Drug Procurement (NCDP) implemented in Xi'an in January 2019. Fluctuations in prices of the same preparations between different years may lead to bias and make the long-term evaluation difficult. However, because pricing fluctuations occurred before the intervention policy was put in place in November 2019 and the total spending of 10 NKMDs increased during that period, its influence on the results of this study are limited.

Our study results have important policy implications. At present, the national policy tends to take the overall consumption and spending change as the indicators of management effect. However, there are potential limitations if only the declining rate of consumption is used as the indicator in evaluating the utilization of Key Monitoring Drugs, nor is it helpful to guide rational drug use in clinical application. Further, indicators are required to comprehensively evaluate the frequency and structure of Key Monitoring Drugs prescribing pattern in hospitals (Wang et al., 2021). On the other hand, the main purpose of the stewardship of Key Monitoring Drugs is to improve rationality of drug use. Considering most secondary or tertiary hospitals have implemented a pre-prescription review system (Liu et al., 2021), this review software can be deployed as a tool to detect, rectify and prevent the occurrence of prescribing problems and improve the quality of pharmaceutical care. After drug-related problems (DRPs) were identified through quick checks of the system, pharmacists reviewed the potentially inappropriate prescriptions. Furthermore, clinical practice guidelines and recommendations for the clinical application of Key Monitoring Drugs should be established as

consensus statements at the national scale, which could help achieve the ultimate goal of rational utilization of NKMDs.

CONCLUSION

This study evaluated the impact of a national stewardship policy on NKMDs use in a tertiary teaching hospital in the Northwestern China. An interrupted time series analysis showed a decrease in consumption quantity and spending of NKMDs in the study hospital following implementation of the national policy, which indicates that the policy could therefore be considered an effective strategy and the intervention measures were successful. Additional comprehensive policies should be introduced to further improve the rational use of NKMDs.

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

Conceptualization: HL and WJ. Data collection: HL, YZ, and XX. Analyzed the data: DM and HL. Methodology: WJ, DM, JD, and HZ. Software: DM. Supervision: WJ and XJ. Original draft: HL and WJ. Critical revision of the manuscript: WJ, DM, JD, HZ, and XJ. All authors have approved the final version of the manuscript.

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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.2022.847353/full#supplementary-material

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Barriers to Optimal Tuberculosis Treatment Services at Community Health Centers: A Qualitative Study From a High Prevalent Tuberculosis Country

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Background: Community health centers (CHCs) are a backbone healthcare facility for tuberculosis (TB) services. Identifying barriers amongst TB service providers at the CHC level is required to help them deliver successful TB treatment.

Aims: The current study aimed to analyze barriers to successful TB treatment from the perspective of TB service providers at the CHC level in a high prevalent TB country.

Methods: A qualitative study was conducted using in-depth interviews and focus group discussions in a province of Indonesia with a high TB prevalence. Two districts representing rural and urban areas were selected to obtain information from TB service providers (i.e., physicians and nurses) at the CHC level. In addition, key informant interviews with TB patients, hospital TB specialists, pharmacists, and activists were conducted. The trustworthiness and credibility of the information were established using information saturation, participant validation, and triangulation approaches. The interviews were also transcribed for the inductive analysis using Atlas.ti 8.4 software.

Results: We identified 210 meaning units from 48 participants and classified them into two main themes: organizational capacity and TB program activities. We identified the inadequacy of human resources, facility, and external coordination as the main barriers to organizational capacity. Furthermore, the barriers were identified regarding TB program activities, that is, inadequate TB case finding, diagnosis, drug supply chain and dispensing management, treatment and monitoring, case recording and reporting, and public-private collaboration.

Conclusion: Strengthening CHCs in the management of TB is critical to reaching the national and global goals of TB eradication by 2035. These findings can be considered to develop evaluation strategies to improve the successful TB treatment in high prevalent TB countries, especially Indonesia.

Keywords: tuberculosis, Indonesia, tuberculosis barriers, healthcare problems, qualitative

1 INTRODUCTION

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis* (M.tb), has been a continuous global threat (Al-Humadi et al., 2017; WHO, 2021). A recent global report has validated that an estimated 9.9 million people developed TB and that 1.3 million people died from TB in 2020 (WHO, 2021). Moreover, TB has been one of the top 10 causes of death and the leading cause of death from a single infectious agent worldwide (WHO, 2020). Drug-resistant-TB (DR-TB), a resistance of M.tb to one or more anti-tuberculosis drugs, is reported as the main challenge in TB treatment that significantly impacts the clinical and economic aspects of the patients (Pradipta et al., 2019a, 2019b; WHO, 2020; Byun et al., 2021). A global meta-analytical study from our group verified that TB patients previously treated for TB have a higher risk of developing multi-drug-resistant TB (MDR-TB) (Pradipta et al., 2018). Evidently, treatment barriers have occurred amongst these TB patients and potentially led to the DR-TB and unsuccessful TB treatment.

The updated global report showed that two-thirds of the new TB cases were developed in the eight high prevalent TB countries that mostly are in the lower-middle-income countries (WHO, 2021). A situational analysis was performed among ten high-burden countries: Bangladesh, China, India, Indonesia, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, and South Africa. The study showed that none of the countries is capable of providing effective care for 50% of the estimated drug-resistant TB patients (Monedero-Recuero et al., 2021). It underlines the need for intensified study in the high prevalent TB countries to provide a comprehensive picture of TB problems for the global strategies.

Globally, Indonesia is the third-ranked country regarding its contribution to developed TB worldwide (WHO, 2021). In 2019, the national TB case rate was estimated at 845,000 cases with a treatment coverage of approximately 66% and a total TB notification of nearly 567,000 cases (WHO, 2020). The situation worsened after the COVID-19 pandemic hit Indonesia. In 2020, TB treatment coverage decreased to a low 47%, and then TB case notification was reduced to roughly 393,000 cases (Ministry of Health Republic of Indonesia, 2021; WHO, 2021). Strengthening TB management is required to achieve global and national targets by 2035.

Community health centers (CHCs) have vital roles in managing tuberculosis in the community. The CHC is a frontline facility in managing TB cases in the high prevalent TB countries. In Indonesia, TB service providers at the CHC level have responsibilities to prevent, detect, diagnose, treat, monitor, notify, and report TB cases at the sub-district level (Ministry of Health Republic of Indonesia, 2010). They need adequate support from organizational and individual perspectives to perform qualified TB care in the community. In an earlier study from our group, several problems of TB care from the patient perspective were identified (Pradipta et al., 2021). The recent study highlighted potential problems from the perspective of TB service providers, such as TB stigma in a health facility, suboptimal treatment service, and negative perception of the quality of CHC facility (Pradipta et al., 2021). To the best of our knowledge, there is still limited study that analyzed problems in managing TB cases at the primary healthcare level from TB service providers' perspective in high prevalent TB countries, including Indonesia. Describing the problems at community health centers in a high prevalent TB country can provide lessons learned for other TB high-burden countries that have similarities of the healthcare system and population characteristics. As such, insight is instrumental in developing effective and comprehensive strategies for improving TB care, and a qualitative study was conducted in Indonesia to explore barriers to treatment success from the perspective of TB service providers in CHCs.

2 MATERIALS AND METHODS

We conducted a qualitative study using a phenomenological approach to provide a deep understanding of "what" was experienced and "how" several individuals experienced it (Creswell and Poth, 2007). The data were obtained employing the methodological beliefs as the philosophical assumption and the social constructivism as the interpretive framework (Creswell and Poth, 2007). Following those principles, the emergent idea was inductively obtained through methodological procedures, such as interviewing, observing, and analyzing the texts (Creswell and Poth, 2007). We obtained the information from the participant's views of the situation regarding the study objective. The meanings were then formed through the interaction among the participants (social construction) rather than starting with a complex theory (Creswell and Poth, 2007).

Given the cultural and potential gender bias, two researchers with different gender were involved in the data collection. ISP (male) is a researcher who has followed training on quantitative and qualitative studies and has experience conducting public health studies involving in-depth interviews, focus group discussions (FGDs), and observational studies. LRI is a hospital pharmacist following a Ph.D. program that focuses on improving treatment outcomes on TB disease. There was no prior relationship between researchers and participants to minimize the potential imbalance of power that can affect the quality of the interviews and discussions. The participants were fully aware that

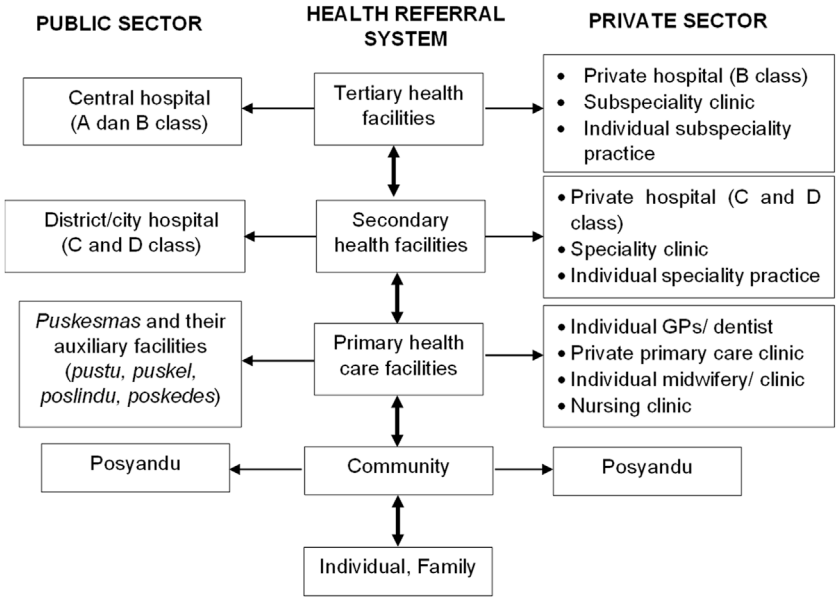

FIGURE 1 | Indonesia health referral system. Volunteers (cadres) operate posyandu for vulnerable population groups at the community level in their area supervised by puskesmas.

all activities performed in this study aimed to improve TB healthcare services in Indonesia.

2.1 Context and Setting

The current study was conducted in a province of Indonesia that has a high TB prevalence nationally (Ministry of Health Republic of Indonesia, 2018). Two districts were selected as the research object representing rural and urban areas considering the different characteristics of the public health facility. Generally, CHC is a public health facility established at the sub-district level managed by the local government in Indonesia (Claramita et al., 2017). Given the catchment area and the high population at the sub-district level, several CHCs were supported by their auxiliary facilities (pustu, puskel, polindes, and poskesdes). The healthcare system in Indonesia is divided into public and private healthcare facilities. The governance of the public health system of Indonesia follows a gradual referral system covered by national health insurance for health services. **Figure 1** describes the Indonesia health referral system modified from Claramita et al. (2017).

In Indonesia, TB units exist in each CHC, and staff members operate the unit. They have responsibilities to prevent, detect, diagnose, treat, monitor, notify and report TB cases at the sub-district level. The number of TB service providers at the CHC level depends on the availability of the healthcare staff members. Commonly, it comprises two to four healthcare personnel who have a medical doctor, nurse, and/or lab analyst background. In the meantime, the staff responsible for TB service should also operate another healthcare or health program at the CHC level. Referral hospitals provide care to support TB care at the CHC level concerning MDR-TB management. Nonetheless, not all referral hospitals at the district level have MDR-TB care. MDR-TB is managed in several centralized hospitals commonly established in a tertiary hospital.

2.2 Sampling Strategy

We applied criterion sampling (Palinkas et al., 2015) to recruit the participants in this study, and we selected five CHCs in each district with high TB cases. Additionally, a TB service provider at CHC was considered eligible for inclusion if having at least 6 months of experience managing TB cases. Data saturation was utilized to determine the final number of participants during the interview process. We defined data saturation as no emergence of new information relevant to the study objectives.

2.3 Ethical Issues

We followed the principle of the Declaration of Helsinki in conducting our study. The study protocol was approved by the ethics committee of the Universitas Padjadjaran, Indonesia (no. 333/UN.6/Kep/EC/2019). All the participants were provided informed consent to participate in this study. Deidentified participant and data protection were also applied during the study analysis to provide the confidentiality of participant information. The data were stored in a computer with password protection that can only be accessed by the principal researcher (ISP).

2.4 Data Collection

The participants were selected using gatekeepers from the district health offices (Hennink et al., 2015). We attempted to maximize the characteristics of the participants considering several characteristics: the distance level of CHC to the central district, existing TB case managed, age, and experiences in TB

management. We then contacted the TB service providers to conduct FGDs. Prior to the focus groups, the written informed consent forms were delivered to the eligible participants at least a week before the FGD, providing sufficient time to decide on participation in this study. Furthermore, we conducted an FGD with a maximum of five participants per group. Considering the culture and level of authority, we separated the FGD on the basis of their backgrounds (physicians and paramedical staff) to have factual information from the participants. To validate the information obtained, we also attempted to collect information using structured interviews from the other participants, such as the TB coordinator at the district level, health district office staff, TB patients, or other relevant subjects, based on the information from the FGDs. The in-depth interviews (IDIs) were applied for the participants who potentially shared sensitive issues and were favored at a specific time due to time availability. The data were collected from February to April 2019.

Each interview started with general questions using Bahasa Indonesia, and then the interviewer explored the information based on pre-established research questions. The general questions were "what are your activities in TB management?" and "what and how are the TB treatment problems?" The interview followed several steps according to the interview guide shown in **Supplementary File S1**.

2.5 Data Processing and Analysis

All the participant information was recorded using audio for IDI and audio-visual for FGD. The recordings were transcribed and sent to the participants for member checking and approval. Thereafter, the approved transcripts were anonymously transferred to the Atlas.ti 8 software for data analysis.

The inductive data analysis was performed. It generally followed several steps, including familiarization, thematic framework identification, codification, and interpretation (Hennink et al., 2015). The familiarization of content aimed to construct a thematic framework. Once the general thematic framework was created, coding was performed by identifying the emergent meaning unit from the transcript and field notes. According to the created general thematic, the codes were classified into themes. Then, the sub-themes were developed by identifying the pattern of shared meaning across the codes, which can support the understanding of a phenomenon and were relevant to the study objective.

Moreover, data interpretation was performed by analyzing the code pattern amongst the participants. Potential relationships across the codes were also investigated through co-occurring codes, which overlapped in a meaning unit. ISP coded the transcript data, classified them into themes/sub-themes, and then discussed them with LRI. The other researchers (AP, IMP, PS, JWA, and EH) reviewed the final concept's codes, themes, and sub-themes. Any disagreements in the data analysis were resolved by the consensus considering the transcript and field notes.

2.6 Trustworthiness and Information Credibility

We combined data and investigator triangulation to enhance the trustworthiness of the information obtained from the participants. We observed the daily activities, facilities, and documents related to the findings in the data triangulation. The essential information from a participant was also confirmed to another participant based on the information context to ensure the information's credibility. Investigator triangulation was performed by confirming the finding across the investigators without prior discussion. Lastly, we provided the member checking where the participants were allowed to read and approve the interview transcript without any pressure and guidance to agree with specific meanings to validate the interview, preserve research ethics, and empower the participants related to the findings (Mero-Jaffe, 2011). The Standard for Reporting Qualitative Research (SRQR) was followed for a systematic and transparent report (O'Brien et al., 2014).

3 RESULTS

The study successfully involved 18 of 20 eligible TB service providers at the CHC level for the FGDs and IDIs. Two TB service providers did not participate in the FGD due to the lack of backfill for daily clinical work in their CHCs. We conducted FGDs and IDIs with other relevant participants to validate and enrich information obtained from the 18 participating TB service providers. The other group comprised TB programmers at the district health office level, pharmacists at the CHC level, TB patients, a patient's family member, TB programmers at the hospital level, and a representative of the pharmaceutical service department at the district health office. Thus, 48 participants distributed across rural (23 participants) and urban (25 participants) areas were included in this study. The average participant's age was 40 years old (minimum = 16; maximum = 56), whilst the average participant's experience in TB was 84 months (min = 6; max = 348). We performed six FGDs amongst 28 participants, that is, TB service providers (physician and nurse) and pharmacy staff at the CHC level, whilst the IDIs were performed amongst 20 participants. The average duration of the FGDs was 95.83 min (min = 69; max = 124), whilst the average duration of the IDIs was 37.80 min (min = 4; max = 117). Due to a hearing problem from a TB patient participant, an interview was ended at the minimum duration of the interview (4 min). We then continued the interview with his wife to explore the information needed. We interviewed the participants in several locations, that is, district health office (20 participants), community health service (21 participants), hospital (5 participants), participant's home (1 participant), and non-government organization office (1 participant). **Table 1** presents the participant characteristics.

We identified 210 meaning units that related to the study objective. The meaning units were inductively coded and classified into two major themes: organizational capacity and TB activities. The organizational capacity consists of three sub-themes: human resources (HR), facility, and coordination. The TB activities theme comprises six sub-themes: TB case finding, diagnosis, drug supply chain and dispensing management, treatment, recording and reporting, and public–private mix (PPM) activities. **Figure 2** depicts the themes, sub-themes, and codes.

TABLE 1 | Characteristics of the participants (*n* = 48).

Characteristics	Male (*n* = 8)		Female (*n* = 40)	
	Rural (*n* = 4)	Urban (*n* = 4)	Rural (*n* = 19)	Urban (*n* = 21)
Tuberculosis service providers				
Physician at CHC level	1	0	4	3
Nurse at CHC level	0	0	5	5
TB service provider at DOH level	0	0	1	2
Pharmacist of the CHC	0	0	5	5
Healthcare workers at the hospital setting				
TB nurse	0	0	0	1
Pharmacist	0	0	0	1
Pulmonologist	0	0	0	1
Internist	0	1	0	0
Other supporting department staff				
Department of Pharmaceutical Services at DOH	1	0	0	1
Tuberculosis activist from a TB NGO	0	0	0	1
TB patients and their family members				
Non-MDR-TB patient	1	2	2	0
MDR-TB patient	1	1	1	1
Family members	0	0	1	0

Information: CHC: community health center; DOH: district health office; TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; NGO: non-governmental organization.

3.1 Organizational Capacity Theme

A total of 69 meaning units were analyzed for the organizational capacity theme. The organizational capacity barriers were related to HR (i.e., the HR shortage, high workload, disproportion of remuneration score system, HC fear, and HR rotation), facility (i.e., limited availability of sputum tests, chest X-rays, rapid molecular tests, and ambulances), and coordination (i.e., ineffective external coordination). More detailed information on the organizational barriers is described below.

3.1.1 HR

Our participants stated that the shortage of HR had been the main problem in managing TB. A TB analyst who operates a sputum test is not always available in every CHC:

> "*We are confused to examine the sputum because we do not have a TB analyst in our laboratory" (CHC's doctor 1).*

Limited healthcare providers also impacted TB treatment care. Our TB patient's participant highlighted that he should find another healthcare facility to inject his medicine taken from the CHC due to the limited staff who operate TB care:

> *"Because the TB staff does not provide TB care every day [*sic*]. They have activities in another programme of CHC, e.g., Posyandu or others, I should inject my TB medicines outside the CHC" (TB patient 1).*

The HR shortage implied the high workload of the TB service provider. It was worsened when TB service providers also confirmed their fears. Our participants stated that they should manage multiple activities other than TB care:

> *"If there is a TB patient, other staff seem not to face the patient. They are worried about getting the infection" (CHC's programmer/nurse 3).* and *"I have multiple jobs in CHC, so my job is not only taking care of TB but also other activities, e.g., emergency unit and another task" (CHC's programmer nurse 1).*

Our participants mentioned that a higher remuneration should be applied amongst healthcare service providers who manage a risky disease. Given that TB pathogen can potentially infect them and spread the disease to their family, they thought that TB is a higher risk service than other services at the CHC level. Thus, the amount of remuneration should be adjusted on the basis of the potential risks:

> *"We do not have a special consideration for the incentive to do the risky work. All programmes get the same remuneration point" (CHC's programmer/nurse 2).*

The participants also disclosed that HR rotation for a skilled TB service provider at the district level is not under their control. It will take more effort to provide individual training when the new staff members do not have experience in TB management:

> *"It makes me in the difficult situation when there is TB staffs' rotation which already had TB knowledge and skills" (district TB programmer 1).*

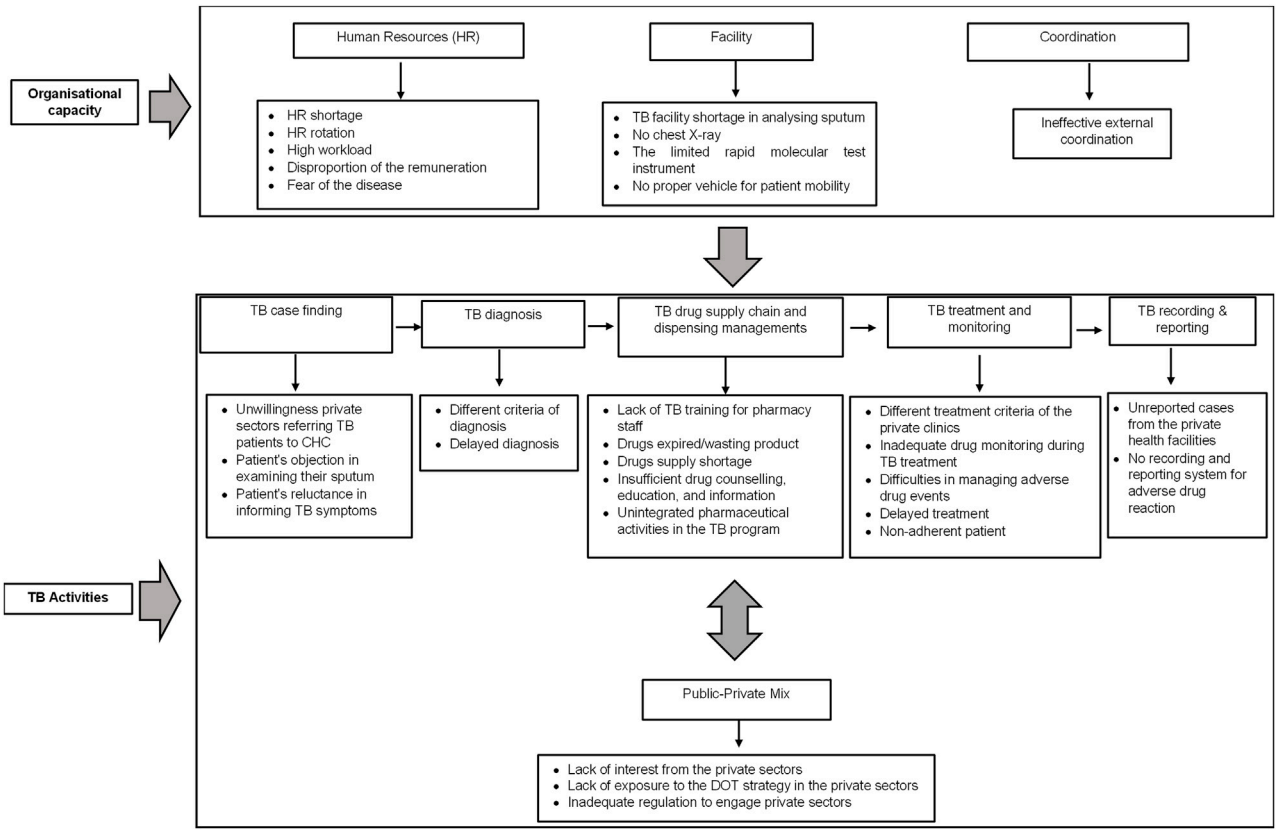

FIGURE 2 | Theme, sub-theme, and code of barriers to successful TB treatment from the TB service provider perspectives.

3.1.2 Facility

The supported facility for TB activities in CHC is also highlighted. Our participants expressed limited facilities for TB diagnosis and transportation:

> *"The problem here is we do not have a sputum corner for taking the patient's sputum. Ideally, to get fast action, the patient can be asked to provide the sputum in our facility" (CHC's doctor 2).*

Our participant stated that no special room could be used for collecting patient sputum at the CHC. The suspected TB patients were asked to provide the sputum specimen from their homes. However, in many cases, the patient did not send the sputum after being asked to send it, or they provided unqualified sputum for the test because of the inability to expel the sputum:

> *"We face difficulty diagnosing TB patients because we only have AFB tests. The positive result from the AFB test is still rare to be found, so we have to refer suspected TB patients to have chest x-ray in the hospital. The problem is not every patient has free access to chest x-ray in the hospital" (CHC's doctor 2).*

As described in the quotations above, our participant stated difficulties diagnosing TB due to no existing chest x-ray instrument at the CHC level. In some cases, suspected TB patients should be referred to the hospital for a chest X-ray examination because there were doubts about the result of the sputum test through the AFB test. However, not all suspected TB patients can access free chest x-ray examinations in the hospital due to not having healthcare insurance:

> *"According to the national regulation, we should use rapid molecular test instrument. However, we only have one instrument covering around 42 CHCs in our district. You can imagine if all the CHC send the TB specimens, it will cause overcapacity and delay the result" (district TB programmer 1).*

Our participants stated that rapid molecular test (RMT) was the essential examination as it was recommended to diagnose TB according to the national guideline. However, there was only an RMT instrument that should cover 42 CHCs. It led to the delayed result of the test:

> *"We have a cooperation with sub-district staff to borrow an office car for TB patients because we should accompany TB patients for MDR-TB treatment at the MDR-TB centre hospital. However, that is,* [sic] *only a usual car, that, is not an ambulance, so the personal safety is poor" (CHC's programmer/nurse 3).*

Our participant described an experience when she accompanied an MDR-TB patient to an MDR-TB center for TB examinations without proper personal safety. No ambulance can be used, and finally, she used a usual car with poor personal safety for around 3 h trip.

3.1.3 Coordination

Our participants mentioned ineffective external coordination with the private healthcare (PRHC) facilities because of the different criteria of the diagnosis and treatment found. The participants communicated that they expressed difficulties coordinating with TB stakeholders in managing TB cases based on the national guidelines. They suggested providing advocacy to improve the coordination system in managing TB cases with the PRHC:

> *"It is better to have an advocacy to all health care staff around the CHCs, medical doctors, nurses, midwives, and pharmacists. All are invited to explain that the management of TB cases should be uniform" (CHC's programmer/nurse 4).*

3.2 TB Program Activity Theme

A total of 141 meaning units were analyzed in the TB program activity theme. We identified the TB activity barriers related to TB case finding (i.e., referral activity, patient's objection in the sputum examination and patient's openness); diagnosis (i.e., different criteria and delayed diagnosis); drug supply chain and dispensing management (i.e., lack of TB training, expired drug/wasting product, drug supply, insufficient drug counseling, education and information, and unintegrated pharmaceutical activities); treatment and monitoring (i.e., different treatment criteria, inadequate treatment monitoring, difficulties in managing adverse drug reaction, delayed treatment, and patient non-adherence); reporting (i.e., unreported case from the private sectors and no recording for adverse drug reaction); and PPM (i.e., lack of interest from private sectors, lack of Directly Observed Therapy (DOT) exposure, and inadequate local regulation). We provided below a detailed description of the barriers in the TB activity theme.

3.2.1 Tuberculosis Case Finding

We identified two barriers related to the TB case finding. According to the Indonesian health system, TB care can also be provided by PRHC. Nevertheless, not all PRHC have the proper facility to diagnose TB disease. This can lead to TB misdiagnosis and inappropriate treatment. Thus, the failure of PRHC to refer or report their TB patient to CHC has been identified as case-finding and reporting problems:

> *"Especially for the private clinics, I have asked them to cooperate with us for patients with TB symptoms. Please check the patient with the rapid molecular test in our facility. If the result has been released, we will send back the patient to them. We also inform to use [*sic*] the DOT strategy for the TB regimen, but unfortunately, they reject our request" (CHC's programmer/nurse 5).*

Moreover, we analyzed that exploring information about TB symptoms from suspected TB patients has been an obstacle in detecting TB cases. The suspected TB patients were reluctant to share information about their symptoms, and the suspected TB patients were reluctant to perform free sputum tests in CHC:

> *"The difficulty is when we try to explore information from the suspected TB patient. Are there coughing symptoms in your family? Then they did not want to open the information. They said that all are fine" (CHC's TB programmer/nurse 6) and "In my case, we have identified ten suspected TB patients who should be tested for the sputum. We have given them the sputum pot, but, although it is free, [*sic*] mostly did not go to check the sputum" (CHC's TB programmer/nurse 4).*

3.2.2 Tuberculosis Diagnosis

Our participants communicated several problems in the TB diagnosis activities: delayed diagnosis and distinct diagnosis criteria from outside health facilities. We found that the misdiagnosis in PRHC facilities caused the patients to experience delayed TB diagnosis:

> *"We commonly find TB patients with delayed diagnosis. They just went to the health facility after they had the TB symptom too long or they already went to health facilities several times, but the diagnosis is not TB" (TB patients 2).*

An MDR-TB patient informed that his sputum was not examined when he had been diagnosed with TB. A chest radiograph was the only supported examination when he had a TB-sensitive diagnosis in a PRHC facility. However, the regimen was changed to an MDR-TB regimen at CHC when the sputum test showed that the pathogen had been resistant to rifampicin:

> *"I did not check my sputum. I just had a chest X-ray procedure and received the TB treatment" (TB patients 1).*

3.2.3 Tuberculosis Drug Supply Chain and Dispensing

This study identified unintegrated pharmacy staff activities in the TB program. Moreover, TB training was not provided for pharmacy staff at the CHCs:

> *"We have not provided tuberculosis training for pharmacy yet" (district TB programmer 2).*

Anti-TB drugs were stored and dispensed in the TB room rather than from the pharmacy, and the drugs were dispensed by a TB service provider (nurse) due to the easiness of providing the drugs for TB patients:

"For drug storage, monitoring and information are conducted by TB programmer. The pharmacist has not performed those activities. The TB flow service is different. TB patients go to the back room directly, so they go to the TB service room operated by TB programmer directly" (CHC's pharmacist 1).

TB service providers insufficiently delivered drug counseling, education, and information. The limited time of TB service providers was due to other responsibilities in the CHC:

"Patient education can take around 20–25 minutes. The problem is when we have a meeting or other patient care, we cannot do that" (CHC's doctor 3).

The study also revealed that expired anti-TB drugs and the shortage of the drug supply had been a concern. Those might be due to improper drug planning, procurement, and monitoring:

"There were cases that the medicines exceeded the expired date. It might be too much procurement and inadequacy of drug monitoring" (pharmacist's HDO 1) and "We already know that we should identify the patient who needs TB prophylaxis, but the problem is the dosage form of the medicine, Isoniazid 300 mg, is not available. All the drugs are in the fixed-dose combination forms" (CHC's programmer/nurse 6).

3.2.4 Tuberculosis Treatment and Monitoring

We identified five barriers in the TB treatment and monitoring activities: delayed treatment, different TB regimens, inadequate drug monitoring, non-adherence to medication, and difficulties in managing adverse drug reactions:

"The patients sometimes come after they get critical conditions. They were not aware of the condition from the appeared symptom" (CHC's TB programmer/nurse 7) and "[. . .] we sometimes receive TB patients who are treated in the outside with different regimens. We think why it is not the same with our guideline" (CHC's doctor 4).

As the described quotation above, our participants communicated that the delayed treatment was due to the unawareness of TB patients in identifying the signs and symptoms of TB. The patients went to the CHC when the condition had been severe. Regarding treatment regimens, in some cases, our participants stated that they found different TB regimens prescribed by another private clinic compared with the regimen of CHC. Therefore, it is more challenging to deliver appropriate drugs at CHCs:

"Based on my observation, development of MDR-TB is commonly not caused by an inappropriate drug, but it is more the absence of patients during the treatment during the period". CHC's TB programmer/nurse 4.

"Some patients were undetected. They did not collect the medicine at CHC. We just knew when the medicine had piled up in the storage cabinet". District TB programmer 2.

"We face problems on the management of adverse drug reaction. From 2015 until now, we have had difficulties managing patients with an adverse drug reaction. We should refer to a hospital, but the patient has been referred again to another hospital. It takes a long time to manage the patient". CHC's nurse 8.

The other problems of medication were also highlighted in the quotation above. We identified that the development of MDR-TB was commonly due to the absence of TB patients in taking the medication. The patients did not come to CHC regularly to collect and take their TB medication. The problem was complex when the management of adverse drug reactions was not performed adequately at the CHC level. Our participants communicated that they face difficulties managing TB adverse drug reactions. Inability in managing TB adverse drug reactions at the CHC led the staff to transfer the patient to the hospital. However, the patients were not always ended in the first referred hospital. In some cases, the patients were referred again to another hospital, which can cause a delay in managing the incidence of TB adverse drug reaction.

3.2.5 Tuberculosis Recording and Reporting

We found that TB recording and reporting problems were related to unreported TB cases from the PRHC facilities and no proper recording and reporting system for the adverse drug reaction (ADR) of anti-tuberculosis drugs. Comprehensive TB case reporting is necessary to estimate TB burden and drug monitoring for successful treatment. As a public health facility, the CHC has to record and report all TB cases in their area. However, TB service providers stated that TB reporting from the PRHC facilities was difficult to collect:

"If we want to report all cases, all the health facilities network must report their cases, including on-going and the completed cases. However, the problem is that we do not know the case when the patient has been treated in the private health facility" (CHC's program/nurse 9).

Furthermore, ADR recording and reporting were not performed optimally at the CHC level. It was confirmed by TB service providers that no ADR recording and reporting system is available in their CHCs:

"Ideally, the adverse drug reaction monitoring form should be provided in CHC, but I have not reported it yet at my CHC" (CHC's doctor 5).

3.2.6 Public–Private Mix (PPM) Program

Given that public health facility holds considerable responsibilities in healthcare, collaboration with the private facilities under the PPM program is strongly recommended.

Nonetheless, we observed that PPM at the CHC level faced several problems: lack of interest from PRHC, lack of exposure to the DOT strategy in the private sectors, and inadequate local regulation to engage PRHC. As described in organizational capacity, HR shortage and external coordination affected the performance of the PPM program at the CHC level:

> *"We do not have any difficulties inviting local communities here, but it is complicated for the private health facilities". CHC's doctor 3.*
>
> *"I think the problem here is the private doctor, hospital, or pharmacy have not been fully exposed to DOT strategy". CHC's doctor 6.*
>
> *"We still do not have a strong regulation, such as a local regulation that explains reward and punishment for engaging private sectors under PPM TB program". District TB programmer 2.*

4 DISCUSSION

Our study demonstrated that organizational capacity is the main barrier affecting TB services at the CHC level. It includes adequate HRs, facilities, and effective external coordination with the relevant stakeholders. Further, barriers to daily clinical practice in managing TB cases at the CHC level were shown, such as inadequate TB case finding, diagnosis, drug supply chain and dispensing management, treatment and monitoring, recording and reporting, and PPM program. Notably, the PPM is essential for optimal TB care because it can associate with TB services at the CHC level.

We found that the absence of adequate staffing levels in the TB program is one of the main issues in managing TB cases at the CHC level. The limited healthcare staff generated a workload burden in the healthcare system in CHC, where they are obliged to provide health services for high numbers of patients per day, and the burden escalated by the additional works in another program or other healthcare activities. As TB is perceived as a high-risk transmission disease, TB service providers felt that the incentive to manage TB should differ from non-high-risk transmission diseases. Incentives could stimulate better performance and the long-lasting effects of the performance in healthcare (Abduljawad and Al-Assaf, 2011). Nevertheless, an incentive scheme should be developed. It can consider monetary and non-monetary incentives according to the financial and organizational conditions of CHC.

Our study demonstrated that replacing the experienced TB staff with the new staff without TB experience has been an obstacle to the continuity and success of the program. Given that the regular training program does not provide for the new staff, the daily TB care will be affected. We analyzed that the limited budget for providing the training and no comprehensive planning for the staff rotation at the local government level may be causal factors for the barriers regarding the staff rotation. It was in line with a survey that trained staff in TB was inadequate in many high prevalent TB countries (Figueroa-Munoz et al., 2005). Since the staff rotation at the CHC level in Indonesia under the local government authority, it should be realized by the local government that TB knowledge and skill deficit could lead to suboptimal TB care and infection control in health facilities (Shrestha et al., 2017). The problem was complex when HC fear was explained in this study because of potential TB transmission. Insufficient knowledge, skill, capability, and facility can be causal factors for HC fear that lead to TB-related stigma in health facilities (Chang and Cataldo, 2014; Nyblade et al., 2019; Probandari et al., 2019). Hence, ensuring the knowledge, skill, capability, and facility in managing TB cases is crucial in minimizing potential problems in TB care, including minimizing poor treatment outcomes and TB-related stigma from healthcare providers.

A shortage of TB facilities was identified in our study. Laboratory capacity to analyze sputum was limited, as well as the unavailability of several essential facilities, such as chest radiograph, rapid molecular test, and ambulance. According to the national guideline (Ministry of Health Republic of Indonesia, 2010), the sputum examination at the CHC level is critical to diagnosing TB. However, not all CHCs have a particular room for sputum collection, sufficient lab facility, and TB analysts. It leads to difficulties collecting and assessing qualified sputum from the suspected TB patients. Our observation and discussion with TB staff at the CHC found that limited laboratory staff and budget have played a vital role in providing particular sputum rooms at the CHC level. Consequently, in many cases, TB patients did not send the sputum to the CHC after being asked to provide the sputum at home, or they provided unqualified sputum for the test because of no guidance and inability to expel the sputum. An observational study in Indonesia supported our finding that a considerable number of TB suspects did not provide sputum in a proper quantity and quality (Sakundarno et al., 2009).

The unavailability of the chest X-ray is associated with the potential misdiagnosis of TB, delayed diagnosis, and treatment in our study. Our physician participant described that they complained about difficulties diagnosing TB without a chest X-ray, especially in the negative sputum smear patients. Additionally, the participant explained that the chest X-ray would be very beneficial because microscopic examination from the sputum of the patient does not always provide satisfactory results. However, although TB care is a mandatory service delivered by the CHC, the availability of chest X-rays at the CHC level is not supported by national regulation for the standard minimum instrument of TB care at the CHC (Ministry of Health Republic of Indonesia, 2019). The importance of chest X-ray for TB was studied in Indonesia. A cohort study showed that additional chest X-ray examination in the routine diagnostic workup for TB (i.e., clinical examination and sputum microscopy) provided high sensitivity and specificity in diagnosing TB in Indonesia (Saktiawati et al., 2019). This finding was also strengthened by a study that displayed the lack of confidence to diagnose TB amongst clinicians at the primary level, leading to delayed treatment (Lestari et al., 2020). Furthermore, we identified that delayed treatment is higher when the rapid molecular test to identify drug sensitivity does not always provide at the CHC level. The

specimen should be referred to another CHC or health facility that takes several days. The government should notice the adequacy of the rapid molecular test in quality and quantity to overcome delayed diagnosis and treatment.

The unavailability of an ambulance for accompanying an MDR-TB patient for having an examination in the MDR-TB center was explained by our TB service provider participant. Given that the distance from CHC to the MDR-TB center is relatively far, she experienced accompanying an MDR-TB patient using a usual car without proper infection control during approximately 2 hours of the trip. Our study confirmed a previous qualitative study in the various settings of Indonesia that described the lack of facility for TB infection control in CHC (Probandari et al., 2019). The poor facility leads to having the unsafe feeling of TB service providers in managing TB patients (Probandari et al., 2019). It potentially discriminates or stigmatizes patients with TB in the health facility. A study in Mozambique exploring factors associated with poor quality TB care cascade underlines the importance of ensuring proper diagnostic facilities (Lisboa et al., 2020). The study concluded that ensuring the availability of diagnostic facilities will reduce delayed and inappropriate TB treatment (Lisboa et al., 2020).

As described by our participants, external coordination makes it difficult to engage the private sector in TB management. This factor can be associated with HR shortage to perform the partnership with the private sectors and insufficient local regulation to strongly engage the private sector in TB management. The regulation should declare the comprehensive PPM system, including the role, communication system, and incentive of all stakeholders related to PPM. We analyzed that the implementation of the PPM program is affected by the exposure of DOT strategies to the private sectors. Our study was supported by a case-control study in Bali, Indonesia. The study revealed that receiving information on DOT strategies is essential for engaging private clinics in managing TB cases (Putra et al., 2013).

In TB case finding and reporting, cooperation with the private sector is essential. Our study asserted that the unwillingness of private sectors to refer TB cases had been a problem in managing TB cases. Similarly, a study in Yogyakarta, Indonesia, has validated that almost one-third of the private practitioner participants never referred a TB suspect to a TB service provider (Mahendradhata et al., 2007). The need for cooperation with private sectors in Indonesia has been strengthened by the study that has confirmed that 73% of TB patients seek their first treatment in private sectors (Surya et al., 2017). Poor cooperation and coordination between the public and private sectors in managing TB cases will potentially lead to the under-reporting and loss of treatment follow-up TB cases. TB case-finding activities are more complex when TB suspects and their families are unaware of TB signs and symptoms. Improving public awareness on how they can identify TB and when and why they should visit a CHC may improve TB case detection.

4.1 Potential Limitations and Strengths

A limitation of this study is the lack of involvement from the private sector. The findings were analyzed from the perspective of the public sector's participants. Thus, the additional information from private sector participants might enrich the findings. However, we believe that applying a collaborative study, defining proper criteria for the participant, performing triangulation and member checking, and following standard reporting for the transparent report in this study will contribute to the validity and reliability of the study.

4.2 Implication for Policy and Practice

Our study demonstrated that organizational capacity is essential in performing high-quality TB care at the CHC level. Given the CHC as a backbone facility in managing TB cases, this study has drawn several future directions that may be applied in the other high prevalent TB countries.

First, since the current national regulation (Ministry of Health Republic of Indonesia, 2019) has not covered the essential findings from this study as the standard minimum for TB care at the CHC level, there is a need to re-review and re-develop the minimum standard of human resources, facility, coordination system, and TB care at the CHC level. The development should consider the current evidence and challenge in improving treatment success and achieving national and global TB targets by 2035. The facilities that support TB care, such as sputum collection room, laboratory, rapid molecular test, and chest X-ray, should be adequately provided at the CHC level for rapid and precise TB diagnosis and treatment. Importantly, the quality and quantity of TB service provider personnel should be analyzed considering the workload, and TB analysts should be provided in each CHC. Second, a comprehensive organizational capacity assessment for the CHC is required nationally. The assessment will be beneficial in identifying the sub-standard care and developing its interventions in improving TB care at the CHC level (Cazabon et al., 2017). Third, the engagement of the private sector for TB care should be systematically performed by the CHC with sufficient guidance, facility, and support from the central and local government. The national guidelines and strategies should also be informed to PRHC facilities for similar concepts and principles in managing TB cases (Putra et al., 2013). Finally, strengthening pharmacy at the CHC in managing drug supply, dispensing, PPM program, and other patient-centered services (e.g., drug counseling and monitoring) can be initiated to improve TB treatment success at the CHC level (Abdulah et al., 2014; Miller and Goodman, 2020). The possibilities to implement digital health technology can be considered to support pharmacists in improving TB medication adherence and treatment outcomes (Ridho et al., 2022). Hence, systematic programs and guidance for the pharmacy staff should be developed to integrate pharmaceutical care in TB management at the CHC level.

In conclusion, as the central issues, several critical aspects in the organizational capacity are identified to improve the treatment success of TB patients: HR, facility, and external coordination. Those affect the activities in managing TB cases: TB case finding, diagnosis, drug supply and dispensing, drug monitoring, reporting, and recording. The willingness of the government to focus and resolve the mentioned issues is crucial to the continuity of the programmer and improving the successful TB treatment rates. Moreover, further studies are critical to quantify and generalize the finding to the population level to guide effective strategies and interventions to improve TB treatment success in high prevalent TB countries, especially Indonesia.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of Universitas Padjadjaran, Indonesia (no. 333/UN.6/Kep/EC/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ISP, EH, JWA, LRI, AP designed the study. ISP and LRI carried out the data collection. ISP wrote the first draft. ISP, LRI, PS, AP, IMP, JWA and EH analysed the data; critically read; modified the draft; read and approved the final version.

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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.2022.857783/full#supplementary-material

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Evaluation of Factors Associated With Appropriate Drug Prescription and Effectiveness of Informative and Educational Interventions—The EDU.RE.DRUG Project

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Background: EDU.RE.DRUG study is a prospective, multicentre, open-label, parallel-arm, controlled, pragmatic trial directed to general practitioners (GPs) and their patients.

Methods: The study data were retrieved from health-related administrative databases of four local health units (LHUs) of Lombardy and four LHUs in Campania. According to the LHUs, the GPs/patients were assigned to (A) intervention on both GPs (feedback reports about appropriate prescribing among their patients and online courses) and patients (flyers and posters on proper drug use), (B) intervention on GPs, (C) intervention on patients, and (D) no intervention (control arm). A set of appropriate prescribing indicators (potential drug–drug interactions [pDDIs], potential and unnecessary therapeutic duplicates [pTDs], and inappropriate prescriptions in the elderly [ERD-list]) were measured at baseline and after the intervention phase. The effectiveness of the intervention was evaluated estimating the absolute difference in percentages of selected indicators carrying out linear random-intercept mixed-effect models.

Results: A cohort of 3,586 GPs (2,567 in intervention groups and 1,019 in the control group) was evaluated. In Campania, the mean pre-intervention percentage of patients with at least one pDDI was always greater than 20% and always lower than 15% in Lombardy. The pre–post difference was quite heterogeneous among the LHUs, ranging from 1.9 to −1.4 percentage points. The mean pre-intervention percentage of patients with pTDs ranged from 0.59 to 2.1%, with slightly higher values characterizing Campania LHUs. The magnitude of the pre–post difference was very low, ranging from −0.11 to 0.20. In Campania, the mean pre-intervention percentage of patients with at least one ERD criterium was considerably higher than in Lombardy (approximately 30% in Lombardy and 50% in Campania). The pre–post difference was again quite heterogeneous. The results from the models accounting for GP geographical belonging suggested that none of

the interventions resulted in a statistically significant effect, for all the three indicators considered.

Conclusion: The proposed strategy was shown to be not effective in influencing the voluntary changes in GP prescription performance. However, the use of a set of explicit indicators proved to be useful in quantifying the inappropriateness. Further efforts are needed to find more efficient strategies and design more tailored interventions.

Keywords: pragmatic trial design, appropriate prescription, educational intervention, drug prescribing, feedback report

1 INTRODUCTION

Since the general practitioner (GP)–patient interaction leads in most cases to a drug prescription, the prescribing quality in general practice is a crucial issue, having a significant impact on the well-being of patients and representing a substantial part of healthcare expenditure (Steinke et al., 1999; Mekonnen et al., 2021).

The failure to prescribe appropriate drug therapy, named "inappropriate prescribing," occasionally simply results in the absence of any clinical effect. In other more serious cases, the consequences may lead to adverse events, namely, aggravation of the illness, additional diagnostic testing, and increased hospitalizations and mortality, especially in older people, or in comorbid individuals who may have compromised physiologic functions (Hamilton et al., 2009). Furthermore, the inappropriate use of medicines can lead to increasing costs for the patient and healthcare system and wastage of scarce health resources (Ofori-Asenso and Agyeman, 2016). Thus, inappropriate prescribing has become a global healthcare concern.

It is essential to identify potentially inappropriate prescribing (PIP) and correct and optimize it where necessary, with the expectation that this will avoid serious harm (Avery, 2008). A wide range of interventions can be implemented to change patients' and prescribers' behaviour to improve drug prescribing. Among them, educational/professional strategies are often aimed at persuading or informing, and this usually involves the use of printed materials, seminars, bulletins, and face-to-face interventions. Continuing medical education (CME) is the most common educational intervention, delivered through various methods, namely, interactive teaching complemented by a decision algorithm, mailed educational material combined with individualized feedback, and face-to-face visits to physicians (Kaur et al., 2009).

The EDU.RE.DRUG (effectiveness of informative and/or educational interventions aimed at improving the appropriate use of drugs designed for general practitioners and their patients) study has been designed to deeply investigate the practice of prescribing among general practitioners in two Italian regions, to highlight the most frequent events of inappropriateness, and to plan tailored intervention for GPs and patients focused on this critical issue. The primary objective was to assess the effectiveness of informative and/or educational interventions addressed to general practitioners and their patients, aimed at improving the prescribing quality and promoting proper medication use.

2 METHODS

2.1 Study Design

EDU.RE.DRUG was a prospective, pragmatic, multicentre, open-label, parallel-arm, and controlled trial, started in April 2017, which has been extensively described elsewhere (Casula et al., 2020). Briefly, it was a non-randomized, open-label, cluster intervention design. All experimental units (GPs and/or patients) in each cluster receive the scheduled treatment. Eight Local Health Units (LHUs) were enrolled: four in the Campania region, in the southern part of Italy, and four in the Lombardy region, in the north of Italy.

2.2 Study Setting and Data Source

The clinical setting of the study was the general practice. The study population was composed of all GPs and all their adult patients aged ≥40 years from the eight LHUs involved.

Data were retrieved from health-related administrative databases containing demographic and pharmacy-refill data of all beneficiaries of the National Health Service (NHS) in the LHUs involved (*Bergamo*, *Lecco*, *Mantova*, and *Monza-Brianza* in Lombardy and *Avellino*, *Caserta*, *Napoli 1 Centro*, and *Napoli 2 Nord* in Campania):

Compliance with national and European laws on personal data was guaranteed by the LHUs through the generation of unique anonymous codes for each patient and each prescriber, with respect to the privacy of every citizen.

2.3 Definition of Inappropriate Prescribing Indicators

Prescription of potential drug–drug interactions (pDDIs) was defined based on MediRisk software (INXBASE https://ravimid.med24.ee/Accessed). In this project, two drugs were considered potentially interacting if their coverage periods (calculated since their dispensation date and based on their defined daily doses) overlapped for at least 1 day. Only pDDIs with major clinical significance (excluded those with low level of documentation) or contraindicated clinical significance (regardless the level of documentation) were considered.

Potential and unnecessary therapeutic duplicates (pTDs) were defined as two or more prescribed drugs with the same ATC code at the second or third or fourth level but a different ATC code at the fifth level (Fulda et al., 2004) with at most 3 days between the two dispensation dates. Specifically, we selected the following classes:

- Drugs for peptic ulcer and gastro-oesophageal reflux disease (ATC codes: A02Bxxx and A02Bxxx).
- Agents acting on the renin–angiotensin system (ATC codes: C09Axxx/C09Bxxx and C09Cxxx/C09Dxxx).
- Statins (ATC codes: C10AAxx/C10BAxx and C10AAxx/C10BAxx).
- Antipsychotics (ATC codes: N05Axxx and N05Axxx).

Only in the elderly population (aged ≥65 years), we defined the ERD-list (EDU.RE.DRUG list; Casula et al., 2020) developed based on the updated Beers criteria (Radcliff et al., 2015), the STOPP&START criteria (O' Mahony et al., 2018), and the EU-(7)-PIM list (Renom-Guiteras et al., 2015). The three lists were merged and adapted to Italian settings by selecting only drugs available on the Italian market and reimbursed by Italian NHS. Moreover, the selection was limited to drugs always to be avoided in elderly patients, excluding drugs that should be used with caution or avoided in certain patients with certain diseases or conditions, as these circumstances cannot be evaluated through administrative databases.

2.4 Study Intervention

The GPs and their patients were assigned to one of the following arms: (A) intervention on GPs and patients; (B) intervention on GPs; (C) intervention on patients; and (D) control group. The intervention addressing GPs consisted in feedback reports (describing inappropriate prescription status of their patients in comparison to the median levels of their own LHUs) and a free online Continuing Medical Education (CME) course about rational prescribing and appropriateness measurement. Notably, participation to CME course was not mandatory.

The intervention designed for patients consisted in flyers and posters distributed in GPs' ambulatories and community pharmacies, focusing on correct drug use (efficacy/safety, adherence to GP indications, and self-medication).

2.5 Study Outcome

The primary outcome was the changes in prevalence of inappropriate prescribing indicators among GPs, assessed through the pre-specified indicators, after the interventions vs. baseline.

Among the secondary outcomes (Casula et al., 2020), here we have reported results about the identification of predictors of poor prescription appropriateness. We firstly evaluated potential predictors in an attempt to identify major covariates to be accounted for in the assessment of the primary outcome.

2.6 Statistical Analysis

2.6.1 Covariates

Several covariates have been assessed, both at the patient's and GP's levels.

From demographic databases, we retrieved birth date and sex of each patient. Using pharmacy-refill and hospitalization databases, we estimated the Charlson Comorbidity Index (Charlson et al., 1987), indicating the comorbidity status.

From demographic databases, we retrieved birth date, sex, and number of registered patients of each GP. We also calculated the percentage of elderly patients. Using pharmacy-refill databases, we estimated the annual number of different active drugs prescribed by each GP (drug portfolio).

2.6.2 Identification of Determinants of Inappropriate Prescribing

Considering only the data relating to the period prior to intervention, analyses were conducted to evaluate the effect of several variables (related to patients, GPs, or LHUs) on the probability of being exposed to 1) pDDIs, 2) pTDs, and 3) inappropriate prescriptions according to the ERD-list. Each of the three outcomes was analysed using a set of four models that differed from each other in the number of covariates used. All the models were logistic random intercepts models complying with the hierarchy data structure in which patients (level 1) were nested within the GPs (level 2), nested within the LHUs (level 3). The dependent variable (i.e., the outcome) assumed value 1 if the patient had been exposed to the inappropriateness indicator under exam, while it assumed value 0 otherwise.

Below are the covariates (fixed effects) included in each of the four models:

- Model 1: no covariates included.
- Model 2: patient level covariates included.
- Model 3: patient and GP level covariates included.
- Model 4: patient, GP, and LHU level covariates included.

In this application, GP and LHU are clustering variables. With the aim of investigating the amount of heterogeneity of each outcome explained by these variables, the median odds ratios (MORs) were calculated for each of the four models (Merlo et al., 2006). Given one clustering variable, the MOR is defined as the median value of the odds ratio between the cluster at the highest risk and the cluster at the lowest risk when randomly picking out two clusters. Hence, it can be conceptualized as the increased risk that (in median) a subject would have when moving to another cluster with a higher risk. The MOR has always values greater than 1, where 1 represents no variation between clusters, and increases as high as the between-cluster variation.

2.6.3 Intervention Effectiveness (Pre–post Analysis)

The primary and secondary outcomes were evaluated in a 12-month period before intervention (pre-intervention phase, April 2016–March 2017) and in a 12-month period after the intervention (post-intervention phase, April 2018–March 2019). The analysis was based on GP, as statistical unit. The difference (Δ pre − post) in the outcomes was estimated separately for each LHU.

The pre–post evaluation was performed with respect to the following three outcomes:

- Absolute difference in the percentage of patients (age ≥40 years) with pDDIs between the period preceding the intervention and the following period.
- Absolute difference in the percentage of patients (age ≥40 years) with pTDs between the period preceding the intervention and the following period.

TABLE 1 | GPs pre-intervention characteristics in the eight Local Health Units. Sex is reported as frequency (%); other variables are considered on a continuous scale and are reported as mean ± SD.

	Monza-Brianza Lombardy	*Caserta* Campania	*Mantova* Lombardy	*Avellino* Campania	*Bergamo* Lombardy	*Napoli 1 Centro* Campania	*Lecco* Lombardy	*Napoli 2 Nord Campania*
	N = 477	N = 542	N = 243	N = 280	N = 591	N = 602	N = 196	N = 655
	None		Patients		GPs		GPs and patients	
Male sex, N (%)	290 (60.8)	410 (75.7)	174 (71.6)	210 (75.0)	392 (66.3)	470 (78.1)	138 (70.4)	533 (81.4)
Age (years), mean ± SD	58.6 ± 6.9	60.5 ± 4.2	59.1 ± 6.2	60.6 ± 4.2	57.1 ± 6.8	61.1 ± 4.0	57.7 ± 7.1	59.5 ± 4.4
Patients (N), mean ± SD	1,489.7 ± 191.5	1,246.1 ± 382.6	1,328.2 ± 313.2	1,187.2 ± 402.2	1,422.2 ± 284.0	1,208.7 ± 362.6	1,462.7 ± 212.5	1,205.8 ± 389.8
Elderly patients (%), mean ± SD	25.8 ± 5.6	19.8 ± 5.3	25.8 ± 6.0	24.1 ± 5.6	22.9 ± 5.6	22.9 ± 5.6	25.2 ± 5.2	14.8 ± 4.3
Drug portfolio* (N), mean ± SD	332.2 ± 29.6	348.8 ± 53.2	317.9 ± 31.1	343.1 ± 60.4	321.6 ± 34.1	368.2 ± 55.1	321.2 ± 29.1	345.9 ± 53.5

*GP, general practitioner. *Drug portfolio: annual number of different active drugs prescribed by the GP.*

- Absolute difference in the percentage of elderly patients (age ≥65 years) with inappropriate prescriptions (according to the ERD-list) between the period preceding the intervention and the following period.

In order to study the effect of the interventions on the outcome (pre–post difference) and to take into account the hierarchical structure of the data, a linear random intercept mixed-effect model was used. The fixed components were: GPs' characteristics (sex, age, number of patients, percentage of elderly patients, and drug portfolio), intervention arm, and pre-intervention percentage of the evaluated indicator. The random intercepts represented the administrative areas. The fit of the models was evaluated considering the marginal and conditional R^2 (Nakagawa and Schielzeth, 2013).

Finally, a stratified analysis was conducted in order to evaluate the effect of GP characteristics on the outcome dividing the physicians with respect to the region of belonging. In both strata, there were four administrative areas and four different interventions (one per area). Under this setting, it is no longer possible to distinguish the effect of the intervention from the effect of the area. However, the effect of the other variables remains interpretable.

2.6.4 Data Analysis

Continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), whereas categorical variables are presented as cases (N) and percentage rate (%). In all analyses, a p-value <0.05 was considered statistically significant. All analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, United States).

2.7 Ethics

The study was approved by the Ethics Committee of the University of Milan on 07 June 2017 (code 15/17).

Procedures aimed at protecting personal data will be implemented in order to safeguard privacy and to prevent the identification of individual data (according to the Italian law D.Lgs. n. 196/2003). Anonymized regional administrative data can be used without a specific written informed consent when patient information is collected for healthcare management and healthcare quality evaluation and improvement (according to art. 110 on medical and biomedical and epidemiological research, Legislation Decree 101/2018).

3 RESULTS

A cohort of 3,586 GPs was evaluated; the pre-intervention characteristics are listed in **Table 1**. The mean age of the GPs was quite similar among the administrative areas, while there was a greater presence of female GPs in the Lombardy areas. Physicians from *Napoli 2 Nord* LHU had an average percentage of elderly patients lower than that of the other LHUs.

3.1 Identification of Predictors of Inappropriate Prescribing

3.1.1 Predictors of Exposure to Potential Drug–Drug Interactions

Results for the fully adjusted model, considering the exposition to pDDI as outcome, are reported in **Table 2**. The risk of being exposed to pDDIs increased with increasing age of the patient (for each 10-year increase: OR 1.53, 95% CI 1.52–1.53). Compared to patients with the Charlson Comorbidity Index equal to zero, patients with higher values showed higher risk; patients with values between 3 and 4 were the most likely to be exposed to interactions (OR 3.17, 95% CI 3.08–3.25). Patients from Campania (OR 1.24, 95% CI 1.10–1.39) had a higher risk, while male patients were less exposed to interactions (OR 0.74, 95% CI 0.73–0.75). The risk decreased with increase in the number of patients per GP (OR 0.95, 95% CI 0.95–0.96). The notable decrease in the MOR at the LHU level passing from Model 2 to Model 3 (from 1.40 to 1.13; data not shown) suggested that the differences in distribution of GP's characteristics between LHUs played a key role in determining the inhomogeneity of the outcome among territories.

TABLE 2 | Results for the fixed effects of the fully adjusted models.

Outcomes	Odds ratio (95% CI)		
	Potential drug–drug interactions	Potential therapeutic duplicates	Inappropriate prescriptions in the ERD-list
Patient			
Sex			
Female	Ref	Ref	Ref
Male	0.74 (0.73–0.75)	1.10 (1.07–1.13)	0.78 (0.78–0.79)
Age (10-year increase)	1.53 (1.52–1.53)	1.42 (1.41–1.43)	1.15 (1.14–1.15)
Charlson Comorbidity Index			
0	Ref	Ref	Ref
1-2	2.28 (2.26–2.31)	1.87 (1.81–1.94)	1.42 (1.40–1.44)
3-4	3.17 (3.08–3.25)	2.36 (2.22–2.50)	1.74 (1.68–1.79)
≥5	2.78 (2.69–2.88)	2.94 (2.74–3.17)	1.77 (1.70–1.84)
Patient's GP			
Sex			
Female	Ref	Ref	Ref
Male	1.04 (1.02–1.07)	1.04 (0.98–1.11)	1.08 (1.04–1.11)
Age (10-year increase)	1.00 (0.99–1.02)	1.03 (0.99–1.08)	1.03 (1.01–1.05)
Number of patients (100-unit increase)	0.95 (0.95–0.96)	0.88 (0.87–0.89)	0.95 (0.95–0.96)
Percentage of elderly patients (1-percentage point increase)	0.97 (0.97–0.98)	0.96 (0.95–0.96)	0.97 (0.97–0.97)
Number of distinct drugs prescribed (10-unit increase)	1.07 (1.06–1.06)	1.14 (1.13–1.16)	1.07 (1.06–1.07)
Patient's LHU			
Location			
Lombardy	Ref	Ref	Ref
Campania	1.24 (1.10–1.39)	0.83 (0.68–1.03)	1.48 (1.25–1.75)

GP, general practitioner; LHU, local health unit.

3.1.2 Predictors of Exposure to Potential Therapeutic Duplicates

Results for fully adjusted model for pTD prescriptions (**Table 2**) show that male (OR 1.10, 95% CI 1.07–1.13) and older patients (for each 10-year increase: OR 1.42, 95% CI 1.41–1.43) had a higher risk of being exposed to duplicate drug prescriptions. Furthermore, the risk increased as the Charlson Comorbidity Index increases (for scores 3–4: OR 2.36, 95% CI 2.22–2.50; for scores ≥5: OR 2.94, 95% CI 2.74–3.17). GPs with a large number of patients were less likely to prescribe therapeutic duplicates (OR 0.88, 95% CI 0.87–0.89) while the risk increased for GPs with a higher number of distinct drugs prescribed (for each 10-unit increase: OR 1.14, 95% CI 1.13–1.16). The MOR at the GP level was quite large even in the fully adjusted model (1.60), showing that the frequency of the outcome was largely attributable to the physician and to his/her unobserved characteristics. The MOR at the LHU level decreased from 1.49 to 1.13 passing from Model 2 to Model 3.

3.1.3 Predictors of Exposure to Inappropriate Drugs in the ERD-list

Results for the fully adjusted model (**Table 2**) show that the risk for a patient to be exposed to ERD drugs significantly increased with increasing age (for each 10-year increase: OR 1.15, 95% CI 1.14–1.15), Charlson Comorbidity Index (for scores 3–4: OR 1.74, 95% CI 1.68–1.79; for scores ≥5: OR 1.77, 95% CI 1.70–1.84). Moreover, the risk was higher in Campania (OR 1.48, 95% CI 1.25–1.75) and in patients registered with a male GP (OR 1.08, 95% CI 1.04–1.11). Conversely, the risk was lower in male patients (OR 0.78, 95% CI 0.78–0.79) and decreased with an increase in the number of patients per GP and in the percentage of elderly people assisted.

The MOR at the LHU level greatly decreased (from 1.58 to 1.24; data not shown) when adding GP characteristics in the model, showing that a part of the between-LHU variation in the outcome was attributable to the fact that in different LHUs, there were physicians with different characteristics.

3.2 Pre–Post Analysis

3.2.1 Efficacy of Intervention on Potential Drug–Drug Interactions

The mean percentage (SD) of patients with pDDIs in the pre-intervention period and the mean value of the absolute difference between the pre- and post-intervention percentages for the eight areas are reported in **Supplementary Table S1**. In Campania, the mean pre-intervention percentage of pDDI patients was always greater than 20%, while it was always lower than 15% in Lombardy. The pre–post difference was quite heterogeneous between the areas, ranging from 1.9 to −1.4 percentage points.

The results from a linear random intercept model accounting for GPs geographical belonging are shown in **Table 3**. Before applying the model, the numerical covariates were centred with respect to the mean. Therefore, the intercept represents the average outcome (pre–post difference) for a female GP whose covariates were equal to the average values observed in the data set and underwent no intervention. None of the interventions resulted in a

TABLE 3 | Linear random intercept model on pDDIs, pTDs, and ERD prescription.

Outcomes	Potential drug–drug interactions		Potential therapeutic duplicates		Inappropriate prescriptions in the ERD-list	
Fixed effects						
Parameter	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
Intercept*	0.17 (–6.19; 6.52)	0.945	0.13 (–0.07; 0.32)	0.148	3.62 (–3.90; 11.13)	0.252
Intervention						
None	Ref	-	Ref	-	Ref	-
GPs	1.19 (–7.78; 10.17)	0.731	0.04 (–0.21; 0.30)	0.652	0.76 (–9.83; 11.34)	0.852
Patients	0.93 (–8.05; 9.92)	0.787	0.13 (–0.14; 0.40)	0.243	2.65 (–7.97; 13.26)	0.527
GPs and patients	1.15 (–7.83; 10.13)	0.741	–0.06 (–0.32; 0.20)	0.560	2.48 (–8.12; 13.09)	0.551
GP sex						
Female	Ref	-	Ref	-	Ref	-
Male	–0.27 (–0.68; 0.13)	0.155	–0.10 (–0.20; –0.01)	0.037	–1.23 (–2.05; –0.42)	0.009
GP age (1-year increase)	0.06 (0.03; 0.09)	<0.001	0.08 (0.02; 0.15)	0.012	0.23 (0.17; 0.28)	<0.001
Number of patients (100-unit increase)	–0.06 (–0.14; 0.03)	0.189	0.06 (0.04; 0.08)	<0.001	0.17 (0.003; 0.33)	0.046
Percentage of elderly patients (1-percentage point increase)	–0.03 (–0.06; –0.001)	0.042	0.08 (0.02; 0.15)	0.014	0.07 (0.002; 0.14)	0.042
Percentage of pre-intervention patients with relevant inappropriateness (1-percentage point increase)	0.40 (0.37; 0.42)	<0.001	0.37 (0.33; 0.40)	<0.001	0.38 (0.35; 0.41)	<0.001
Number of distinct drugs prescribed (10-unit increase)	-0.15 (-0.21; -0.08)	<0.001	-0.05 (-0.06; -0.03)	<0.001	-0.33 (-0.46; -0.20)	<0.001
Random effects						
Parameter	**Estimate**	***p*-value**	**ICC**	**Estimate**	***p*-value**	**ICC**	**Estimate**	***p*-value**	**ICC**
Random intercept variance	10.41	0.081	<0.36	0.01	0.284	0.01	14.38	0.09	0.16
Residual variance	18.73	0.001		1.04	<0.001		75.69	<0.001	
Model fit									
Marginal R^2	0.28			0.13			0.32		
Conditional R^2	0.54			0.14			0.43		

*GP, general practitioner. ICC, intra-class correlation coefficient. *Numerical covariates were centred with respect to the mean. Therefore, the intercept represents the average outcome (pre-post difference) for a female GP whose covariates were equal to the average values observed in the dataset and underwent no intervention.*

statistically significant effect compared to the group that did not receive any intervention. An increase in the age of the GP or the pre-intervention percentage of pDDI patients was significantly associated with a decrease in the percentage of patients with pDDI from the pre-intervention period to the subsequent. Conversely, higher percentage of elderly patients or higher number of distinct drugs prescribed in the pre-intervention period was significantly associated with lower pre–post difference.

Stratifying by region (**Supplementary Table S2**), a higher percentage of elderly patients was significantly associated with lower pre–post difference in the Lombardy LHUs, while the association was not significant in Campania LHUs. Globally, no relevant differences were found between the two regions.

3.2.2 Efficacy of Intervention on Potential Therapeutic Duplicates

The mean pre-intervention percentage of patients with duplicate drugs (**Supplementary Table S3**) was low in all the LHUs, ranging from 0.59 to 2.1%; slightly higher values characterized the Campania LHUs. The magnitude of the pre–post difference was very low, ranging from –0.11 to 0.20.

The results from a linear random intercept model accounting for GPs geographical belongings are shown in **Table 3**. None of the interventions resulted in a statistically significant effect compared to the control group. The increase in the age of the GP, number of patients, percentage of elderly patients, and pre-intervention percentage of patients with duplicate drugs was significantly associated with a decrease in the percentage of patients with duplicate drugs from the pre-intervention period to the subsequent. Conversely, male sex and an increased number of distinct drugs prescribed in the pre-intervention period were significantly associated with lower pre–post difference.

The age of the GP was directly associated with pre–post difference in Campania, while the association was not significant for the GPs from Lombardy. Conversely, the percentage of elderly patients was directly associated with pre–post difference in Lombardy LHUs, while no significant association was found for Campania LHUs (**Supplementary Table S4**).

3.2.3 Efficacy of Intervention on Prescription of Drug in the ERD-list

In Campania, the mean pre-intervention percentage of patients exposed to ERD drugs was considerably higher than in Lombardy (**Supplementary Table S5**). The pre–post difference was quite heterogeneous between the areas. On average, *Napoli 2 Nord* LHU showed the greatest reduction in the percentage of patients with inappropriate prescriptions (+11.3 percentage points), while GPs from *Lecco* LHU increased the percentage of patients with

prescriptions of drug in the ERD-list on average by 0.5 percentage points.

The effect of the intervention arm and GP characteristics on the pre–post difference in the percentage of patients exposed to ERD drugs is shown in **Table 3**. None of the interventions resulted in a statistically significant effect compared to the group that did not receive any intervention. The increases in the age of the GP, number of patients, percentage of elderly patients, and pre-intervention percentage of patients with inappropriate prescriptions (ERD-list) were significantly associated with a decrease in the percentage of patients with ERD drugs in the post-intervention period, compared to the pre-intervention period. Conversely, male sex and a higher number of distinct drugs prescribed in the pre-intervention period were significantly associated with lower pre–post difference.

The results of the analysis stratified by region (**Supplementary Table S6**) showed that an increase in the age of the GP resulted in greater pre–post difference in both regions, with the effect that appears to be more pronounced in Campania (0.49 vs. 0.08). An increase in the number of drugs prescribed by the GP in the pre-intervention period was significantly associated with a lower value of the outcome in Campania, while no association was found for the areas of Lombardy.

4 DISCUSSION

Medication prescription is one of the most powerful tools for GPs in the prevention and treatment of diseases and the alleviation of symptoms. However, drug-related problems represent an important source of patient morbidity, and many cases of which could be prevented through the highest-quality medicine prescribing and management (Howard et al., 2003; Pirmohamed et al., 2004; Howard et al., 2007; Howard et al., 2008).

Our first analysis allowed to investigate whether some factors could affect the prescriptive inappropriateness or not. The results for fixed and random effects models show that the risk for a patient to be exposed to ERD drugs, pDDIs, or pTDs significantly increased with increasing age and Charlson Comorbidity Index. Male sex decreased the risk of being prescribed with ERD drugs or pDDIs, while increased the risk of pTDs. Regarding GPs' characteristics, the risk was higher with male sex, increased with the number of distinct drugs prescribed by the physician, and decreased with the increase in the number of patients per GP and in the percentage of elderly people assisted. The age of the GPs seemed not to have a major influence on the probability of inappropriate prescriptions, even if we observed a trend (statistically significant only for ERD drug prescriptions) towards an increased risk with increasing GP age. Consistent with literature, our data confirmed that the presence of comorbidities and the concomitant use of multiple drugs increase the risk of inappropriateness. In a German study (Stock et al., 2014), the risk to receive an inappropriate prescription in an elderly cohort increased with age, and women had a significantly higher risk compared with men. Previous studies from the United States and other German cohorts consistently reported age and female sex as risk factors for receiving inappropriate prescriptions. Moreover, comorbidity was identified as an additional risk factor for potentially inappropriate medication prescription (Almeida et al., 2019; Magalhaes et al., 2020). Regarding GPs characteristics, some studies also showed that female prescribers may be more likely to prescribe carefully and conservatively than male prescribers; evidence suggests that female physicians spend more time with their patients and are more likely to adhere to guidelines (Rochon et al., 2018; Mishra et al., 2020). Finally, the geographical variability in prescribing performance was observed also in other studies. This could be explained by variations in the health condition of the population, socioeconomic differences, and also the independent local management of the GPs by the LHUs (Lund et al., 2013; Saastamoinen and Verho, 2021).

A wide range of interventions can be implemented to change patients' and prescribers' behaviour and ameliorate drug prescribing and use. This could lead to significant improvements in patient outcomes and effective use of healthcare expenditure. Within the EDU.RE.DRUG project, an audit and feedback plus educational interventions approach was delivered in a prospective, pragmatic, multifactorial, open-label, parallel-armed, controlled trial. In the evaluation of the effectiveness of our intervention, the results from a linear random intercept model accounting for GPs geographical belonging showed that none of the interventions resulted in a statistically significant effect compared to the control group (the intervention did not effectively influence the voluntary changes in prescription performance by GPs).

Trying to examine potential explanation, we first considered the role of LHU heterogeneity. As in our study, the single statistical units (GPs) were not randomly assigned to the interventions, but the assignment of interventions took place by clusters (administrative areas), and to isolate the effect of the interventions from the effect of the groups (if a group effect is present) is challenging. The power of the study in identifying the effect of a treatment is influenced not only by the factors common to a classical randomized and controlled study but also by the intra-class correlation coefficient (ICC) and the number of groups assigned to each intervention. To address this point, a simulation analysis was carried out. Different scenarios were hypothesized (i.e., different combination of ICC and intervention effect values), and 2,000 data sets were simulated for each scenario. Each data set was analysed using a mixed effects model, as done in the main analysis. The results from these analyses showed that the difficulty in detecting even small variations in the outcomes of interest is partly attributable to the heterogeneity of the LHU involved, an aspect necessarily present in the setting of a pragmatic trial.

Other interventions aimed at improving GP's prescribing practice, conducted using pragmatic trials, have often not been successful. In a pragmatic, cluster randomized controlled trial performed in Germany (Muth et al., 2018), participants (≥60 years, ≥3 chronic conditions under pharmacological treatment, and ≥5 long-term drug prescriptions with systemic effects) were involved in a checklist-based interview on medication-related problems. Assisted by a computerised decision support system, the GPs

optimised medication, discussed it with their patients, and adjusted it accordingly. The control group was managed with the usual care. The primary outcome was a modified Medication Appropriateness Index (MAI) assessed in blinded medication reviews and calculated as the difference between the baseline and after 6 months. Intervention had no significant effect on the primary outcome. Another pre–post study in a tertiary Malaysian hospital aiming at investigating the impact of a multifaceted intervention with a smartphone app on physicians' and clinical pharmacists' behaviour (Akkawi et al., 2020) did not significantly affect the prevalence of potentially inappropriate medication among hospitalized older adults. A systematic review that aimed to determine which interventions, alone or in combination, would be effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people found no clear evidence of a clinically significant improvement for any specific type of intervention (Rankin et al., 2018).

The difficulty in demonstrating the effectiveness of interventions in pragmatic studies is partly due to the design itself. Indeed, in this type of trial, it is not possible to control the real application of the intervention as it would happen in a controlled explanatory study. In the EDU.RE.DRUG project, while potentially involving all the GPs and/or patients, no obligation to read and use the materials of the interventions was imposed. Therefore, it was not possible to force the active participation to the proposed activities (reports and CME course), nor the translation in a behavioural change. It was not even possible to check whether the GPs had read and/or taken into consideration the reports. Thus, the results of the project accounted also for the poor participation rate of the GPs involved.

Another possible explanation of our results can be found in the time windows used. If the intervention had an immediate effect, even minimal, possibly not maintained later on, it would have been evaluated immediately after its delivery. Unfortunately, we cannot know when (and if) the GP read the report or when he attended the CME course (made available for several months, in order to allow wider access). Therefore, the measurement of outcomes over a 1-year post-intervention period (for comparison with 1-year pre-intervention period) may have diluted the results. It could be useful to repeat the intervention, perhaps after 6 months to keep the GP's attention on these issues.

Moreover, in the present study, the topics involved were many and wide-ranging, though all related to the problem of prescribing inappropriateness. We can argue that, behind the difficulty in modifying a consolidated and routine exercise, such as the prescription practice, this probably mitigates the strength of the intervention on several fronts, "confusing" and overloading the GP with respect to the inappropriateness to be changed and improved and the targets to be achieved.

4.1 Strengths and Limitations

We conducted a pragmatic trial, which may have limited the effect of the intervention, as the GPs were not obliged to consider the proposed material and to change their practice. Nevertheless, the study design has the enormous advantage of being very close to real clinical practice and is essential to improve prescription appropriateness in a real-life context.

In our study, we used secondary data, as they are routinely gathered at the individual level for administrative purposes and as a part of the healthcare system in Italy. The use of the existing data represents a powerful and relatively low-cost research tool; however, drugs traced in these databases are limited to those that are reimbursed by the Italian NHS (class A drugs), probably leading to an underestimation of PIP prevalence. In addition, these administrative databases do not contain information on the patient clinical history (together with other lifestyle and sociodemographic factors that could drive the choice of drug prescriptions), GP instructions, dose and times of administration, or indication for treatment. Therefore, the rationale for prescribing or starting medications is not known and patients might be wrongfully classified as being prescribed an inappropriate drug. Despite these limitations, large population administrative databases would have several advantages, such as the detection of different patterns of prescribing in the real world setting and the analysis of the complexity of drug prescriptions. They are a great source of information on drug utilization and GPs' behaviours in routine clinical practice.

4.2 Implications for Practice

The evidence obtained from this project certainly has a relevant clinical value and can inform decision-making strategies and future research insights.

Prescription inappropriateness is a relevant problem in our territory, with greater burden in elderly population. Although there was no significant improvement overall, this study allowed to identify which are the most critical areas where strategies can be implemented to support the improvement of medication appropriateness. In the national context, the difference between regions is also an important alarm bell, in the perspective of making access and management homogeneous. These results can be a starting point for further studies focusing only on specific situations.

Medical practice is difficult to change and more effective strategies must be found. Evidence has shown that the acceptance of recommendations by GPs plays a critical role in the achievement of results, but there is no consensus on which is the best strategy. Future studies should ensure greater methodological rigor in the evaluation of interventions to reduce the prevalence of inappropriate prescriptions. Further evaluations are required to investigate the effectiveness of other types of individual and combined interventions. Qualitative studies involving health professionals and patients can provide important information about barriers for the implementation or acceptance of an intervention. As already discussed, it would be interesting to evaluate the effects of more focused and repeated interventions over time. We can also note that the tools implemented (reports and CME course) are routinely used by the LHUs for educational/training purposes and to

direct the prescribing practice. It is therefore possible that, also given the nonmandatory nature of the intervention, these resources have been scarcely taken into consideration by doctors already highly exposed to these kinds of inputs. This may also suggest a general lack of effectiveness of these strategies usually used by local health authorities. It would therefore be advisable to find different intervention strategies, which can further stimulate the prescribers.

5 CONCLUSION

In our multifactorial pragmatic and controlled trial, we did not appreciate a decrease in potentially inappropriate prescriptions after 1-year follow-up. Implementing prescription practice with audit and feedback approaches was found to be poorly effective, overall, in primary care (Soleymani et al., 2019; Kroon et al., 2021). Nevertheless, our study allowed to identify factors associated with inappropriate prescribing, informing healthcare administrators and policy makers to better design corrective interventions.

Considering the limitations unveiled by our study, other strategies and management models should be designed, applied, and tested in order to lead to a relevant improvement in the overall prescribing qualities in the adult population.

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DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: raw data were generated at the local health units. Derived data supporting the findings of this study are available from the corresponding author (MC) on request. Requests to access these data sets should be directed to Manuela Casula, manuela.casula@unimi.it.

ETHICS STATEMENT

The protocol has been registered in ClinicalTrials.gov (identifier NCT04030468) and in EU Clinical Trials Register (identifier: EudraCT 2017-002622-21).

AUTHOR CONTRIBUTIONS

MC, EM, and ET conceived and designed the study and prepared the study protocol. EM and ET are responsible for study management and supervision. EO, MF, and IM provided methodological and statistical knowledge. ET and FG are responsible for study conduction and monitoring. MC and EO prepared the manuscript. AC, the Principal Investigator of the study, made the final review of the manuscript.

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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.2022.832169/full#supplementary-material

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Aging and the Prevalence of Polypharmacy and Hyper-Polypharmacy Among Older Adults in South Korea: A National Retrospective Study During 2010–2019

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Cho HJ, Chae J, Yoon S-H and Kim D-S (2022) Aging and the Prevalence of Polypharmacy and Hyper-Polypharmacy Among Older Adults in South Korea: A National Retrospective Study During 2010–2019. Front. Pharmacol. 13:866318. doi: 10.3389/fphar.2022.866318

Background: Polypharmacy has become a global health problem and is associated with adverse health outcomes in the elderly. This study evaluated the prevalence of polypharmacy and hyper-polypharmacy in elderly patients in South Korea during 2010–2019.

Methods: We analyzed the outpatient care of persons aged ≥65 years covered by National Health Insurance (NHI) using NHI claims data from 2010 to 2019. Polypharmacy was defined as the use of ≥5 medications, and hyper-polypharmacy was defined as the use of ≥10 medications, and we examined them over periods of ≥90 days and ≥180 days. The average annual percent change (AAPC) was calculated using Joinpoint statistical software.

Results: The prevalence of polypharmacy among ≥90 days of medication use elderly decreased from 42.5% in 2010 to 41.8% in 2019, and the prevalence of hyper-polypharmacy for ≥90 days increased from 10.4% to 14.4%. The prevalence of polypharmacy for ≥180 days increased from 37.8% in 2010 to 38.1% in 2019, and the prevalence of hyper-polypharmacy for ≥180 days increased from 6.4% to 9.4%. The prevalence of polypharmacy for ≥90 days and ≥180 days steadily increased among elderly patients, with AAPCs of 3.7 and 4.5, respectively.

Conclusion: The prevalence of polypharmacy for ≥90 days and ≥180 days remained stably high, with rates of about 42 and 38%, respectively, and hyper-polypharmacy increased over the past 10 years in South Korea. Therefore, strategies to address polypharmacy need to be implemented. Further research is also required to identify the clinical outcomes (including mortality risks) associated with polypharmacy.

Keywords: polypharmacy, hyper-polypharmacy, elder patients, outpatient care, aging

INTRODUCTION

South Korea is the most rapidly aging country of the Organization for Economic Co-operation and Development (OECD) (OECD, 2021). As of 2020, 15.7% of the population consists of seniors aged 65 years or older, and the proportion is expected to increase to 43.9% by 2060 (Statistics Korea, 2020). Compared to other age groups, older adults more often have multimorbidity and more frequently use medical services (Barnett et al., 2012). Thus, they are more likely to routinely visit multiple medical institutions simultaneously and are thus more vulnerable to drug-related problems such as polypharmacy, the use of inappropriate medications, and adverse drug reactions (Barnett et al., 2012).

Polypharmacy refers to the concurrent use of multiple medications. Despite the lack of a clear universal definition, polypharmacy is often defined as the routine use of 5 or more medications according to the World Health Organization (WHO, 2019). A recent systematic review on definitions of polypharmacy showed that 46.4% of studies used a numerical definition, such as 5 or more medications or 10 or more medications (Masnoon et al., 2017). However, this is a relatively simple definition of polypharmacy, and using only the number of medications could make it difficult to evaluate appropriate polypharmacy (rational prescribing of multiple drugs based on the best available evidence and considering the individual patient context) (Masnoon et al., 2017). Other studies have defined polypharmacy as the prescription of at least 1 medication that is clinically inappropriate or offers no additional benefit (Colley and Lucas, 1993; Carlson, 1996; Chumney and Robinson, 2006). In that sense, it is also necessary to consider the possibility of drug overdoses, prescriptions for drugs that are not necessary, and the duration of mediation use (Colley and Lucas 1993; Carlson 1996; Chumney and Robinson 2006). Several systematic reviews reported that the adverse health outcomes of polypharmacy in older people include a decrease in patient compliance and an increased likelihood of drug-drug interactions and adverse drug reactions, which thereby increase the risk of hospitalization, additional medical expenses and death (Fried et al., 2014; O'Dwyer et al., 2016; Leelakanok et al., 2017; Ming and Zecevic, 2018; Al-Musawe et al., 2019; Katsimpris et al., 2019; Leelakanok and D'Cunha, 2019; Palmer et al., 2019; Davies et al., 2020).

Previous studies in various countries have shown that the prevalence of polypharmacy varied according to the healthcare service setting and definition. The prevalence of excessive polypharmacy or hyper-polypharmacy (10 or more medications) among the elderly was 5.8% in Scotland (Guthrie et al., 2015), 5.4% in Taiwan (Wang et al., 2018), 5.1% in Sweden (Zhang et al.,. 2020), and 1.3% in New Zealand (Nishtala and Salahudeen, 2015). According to previous literature, the prevalence of patients who had been simultaneously prescribed 5 or more medications ranged from 26 to 44% (Khezrian et al., 2020). The prevalence of polypharmacy (5 or more medications) among the elderly was 20.8% in Scotland (Guthrie et al., 2015), 19.1% for chronic polypharmacy within consecutive 6 months in Poland (Kardas et al., 2021), 41.2% in Switzerland (Blozik et al., 2018), 36.8% in the United States (Young et al., 2021), 28.7% in Japan (Mabuchi et al., 2020), and 19% in Sweden (Zhang et al., 2020).

In studies that reviewed the status of polypharmacy among seniors in South Korea, Kim et al., 2014 and Nam et al., 2016 reported that 86.4 and 65.2% of seniors had been prescribed 6 or more simultaneous drugs at least once in a single year (Kim et al., 2014; Nam et al., 2016), and Park et al., 2016 and Chang et al., 2020 reported that 44.1 and 46.6% of South Koreans aged 65 years or over were prescribed 5 or more medications (Park et al., 2016; Chang et al., 2020).

However, no studies have analyzed trends in polypharmacy by year across the entire population. Therefore, we aimed to analyze yearly trends in polypharmacy from 2010 to 2019 for the entire elderly population of South Korea. Furthermore, we distinguished between polypharmacy and hyper-polypharmacy for the analysis, based on both the number of medications taken and the duration of use.

METHODS

Data Source

We conducted a retrospective cohort study of the elderly population using the National Health Insurance (NHI) data.

The NHI data was the details for claims from medical institutions and then the Health Insurance Review & Assessment Service (HIRA) reviews these for payment. In Korea, the NHI covers 97% of the Korean population, and the claims data include patients' demographic characteristics, as well as the diagnosis codes of diseases, the international non-proprietary names of drugs, the prescribed doses per day, and the days of therapies.

In the analysis, we used outpatient prescriptions from January 2010 to December 2019 from medical institutions including tertiary hospitals, secondary hospitals, general hospitals, nursing homes, clinics, and public health centers. In the case of people who had been admitted to hospitals, we included their outpatient prescriptions. The proportion of subject elderly patients was 95% of the total elderly population (total elderly population was 5,429,802 in 2010 and 8,018,762 in 2019).

Patient Population and Definition of Polypharmacy

The study population included all individuals aged 65 years or older, and all outpatient medical encounters of this population were used in the analysis. This study analyzed orally administered drugs that had been listed in the national health insurance benefits scheme between 1 January 2010, and 31 December 2019.

The outcome measures of this study were the number of patients with polypharmacy patients and the number of patients with hyper-polypharmacy patients according to their use of medication for ≥90 days and ≥180 days from 2010 to 2019. We differentiated between polypharmacy (being prescribed ≥5 or more drugs) and hyper-polypharmacy (being prescribed ≥10 drugs).

TABLE 1 | General characteristics of elderly patients with outpatient prescriptions.

Year	2010		2011	2012	2013	2014	2015	2016	2017	2018	2019		Annual Increase Rate (%)
No. of patients	5,201,276		5,411,592	5,713,734	5,974,108	6,235,700	6,474,327	6,693,802	7,046,476	7,357,078	7,722,213		5.39
Sex													
Male	2,099,908	(40.4)	2,201,909	2,345,343	2,473,240	2,599,708	2,717,929	2,825,863	2,997,317	3,148,275	3,326,394	(43.1)	6.49
Female	3,101,368	(59.6)	3,209,683	3,368,391	3,500,868	3,635,992	3,756,398	3,867,939	4,049,159	4,208,803	4,395,819	(56.9)	4.64
Age													
65–69 years	1,800,317	(34.6)	1,789,202	1,799,905	1,882,353	1,972,321	2,079,577	2,132,322	2,239,501	2,306,639	2,440,720	(31.6)	3.95
70–74 years	1,498,662	(28.8)	1,570,977	1,707,598	1,735,553	1,734,561	1,722,208	1,715,513	1,727,090	1,814,482	1,904,724	(24.7)	3.01
75–79 years	1,008,529	(19.4)	1,090,106	1,160,533	1,232,649	1,306,653	1,344,631	1,413,640	1,537,649	1,573,012	1,578,401	(20.4)	6.28
80–84 years	553,756	(10.6)	593,460	642,702	685,867	743,492	811,064	878,909	937,345	1,003,923	1,072,901	(13.9)	10.42
≥85 years	340,012	(6.5)	367,847	402,996	437,686	478,673	516,847	553,418	604,891	659,022	725,467	(9.4)	12.60
Mean ± SD	73.3 ± 6.4		73.5 ± 6.4	73.6 ± 6.5	73.7 ± 6.6	73.8 ± 6.7	73.9 ± 6.7	74.1 ± 6.8	74.1 ± 6.9	74.2 ± 7.0	74.2 ± 7.1		
Disease													
Hypertension	2,581,068	(49.6)	2,698,944	2,871,014	3,020,143	3,127,229	3,251,965	3,377,110	3,520,861	3,690,716	3,880,467	(50.3)	5.59
Cardio-cerebrovascular diseases	708,464	(13.6)	738,118	769,820	794,857	808,563	824,746	842,376	865,736	908,699	965,318	(12.5)	4.03
Hyperlipidemia	861,160	(16.6)	1,005,204	1,143,690	1,286,479	1,455,729	1,623,152	1,839,357	2,019,675	2,223,874	2,464,689	(31.9)	20.69
Diabetes mellitus	1,101,025	(21.2)	1,199,610	1,296,502	1,390,443	1,471,894	1,555,136	1,646,875	1,757,277	1,873,910	2,011,237	(26.0)	9.19
Gastric ulcer/gastroesophageal reflux disease	900,849	(17.3)	921,419	972,808	955,284	938,610	926,121	924,474	919,140	926,743	901,305	(11.7)	0.01
Chronic renal failure	53,226	(1.0)	66,545	81,899	93,443	101,129	113,049	129,431	144,899	165,262	187,896	(2.4)	28.11
Liver disease	404,017	(7.8)	429,352	467,627	500,677	511,073	542,900	585,088	622,770	706,072	804,115	(10.4)	11.00
Respiratory disease	772,877	(14.9)	813,996	924,936	904,180	939,409	957,361	944,269	934,592	1,000,483	978,788	(12.7)	2.96
Cancer	3,387,661	(7.5)	366,883	407,504	446,303	480,045	515,727	555,593	599,626	652,336	705,116	(9.1)	9.10
Musculoskeletal disease	2,078,698	(40.0)	2,194,343	2,329,917	2,442,143	2,550,716	2,652,127	2,771,548	2,904,274	3,054,021	3,251,092	(42.1)	6.27
Dementia	262,711	(5.1)	312,570	370,475	429,201	482,337	542,291	622,885	721,893	833,164	946,865	(12.3)	28.94
Fracture	361,346	(6.9)	362,549	401,783	447,012	450,389	471,148	488,964	528,840	568,701	600,456	(7.8)	7.35
Healthcare utilization													
Healthcare spending (billion USD)	3.2		3.5	3.8	4.2	4.6	4.9	5.4	6.0	6.9	7.9		16.33
Prescription spending (billion USD)	2.9		3.1	3.1	3.2	3.4	3.7	4.1	4.5	4.9	5.5		9.73
Number of visits (day)	28.4		28.9	31.0	31.0	30.9	30.3	30.4	30.0	30.1	30.3		0.74
Number of medications per day, Mean ± SD (Median)	4.7 ± 2.4 (4.2)		4.6 ± 2.4 (4.1)	4.7 ± 2.5 (4.1)	4.7 ± 2.6 (4.1)	4.7 ± 2.6 (4.2)	4.7 ± 2.6 (4.2)	4.8 ± 2.7 (4.2)	4.8 ± 2.7 (4.2)	4.9 ± 2.8 (4.3)	4.9 ± 2.9 (4.3)		0.47
Spending per patient (USD)	618.3		645.8	671.7	700	733.3	753.3	800.8	850	936.7	1,029.2		7.38
Prescription spending per patient (USD)	561.7		579.2	535.0	535.8	549.2	565.8	612.5	635	672.5	710		2.93

SD: standard deviation.

The number of active substances prescribed each day was determined for each patient unit over a period of 365 days. We calculated the number of medications with the same active substances regardless of dose or formulation, such as a tablet or sustained-release tablet. We classified a patient as experiencing continuous polypharmacy or hyper-polypharmacy if the total number of days of the patient's multiple drug use (5 or more, 10 or more) was accumulative 90 or 180 in the same year. Thus, if a patient used 6 drugs for 50 days cumulatively in year t and 6 drugs for 95 days in year t+1, he or she would be classified into the non-polypharmacy group in year t and the continuous polypharmacy group in year t+1. In addition, if the treatment started in October and the prescription continued until March of the following year, the 3-months prescription in year t and the 3-months prescription in t+1 would be attributed to each separate year.

Statistical Analysis

A descriptive statistical analysis was performed. Differences in polypharmacy and hyper-polypharmacy across sex, age groups, and chronic diseases were examined between 2010 and 2019. In addition, to examine changes in the prevalence of polypharmacy and hyper-polypharmacy by year, Joinpoint regression analysis was performed. We calculated the annual percent change (APC) and average annual percent change (AAPC) using the proportion of people with polypharmacy to assess the temporal trends of polypharmacy and hyper-polypharmacy. The APC is a way to characterize trends in prevalence over time. To estimate the APC for a series of data, regression in a logarithmic scale model is used. The joinpoint model uses statistical criteria to determine when and how often the APC changes. Finding the joinpoint model that best fits the data allows us to determine how long the APC remained constant, and when it changed. The AAPC is a summary measure over a fixed pre-specified interval that makes it possible to use a single number to describe the average APCs over a period of multiple years (NIH).

The annual percent change (APC) was obtained for each trend line using the Joinpoint program developed by the National Cancer Institute of the United States, and the average APC (AAPC) value was obtained to assess the trend by year (Clegg et al., 2009). A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

General Characteristics of Elderly Patients by Year

As shown in **Table 1**, from 2010 to 2019, the number of patients aged 65 years or older increased from 5.2 million in 2010 to 7.7 million in 2019. The proportion of patients aged 65–69 years was the highest, with 31.6% (2.4 million) in 2019, and the population aged 85 years or older more than doubled from 0.3 million in 2010 to 0.7 million in 2019, showing the largest increase. There were more women than men, and the number of patients aged 85 years or older gradually increased, reflecting the aging of South Korea's population. Although the proportion of women among the elderly was higher (56.9% in

TABLE 2 | The trend of the prevalence of polypharmacy and hyper-polypharmacy among the elderly patients prescribed ≥90 and ≥180 days in 2010–2019 period.

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC (95% CI)
Patients aged ≥65 years	5,201,276	5,411,592	5,713,734	5,974,108	6,235,700	6,474,327	6,693,802	7,046,476	7,357,078	7,722,213	3.6 (3.4, 3.8)
Elderly prescribed ≥90 days											
Patients aged ≥65 years prescribed ≥90 days	3,866,631	4,129,037	4,461,220	4,746,381	4,996,503	5,224,343	5,487,779	5,847,509	6,171,951	6,570,508	
Polypharmacy (%)	1,645,208 (42.5)	1,753,525 (42.5)	1,886,321 (42.3)	1,999,604 (42.1)	2,097,061 (42.0)	2,181,402 (41.8)	2,296,197 (41.8)	2,436,875 (41.7)	2,584,820 (41.9)	2,748,452 (41.8)	−0.2 (−0.3, −0.1)
Hyper-polypharmacy (%)	403,249 (10.4)	435,327 (10.5)	491,481 (11.0)	547,690 (11.5)	589,920 (11.8)	629,325 (12.0)	689,583 (12.6)	763,321 (13.1)	846,462 (13.7)	944,458 (14.4)	3.7 (3.2, 4.2)
Elderly prescribed ≥180 days											
Patients aged ≥65 years prescribed ≥180 days	3,322,548	3,584,969	3,924,215	4,216,244	4,459,449	4,676,878	4,947,263	5,305,607	5,630,649	6,031,756	
Polypharmacy (%)	1,256,349 (37.8)	1,353,377 (37.8)	1,475,772 (37.6)	1,587,584 (37.7)	1,671,917 (37.5)	1,749,234 (37.4)	1,863,607 (37.7)	1,997,042 (37.6)	2,135,168 (37.9)	2,296,323 (38.1)	0.1 (−0.0, 0.2)
Hyper-polypharmacy (%)	212,106 (6.4)	230,202 (6.4)	267,883 (6.8)	305,300 (7.2)	331,840 (7.4)	357,176 (7.6)	396,994 (8.0)	445,685 (8.4)	501,117 (8.9)	567,651 (9.4)	4.5 (4.1, 4.9)

AAPC: average annual percent change, CI, confidence interval.

2019), the annual increase rate was 6.49% for men, which was higher than that of 4.64% for women.

The number of patients with hypertension was the highest (3.8 million in 2019), followed by musculoskeletal diseases (3.2 million in 2019). The proportion of patients with dementia showed the largest increase from 5.1% in 2010 to 12.3% in 2019, and the annual rate of increase was the highest (28.94%), followed by chronic renal failure, the prevalence of which increased from 1.0% in 2010 to 2.4% in 2019, with an annual increase rate of 28.11%, and hyperlipidemia (the prevalence of which increased significantly from 16.6% in 2010 to 31.9% in 2019, with an annual increase rate of 20.69%). Meanwhile, the percentage of patients with gastric ulcers/gastroesophageal reflux disease decreased from 17.3 to 11.7%.

An overall increasing trend was found in the number of outpatient care visits, outpatient care spending, prescription days, and prescription spending of patients aged 65 years or older. The number of outpatient visits increased from 28.4 days in 2010 to 31 days in 2013 and then slightly decreased. The outpatient care spending per patient steadily increased, while the number of prescription medications per day declined in 2011 and increased slightly from 4.7 in 2010 to 4.9 in 2019. The outpatient care spending per patient increased during 2010–2019, whereas the prescription spending per patient decreased between 2012 and 2014 and thereafter increased.

Annual Prevalence of Polypharmacy in Elderly Patients

As shown in **Table 2**, the prevalence was approximately 41.8% for ≥90-days polypharmacy and approximately 14.4% for ≥90-days hyper-polypharmacy in 2019. The prevalence was approximately 38.1% for ≥180-days polypharmacy and approximately 9.4% for ≥180-days hyper-polypharmacy.

Figure 1 shows the AAPCs in the trends of the prevalence of polypharmacy and hyper-polypharmacy. Among the elderly with prescriptions for over 90 days, there was a significantly decreasing trend in polypharmacy from 2010 to 2015. But there were no notable changes after 2015, and the AAPC for 2010 to 2019 was −0.2, indicating a decreasing trend in polypharmacy. Meanwhile, the rate of hyper-polypharmacy continued to increase, with an AAPC of 3.7. Specifically, the rate of hyper-polypharmacy

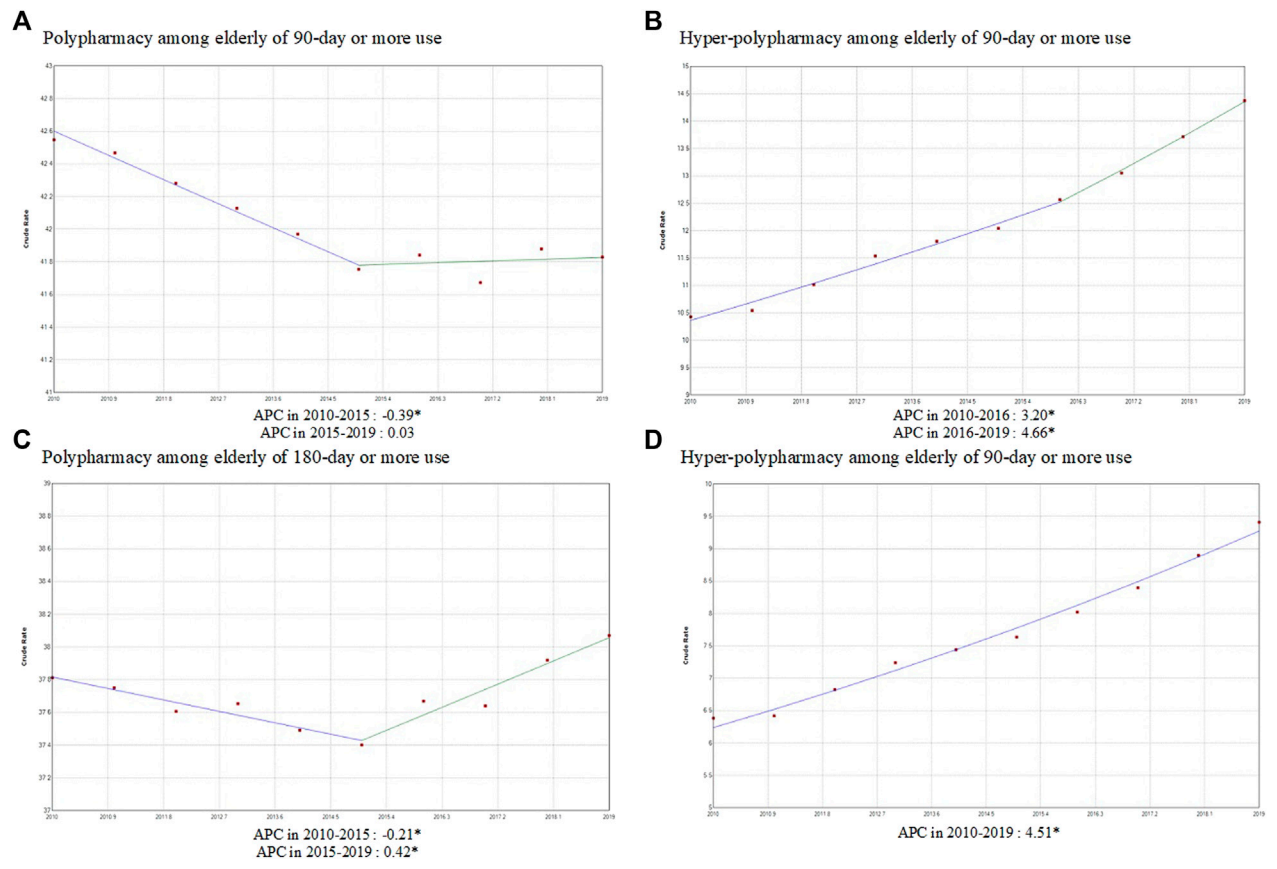

FIGURE 1 | The trend of the prevalence of polypharmacy and hyper-polypharmacy among the elderly prescribed ≥90 days and ≥180 days from 2010 to 2019. APC: Annual percent change, CI, confidence interval.

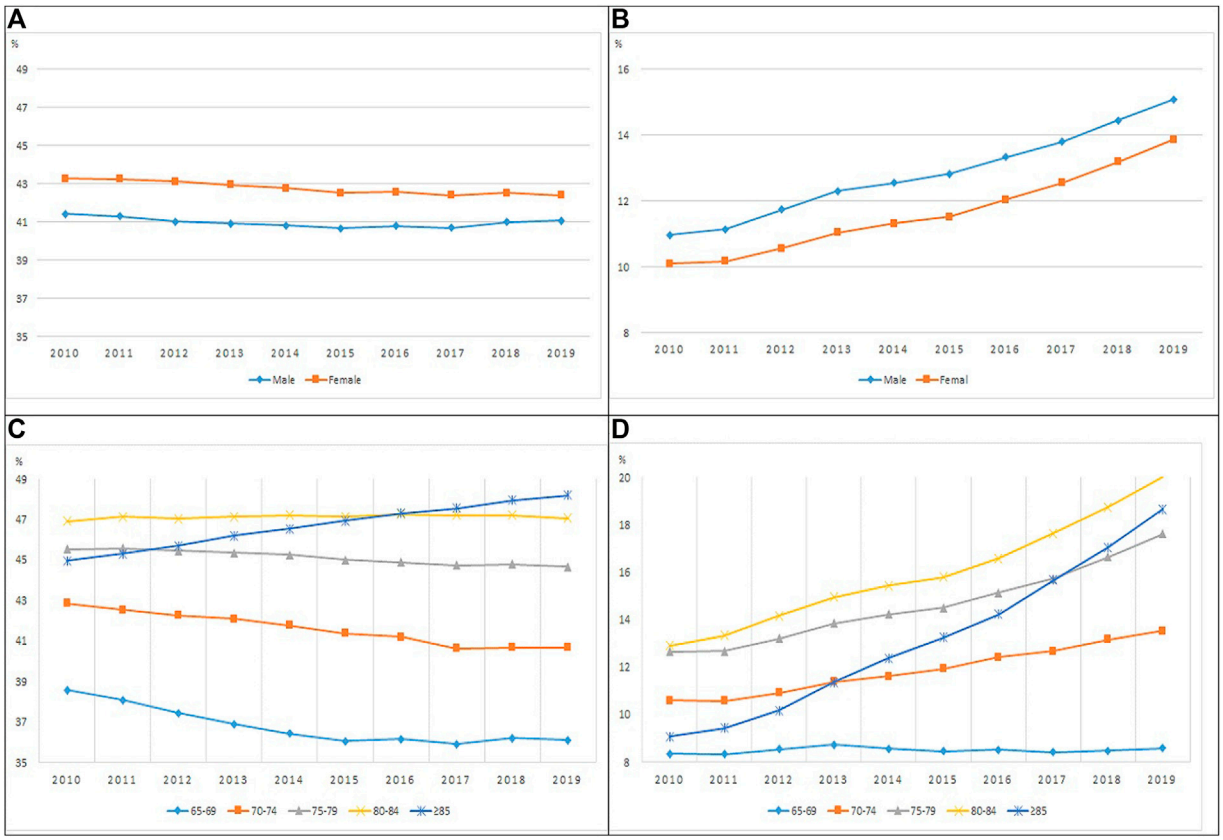

FIGURE 2 | The proportion of polypharmacy and hyper-polypharmacy among ≥90 days use elderly by sex and age group **(A, C)** Polypharmacy, **(B, D)** Hyper-polypharmacy).

increased more rapidly from 2016 to 2019 than it did from 2010 to 2016.

In case of the 180-days polypharmacy, there was a significantly decreasing trend in polypharmacy from 2010 to 2015, but there was an increasing trend after 2015. The AAPC for 2010 to 2019 was 0.1, but it was not significant given the large change in the trend. In contrast, hyper-polypharmacy continued to increase, with an AAPC of 4.5.

The Prevalence of Polypharmacy by Subgroup

Figures 2, **3** show the proportions of polypharmacy and hyper-polypharmacy for ≥90 days and ≥180 days among older adults with medication use. Polypharmacy for ≥90 days decreased among both men and women, while ≥180-days polypharmacy slightly increased in men. Both ≥90-days and ≥180-days hyper-polypharmacy increased in men and women. Among the elderly who received prescriptions more than 90 days and for more than 180 days, polypharmacy (use of 5 or more medications) gradually decreased in other age groups, but increased in those aged 80–84 years, and showed a sharp increase in those aged 85 years and older. Hyper-polypharmacy (use of 10 or more medications) decreased among those aged 65–69 years, increased sharply in those aged 70 years and older, and nearly doubled in those aged 85 years and older. In addition, hyper-polypharmacy sharply increased among those aged 85 years or older.

DISCUSSION

To our knowledge, this is the first population-level study conducted in South Korea targeting the entire elderly population that received prescriptions in the outpatient settings to investigate the 10-years trend of polypharmacy and hyper-polypharmacy among the elderly. Notably, in our study, we considered the number of medications prescribed and the duration for which the medications were taken when defining polypharmacy.

In our study, the prevalence of polypharmacy and hyper-polypharmacy in the elderly was 41.8 and 14.4%, respectively, for ≥90 days, and 38.1 and 9.4%, respectively, for ≥180 days. These results for polypharmacy are similar or higher to those of previous studies, which found that 26–44% of the elderly patients had taken 5 or more medications (Payne et al., 2014; Guthrie et al., 2015; Page et al., 2019; Khezrian et al.. 2020; Mabuchi et al., 2020; Zhang et al.,

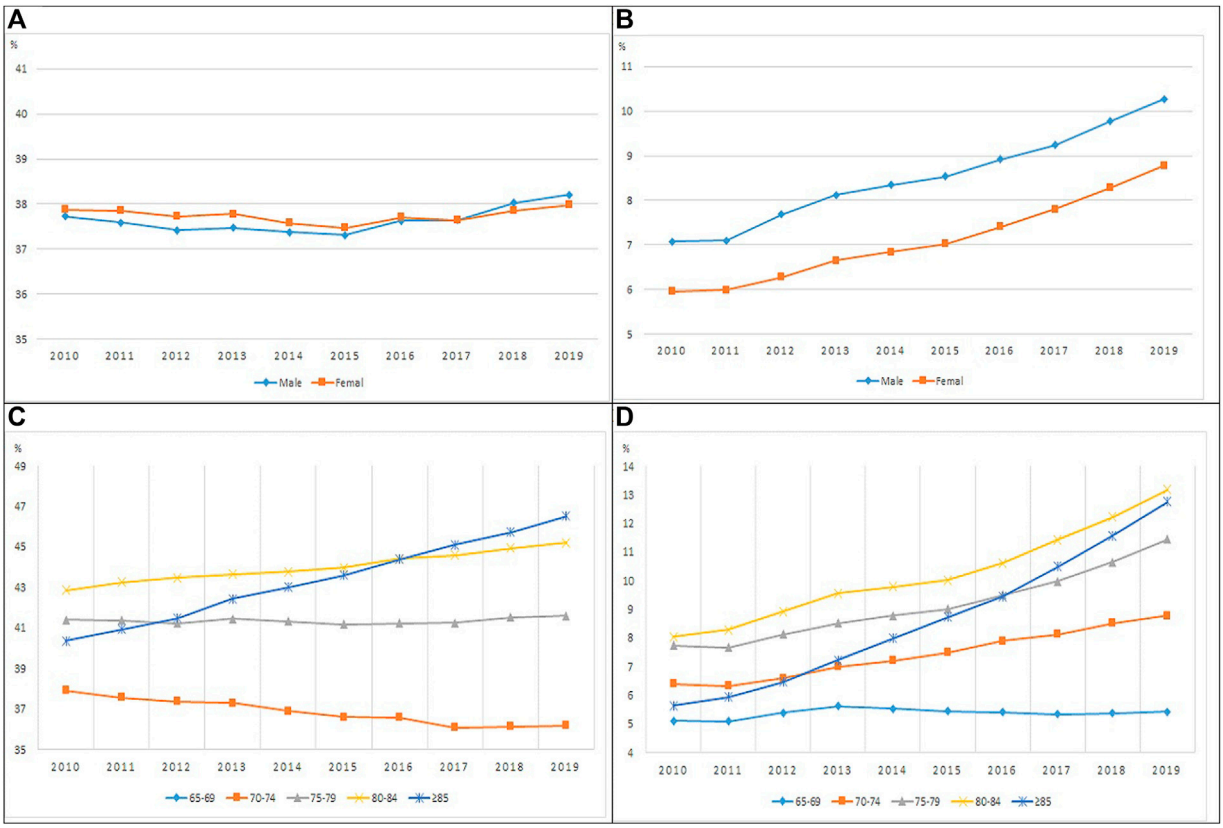

FIGURE 3 | The proportion of polypharmacy and hyper-polypharmacy among ≥180 days use elderly by sex and age group **(A, C)**: Polypharmacy, **(B, D)**: Hyper-polypharmacy).

2020; Kardas et al., 2021; Kardas et al., 2021; Young et al., 2021) and the polypharmacy prevalence in community-dwelling older adults ranged from 7 to 45% (Hsu et al., 2021). The prevalence of hyper-polypharmacy was higher than those reported by other studies (Guthrie et al., 2015; Nishtala and Salahudeen. 2015; Wang et al., 2018; Zhang et al., 2020). However, previous studies conducted in South Korea reported a wide range (44.1–86.4%) of the proportion of individuals aged 65 years or over who were prescribed 5 or more medications (Kim et al., 2014; Nam et al., 2016; Park et al., 2016; Chang et al., 2020). The difference may be because the current study considered both the days of therapy and the number of medications simultaneously, whereas two other studies defined polypharmacy as being prescribed 6 or more drugs at least once in a single year (Kim et al., 2014; Nam et al., 2016).

Second, among the elderly who received prescriptions for more than 90 or 180 days, polypharmacy and hyper-polypharmacy showed a sharp increase in those aged 85 years and older. Due to population aging, the use of multiple drugs in those aged 85 years or older is showing a rapid increase. Polypharmacy fluctuated by year, but hyper-polypharmacy continued to increase. Among the elderly who had prescriptions for more than 180 days, the proportion of men with polypharmacy increased after 2016 compared to women. Since 2016, the NHI benefit scheme has been expanded for four diseases (cardiovascular and cerebrovascular diseases, cancer, and rare diseases) and the number of prescription medicines increased because medicines that were previously not covered were included under NHI benefits.

Third, the previous studies reported that age, number of drugs at admission, hypertension, ischemic heart disease, heart failure, and chronic obstructive pulmonary disease were independently associated with polypharmacy (Nobili et al., 2011). In the current study, most chronic diseases increased yearly except gastric ulcer/gastroesophageal reflux disease. Through this study, we present empirical evidence that the increase in life expectancy has led to an increase in the use of multiple drugs. The medication safety is an important factor that must be considered when treating the older population, particularly those vulnerable to polypharmacy (Avery et al., 2012), and integrated patient-centered management should be implemented.

In addition, we found that the number of outpatient visits and the outpatient care spending per patient steadily increased, whereas the prescription spending per patient decreased between 2012 and 2014 and then increased thereafter. The temporary reduction of prescription spending per patient during 2012–2014 occurred due to the drug price regulation

policy implemented from April 2012 to December 2014 which decrease the price of the already listed generic medicines.

To the best of our knowledge, the current study investigated the overall annual changes in polypharmacy and hyper-polypharmacy considering the duration of therapy among the elderly population in South Korea using NHIS claims data. The NHIS reimburses medical institutions on a fee-for-service basis, and the average number of doctor consultations per person was 17.2 visits in 2019, which is the highest rate of medical service usage among all other OECD countries (with an average of 6.6 visits across 33 countries) (OECD 2021).

Also due to the high access to NHI and high healthcare utilization in the Korean medical settings, even mild diseases such as the common cold are treated at medical institutions in South Korea, therefore it is a strength that most drugs prescribed to patients were likely included in the analysis. Furthermore, in this study, all injuries and diseases claimed per patient visit were collected for each patient to identify the presence or absence of injuries and diseases in the subjects. Since all major and minor injuries and diseases experienced by patients over a period of 1 year were included, it can be assumed that all chronic diseases experienced by patients were included. In addition, we attempted to analyze polypharmacy using multiple criteria by conducting a subgroup analysis according to the duration for which medications were taken (≥90 and ≥180 days), and the average number of medications patients took on a daily basis (5 or more and 10 or more medications) during a 1-year period.

Nevertheless, this study has the following limitations. First, since only outpatient injuries and diseases and outpatient prescription records were analyzed, longer-term hospitalization were not included in the analysis. Therefore, the prevalence of polypharmacy was calculated by summing the number of outpatient prescription drugs, excluding drugs administered in an inpatient setting. Since the current study only included the number of outpatient prescriptions, including the number of drugs received during hospitalization would cause the number of drugs actually taken to increase. Second, the analysis was based only on claims data; therefore, we cannot rule out the possibility that some patients did not take the medications prescribed to them. This is likely due to the unique fee-for-service system of South Korea, in which each medication is prescribed by a separate doctor, thereby resulting in frequent overlap in prescriptions for gastrointestinal protective agents and anti-inflammatory drugs. Third, in the current study, polypharmacy was defined based on a numerical definition. Although polypharmacy can be appropriate, the fact that we could not distinguish between appropriate and inappropriate polypharmacy is a limitation of this study. Lastly, since injections are used for a short time and the dose of topical treatments is not high, this study was limited to oral drugs, as in previous studies (Fincke et al., 2005; Chang et al., 2020). Moreover, polypharmacy represents a less-than-desirable state with duplicative medications, drug-to-drug interactions, and inadequate attention to pharmacokinetic and pharmacodynamic principles (Monane, Monane et al., 1997). Thus, complications due to polypharmacy include increased adverse drug reactions and noncompliance (Colley and Lucas 1993).

In conclusion, we investigated annual changes in polypharmacy and hyper-polypharmacy over a period of 10 years using population-level health insurance claims data. As demonstrated in our study, the magnitude of hyper-polypharmacy continued to increase over time, while the prevalence of polypharmacy maintained high rates of about 40%; therefore, it is necessary to establish policy strategies to address polypharmacy. Further studies are also required to identify the clinical outcomes (including mortality risks) associated with polypharmacy.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Data are not accessed because only those with restrictions can perform the analysis in our institution. Requests to access the datasets should be directed to https://opendata.hira.or.kr/home.do.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of HIRA. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HC: Data management, analysis, and writing a draft paper. JC: Data management and analysis. S-HY: Revising the draft. D-SK: Design of study, writing, and revising the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.866318/full#supplementary-material

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How Sensitive is Sensitivity Analysis?: Evaluation of Pharmacoeconomic Submissions in Korea

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Purpose: We aimed to describe the types of uncertainties examined in the economic evaluations submitted for reimbursement in Korea and their impact on the incremental cost-effectiveness ratio (ICER).

Method: Fifty dossiers were submitted by pharmaceutical companies to the economic subcommittee of the Pharmaceutical Benefit Coverage Advisory Committee (PBCAC) from January 2014 to December 2018. The types of uncertainties were categorized as structural and parametric, and the frequencies of the sensitivity analysis per variables were analyzed. The impact of uncertainties was measured by the percent variance of the ICER relative to that of the base case analysis.

Results: Of the 50 submissions, varying discount rate (44 submissions), followed by time horizon (38 submissions) and model assumptions (29 submissions), were most frequently used to examine structural uncertainty, while utility (42 submissions), resource use (41 submissions), and relative effectiveness (26 submissions) were used to examine parametric uncertainty. A total of 1,236 scenarios (a scenario corresponds to a case where a single variable is varied by a single range) were presented in the one-way sensitivity analyses, where parametric and structural sensitivity analyses comprised 679 and 557 scenarios, respectively. Varying drug prices had the highest impact on ICER (median variance 19.9%), followed by discount rate (12.2%), model assumptions (11.9%), extrapolation (11.8%), and time horizon (10.0%).

Conclusions: Variables related to long-term assumptions, such as model assumptions, time horizon, extrapolation, and discounting rate, were related to a high level of uncertainty. Caution should be exercised when using immature data.

Keywords: economic evaluation, uncertainty, structural uncertainty, parametric uncertainty, sensitivity analysis, incremental cost effectiveness ratio

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INTRODUCTION

Model-based analysis synthesizes clinical, economical, and epidemiological evidence from various sources and extrapolates the expected value over the long term (Briggs et al., 2012). Since the evidence directly related to the research question is frequently missing, or multiple sources are available with conflicting results, model-based analysis almost always suffers from various forms of uncertainties (Bilcke et al., 2011).

Uncertainties can be classified as stochastic uncertainty (first-order), parametric uncertainty (second-order), structural uncertainty, and heterogeneity (Briggs et al., 2012). Stochastic uncertainty implies random variability and is intrinsically unavoidable, whereas parametric uncertainties imply the uncertainties in parameter estimation and can be examined via deterministic sensitivity analysis (DSA), where parameter values are varied based on defensible ranges of values to examine the robustness of the results, or via probabilistic sensitivity analysis (PSA), where parameter values are sampled from a predefined distribution and vary simultaneously (Doubilet et al., 1985). Structural uncertainty, which is inherent in the assumptions of the decision model, is a difficult type of uncertainty to define and can be examined by scenario analysis. Heterogeneity deals with the variability of patients of interest and is usually explored through a subgroup analysis. Interestingly, recommendations on how to tackle structural uncertainties or heterogeneity are largely vague in many international pharmacoeconomic guidelines, including Korea, while several provide specific details on parametric uncertainties (Ghabri et al., 2018).

Structural uncertainties are associated with a wide variation in the incremental cost-effectiveness ratio (ICER) (Le, 2016), and given that clinical trials usually last shorter than expected in the economic evaluation, extrapolating beyond the time horizon is frequently required, which introduces additional uncertainties (Kearns et al., 2020). When policymakers set priorities among competing demands based on model-based analysis, uncertainties related to the point estimates, how those uncertainties were examined or reported, and variance of the ICERs are deeply considered (Jackson et al., 2011; Bae et al., 2013), few studies have described how sensitivity analyses in the dossiers submitted for the reimbursement decision are handled, including parametric and structural uncertainties, much less the variance of ICER relative to the base case.

Many HTA organizations review DSA as well as PSA due to the advantage of being able to transparently check the effect of uncertainty of each variable on the results (Australian Government: Department of Health, 2016; The Canadian Agency for Drugs, 2017; The National Institute for Health and Care Excellence (NICE), 2013), Yet DSA, especially one-way SA, has a problem of underestimating the overall uncertainty because it examines only the effects of variations that one variable can have while other variables are fixed (Claxton, 2008). In addition, there is a limitation that the nonlinearity of the model is not reflected, and if there is a correlation between variables, it cannot be considered appropriately (Briggs et al., 2012; McCabe et al., 2020; Vreman et al., 2021). Moreover, despite many guidelines stipulated that that "clinically and statistically feasible ranges" are recommended, the ranges of the DSA are often chosen arbitrarily (Vreman et al., 2021).

This study examines how uncertainty is explored in economic evaluations submitted by pharmaceutical companies in Korea, which is a necessary part of the reimbursement decision-making process. Specifically, we examine how variables related to long-term effects are analyzed. Additionally, the impact of uncertain variables on ICER was explored through variation in the ICER.

METHODS

Economic evaluation dossiers submitted by the pharmaceutical industry to the economic subcommittee of the Pharmaceutical Benefit Coverage Advisory Committee from January 2014 to December 2018 were evaluated by two independent reviewers (SB and EB).

Uncertainties were categorized as DSA and PSA, and DSA was further categorized into structural and parametric uncertainties. Stochastic uncertainty, which is intrinsically unavoidable, and heterogeneity, which is known variability, are not included in the analysis. The number of sensitivity analyses per submission is used to identify the frequently tested parameters or structural assumptions. The parametric uncertainties considered in our study are drug prices, resource use (unit cost or resource utilization other than drug), utility weights, relative effectiveness of the intervention (including odds ratio, relative risk, or hazard ratio), baseline risk (natural history of the disease not related to specific treatment), and others (parameters relevant to specific treatment, such as incidence of the adverse event). The plausible range of values used in the sensitivity analysis is categorized as a 95% confidence interval (CI) of a specific parameter (statistically obtained from clinical studies), arbitrarily selected values (± 20%), or sourced from other studies.

The structure of a model varies by disease type, yet we refer to variables that are universally applicable and can be clearly defined, such as time horizon, discount rate [variation from the recommended 5% (Bae et al., 2013)], extrapolation method used (i.e., Weibull vs. lognormal), model assumptions [i.e., treatment duration, duration of the effectiveness, selection of comparator(s)], and patient characteristics (i.e., age, disease severity, weight, or race).

The frequency of the sensitivity analysis in this study is estimated on a submission or scenario basis. When presenting the proportion of submissions with sensitivity analysis for each category of variables, it is analyzed per submission, and the frequency of sensitivity analysis for each variable is analyzed for each scenario. To examine the ranges of the values used and their ICERs relative to the base case, we count scenarios; a single scenario for the sensitivity analysis corresponds to a case where a single parameter is varied by a single plausible range. A paired case (i.e., ± 20%) is also defined as a single scenario.

The variance of the ICER related to the sensitivity analyses is measured in percentage,

$$\frac{\left|ICER_{sensitivity\ analysis} - ICER_{base\ case}\right|}{ICER_{base\ case}} \times \mathbf{100},$$

where paired (±95% CI) values are estimated as follows:

$$\frac{\mathrm{ICER}_{\max} - \mathrm{ICER}_{\min}}{2 \times \mathrm{ICER}_{\text{base case}}} \times 100.$$

TABLE 1 | Basic characteristics of the 50 dossiers submitted to the Economic Sub-Committee for listing at the Korean National Health Insurance.

Variables	Submissions	
	n	%
WHO ATC Code[1]		
A	3	6
B	2	4
C	3	6
D	1	2
H	1	2
J	3	6
L	26	52
M	2	4
N	4	8
R	5	10
Formulation		
Gel	1	2
Tablet	13	26
Capsule	7	14
Injection	24	48
Spray	1	2
Pen	3	6
Inhaler	1	2
Submission Date		
2014	10	20
2015	8	16
2016	8	16
2017	12	24
2018	12	24
Types of Economic evaluation		
CEA[2] only	2	4
CUA[3] only	18	36
CEA & CUA	28	56
CMA[4] only	2	4
Total	50	100

[1]*A, Alimentary tract and metabolism; B, Blood and blood forming organ; C, Cardiovascular system; D, Dermatologicals; H, Systemic hormonal preparations excl. sex hormones and insulins; J, Antiinfectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculo-skeletal system; N, Nervous system; R, Respiratory system; S, Sensory organs*
[2]*CEA, cost-effectiveness analysis.*
[3]*CUA, cost-utility analysis.*
[4]*CMA, cost-minimization analysis.*

TABLE 2 | Types of sensitivity analysis of the 50 dossiers examined.

Variables	Submissions	
	n	%
Sensitivity Analysis		
Deterministic sensitivity analysis	49	98
Probabilistic sensitivity analysis	18	36
No Sensitivity Analysis	1	2
Deterministic sensitivity analysis (*n* = 49)		
Structural Uncertainty		
Discount rate	44	90
Time horizon	38	71
Model assumptions	29	59
Extrapolation	19	39
Patient characteristics	19	39
Parameter Uncertainty		
Utility	42	86
Resource use	41	84
Relative effectiveness	26	53
Drug Price	16	33
Baseline risk	16	33
Other[1]	15	31
Total	49	100
Probabilistic sensitivity analysis (*n* = 18)		
Cost	17	94
Utility	16	89
Relative effectiveness	10	56
Baseline risk	8	44
Other[2]	9	58
Total	18	100

[1]*Parameters relevant with specific treatment, such as the incidence of the adverse event, or hospitalization rate.*
[2]*Probability of discontinued treatment.*

RESULTS

Of the 50 dossiers submitted to the economic subcommittee, 26 (52%) fall under antineoplastic and immunomodulating agents, and 24 (48%) are injection formulations and were submitted evenly across the observation period (**Table 1**). 46 submissions (92%) employed cost-utility analysis, and DSA was conducted in 49, all of which conducted one-way sensitivity analysis (**Table 2**), and only two of them conducted multivariate (2-way) sensitivity analysis (data not shown). Regarding structural uncertainties, the discount rate was the most frequently examined (44 submissions), followed by the time horizon (38 submissions), and model assumptions (29 submissions) (**Table 2**). For parametric uncertainty, utility was most frequently used (42 submissions), followed by resource use (41 submissions), and relative effectiveness (26 submissions) (**Table 2**). PSA was conducted in 18 submissions and cost was most frequently examined (17 submissions), followed by utility (16 submissions) and relative effectiveness (10 submissions).

A total of 1,236 scenarios were presented in the one-way sensitivity analyses, where structural and parametric sensitivity analyses comprised 557 and 679 scenarios, respectively (**Table 3**). The ranges of parametric uncertainties were arbitrarily selected in 48% of them (326 scenarios), followed by alternative sources (256 scenarios, 38%) and 95% CI (97 scenarios, 14%). The 95% CI was more likely to be employed in the relative effectiveness (36%), yet arbitrary values were frequently used in resource use (78%) and drug price (70%).

Regarding structural uncertainties, the discounting rate (202 scenarios) was most frequently examined, followed by time horizon (130 scenarios), model assumptions (i.e., treatment duration, duration of the effectiveness, comparator, adjusting for cross-over design; 94 scenarios), extrapolation (95 scenarios), and patient characteristics (age, disease severity, weight, or race; 36 scenarios).

The relative variance of ICER for each variable is presented in **Figure 1** as box plots, where the distributions of each variable are

TABLE 3 | The ranges of values used in the parametric sensitivity analysis of the 50 dossiers submitted to the Economic Sub-Committee for listing at the Korean National Health Insurance.

	Scenarios (%)			
	95% Confidence interval[1]	Alternative sources[2]	Arbitrary values[3]	Total
Utility	46	108	54	208 (31%)
Resource use	0	45	163	189 (28%)
Relative effectiveness	43	53	23	119 (18%)
Baseline risk	0	32	33	59 (9%)
Drug Price	0	12	28	65 (10%)
Other[4]	8	6	25	39 (6%)
Total	97 (14%)	256 (38%)	326 (48%)	679 (100%)

[1]*95% confidence intervals of the corresponding parameters were estimated from the clinical trials.*
[2]*Values obtained from source(s) other than the base case were used for the sensitivity analysis.*
[3]*Authors explore the ranges of the sensentivity analysis without clinical or statistical rationales, such as ± 10%.*
[4]*Parameters relevant with specific treatment, such as the incidence of the adverse event, or hospitalization rate.*
A single scenarios for the sensitivity analysis corresponds to a case where a single variable is varied by a single plausible range, and a paired case (i.e.,, ± 20%) was defined as a single scenario.

skewed. In general, structural uncertainties showed wider interquartile ranges, compared with parametric uncertainties. The median of the relative variances in terms of percentage indicates that drug price has the highest impact (19.9%), followed by discount rate (12.2%), model assumptions (11.9%), extrapolation (11.8%), and time horizon (10.0%), suggesting that the most frequently examined variables do not always have the highest level of uncertainty. As shown in **Figure 1**, the median value of the percentage change is within 10% for most variables, excluding drug price, discount rate, model assumption, and extrapolation.

DISCUSSION

This study examined how uncertainty was explored in economic evaluations submitted for coverage decision-making in South Korea. The second version of the PE guidelines required that DSA be performed on all uncertain variables and encouraged submitters to conduct PSA for parametric uncertainty (Bae et al., 2013). When analyzing the submissions, 49 out of 50 cases, including a case of CMA, presented the results of DSA, and 18 of them additionally presented PSA.

Although most cases involved DSA, the assessment of uncertainty was somewhat limited. Relative effectiveness is one of the most critical parameters in cost-effectiveness analysis, yet only 52% of submissions conducted sensitivity analysis. Even though most of the submitted cases (48 out of 50) were analyzed using the model, only 58% of them performed sensitivity analysis on the model assumptions, and 4 cases did not perform DSA for utility among 46 cases that performed a cost-utility analysis (data not shown). In addition, 8 cases did not submit the DSA for the extrapolated model, even though survival analysis was performed.

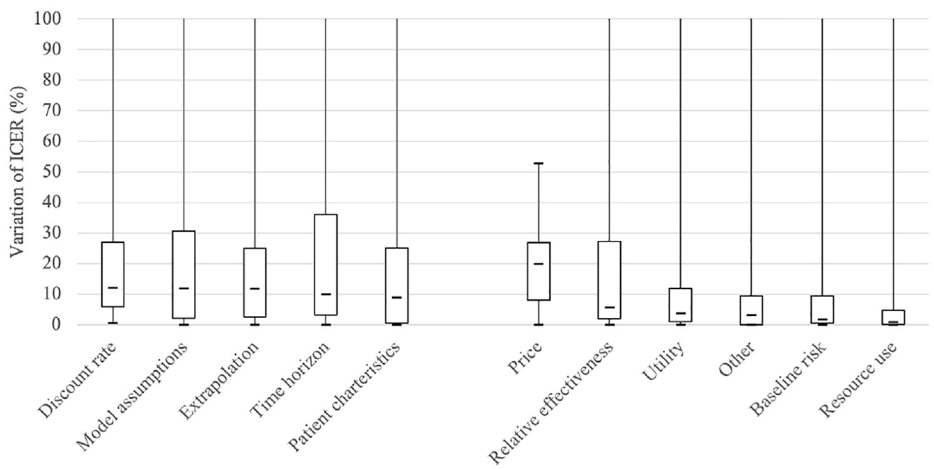

FIGURE 1 | Boxplot comparing the variance of ICER (Incremental cost effectiveness ratio) for each scenario with reference to that of the base case. The "Other" implies parameters relevant with specific treatment, such as the incidence of the adverse event, or hospitalization rate.

The selection of the structural aspect of the model is an important decision that determines the model's predictability (Afzali and Karnon, 2015). According to previous studies, the impact of structural uncertainty is similar to that of parametric uncertainty (Kim and Thompson, 2010; Frederix et al., 2014). However, it is known to be insufficiently reviewed compared to parametric uncertainty (Afzali and Karnon, 2015). Ghabri et al. (2016) reported that, as a result of reviewing manufacturers' submissions to the French National Authority for Health (HAS), structural uncertainty was less frequently explored than methodological or parametric uncertainty, consistent with our assumptions (Ghabri et al., 2016). According to the analysis results of this study, however, there is no basis for concluding that structural uncertainty is more overlooked than parametric uncertainty, even though the term "structural uncertainty" is more widely defined in this study as including both methodological and structural uncertainty.

As shown in **Figure 1**, which shows the impact of each variable on the ICER, the median value of the percentage change is within 10%, excluding drug price, discount rate, model assumption, and extrapolation, which is smaller than the variances estimated in previous studies (Frederix et al., 2014; Kearns et al., 2020). Frederix et al. (2014) found that the ICER varied by 2–3 times depending on the difference in the structural aspects of the model and its parameterization (Frederix et al., 2014). In Kearns et al. (2000), it was confirmed that the ICER changed by 46.2% when different extrapolation methods were used (Kearns et al., 2020). Among the applications reviewed in this study, however, the median percentage change of ICER was 11.8%, and the upper quartile was only 24.9% in the cases where the sensitivity analysis was performed for the extrapolation method. Even considering that Kearns' study used a hypothetical dataset, it is questionable whether pharmaceutical companies have performed sensitivity analysis over a sufficient range.

A clear criterion such as 95% CI is used for only 14% of the sensitivity analyses, most of which are for relative efficacy. Arbitrary values or values cited from other studies are used in most cases. Even when published sources were cited, it is not easy to assess whether DSA was performed within a plausible range unless these sources were searched systematically. According to Ghabri et al. (2016), 43% of the submissions to HAS also lacked justification for the plausible range surrounding the point estimate of the parameter (Ghabri et al., 2016), which is similar to what we have observed in our analysis (48%).

Generally, high uncertainty has a negative impact on the reimbursement recommendation. Although our data do not provide any information about the association between the uncertainty and reimbursement decision, the authors' experience of participating in the economic subcommittee of PBCAC suggested that when the uncertainty has a significant impact on the results, additional data is requested or negative appraisals are made. In this case, pharmaceutical companies are likely to be tempted to report with reduced uncertainty.

Therefore, when performing or reviewing sensitivity analysis, it is necessary to check the plausibility of the range used for sensitivity analysis. It is most desirable to determine the range through a systematic approach such as 95% CI. When such information is not available, systematically reviewing the existing literature is generally recommended to obtain a plausible range (Australian Government: Department of Health, 2016; The Canadian Agency for Drugs and Technologies in Health, 2017; The National Institute for Health and Care Excellence (NICE), 2013). If there is no proper prior research, it is necessary to seek expert opinions in a systematic way and set the range based on this.

From **Figure 1**, it is apparent that the influence of the variables related to the long-term effect is relatively large, except for the drug price, which pharmaceutical companies can strategically select. The discount rate, time horizon, and extrapolation are all in this case. In estimating the long-term effect based on short-term observations, the results vary greatly depending on the model assumptions, particularly the assumptions about the effect after the observation period. Accordingly, each country's guidelines focus on the uncertainty that long-term extrapolation may have. Korea also emphasizes this point, as it revised the guidelines in 2021.

Similarly, 57% of submissions to the French HAS had the problem of unfounded extrapolation beyond the clinical trial (Ghabri et al., 2016). Masucci et al. (2017) also reported that the time horizon (56%) and model structure (36%) were frequently discussed by the economic reviewers of the pan-Canadian Oncology Drug Review (Masucci et al., 2017).

Recently, as drugs claiming long-term effects such as immune therapy and advanced therapy medicinal products have appeared, it is becoming more critical to evaluate the uncertainty in estimating long-term effects (Jönsson et al., 2019; Huygens et al., 2021) Due to insufficient patients or ethical reasons, new drugs used for rare severe diseases are often authorized based on a single-arm study rather than a randomized controlled trial. Additionally, the evidence for long-term effects is often uncertain because survival data are immature, along with other reasons. However, due to social pressure for early access, approvals or reimbursement decisions for these drugs are often made with very high uncertainty about clinical benefits (Grimm et al., 2020; Huygens et al., 2021). According to Kim and Prasad (2015), who followed up on the survival improvement of drugs approved based on the surrogate endpoint at the time of FDA approval (median follow-up 4.4 years), only 5 out of 36 cases demonstrated survival gain (Kim and Prasad, 2015). However, few efforts have been made to assess the validity of survival predictions compared to actual data (Latimner, 2013; Vickers, 2019).

In previous studies, several methods for exploring and managing uncertainty regarding long-term effects have been proposed, such as developing more specific guidance on exploring uncertainty surrounding extrapolation, requiring to follow up data after entry, using mature external data, or combining observed survival data with expert opinion in estimating long-term survival (Frederix et al., 2014; Cope et al., 2019; Huygens et al., 2021).

This study has several limitations. By reviewing the sensitivity analysis included in the first report submitted by the pharmaceutical company, we analyzed which variables were subjected to sensitivity analysis and their impact on ICER. However, no qualitative evaluation was performed to determine whether the range of values subjected to sensitivity analysis for each variable was appropriate. Moreover, the

values identified in this study are those included in the first report and may differ from those used in the committee's final deliberation. PSA was not reviewed in detail in this study because it was not a mandatory requirement for the study period, and the intention of this study is to confirm which variables were reviewed for structural and parametric uncertainties and the impact of each uncertain variable.

This study is the first attempt to explore the uncertainty in economic evaluations submitted for reimbursement decision-making in South Korea. Several studies explored the impact of uncertainty in economic evaluations, but only a few examined actual documents submitted to the HTA agencies. Given the growing importance of uncertainty, by reviewing how pharmaceutical companies are handling uncertainty in submissions to relevant authorities, we can find implications for what points should be emphasized to better address the uncertainty in cost-effectiveness. In particular, the fact that the ICER variation in this study was smaller than what was reported in the previous studies suggests that more prescribed guidance is necessary. Further study is necessary to assess the real impact of uncertainty in terms of the difference between what was predicted at the time of listing and how they actually performed in the follow-up studies.

CONCLUSION

Most dossiers submitted to the committee for reimbursement decisions presented DSA results as suggested in the guidelines. However, considering the variance of ICER, in terms of the impact of each uncertainty, variability was not significant in most scenarios, which raises doubts as to whether the uncertainty evaluation was carried out within a sufficiently plausible range for each variable. Specific guidance regarding the ranges of the sensitivity analysis is necessary. Long-term benefits are often modeled based on uncertain short-term clinical data; therefore, the evaluation and management of uncertainties become more critical than before.

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

SB and EB contributed to the study design and prepared the first draft of the manuscript. SB and EB extracted and analyzed data. JL visualized data and reviewed literature. All the authors reviewed and commented on the manuscript at all stages.

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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.2022.884769/full#supplementary-material

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Chemo-Immunotherapy Regimes for Recurrent or Metastatic Nasopharyngeal Carcinoma: A Network Meta-Analysis and Cost-Effectiveness Analysis

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Introduction: In 2021, two phase III clinical trials confirmed that toripalimab or camrelizumab combined with gemcitabine and cisplatin (TGP or CGP) provide more benefits in the first-line treatment of R/M NPC than GP. Fortunately, TGP and CGP were recently approved as first-line treatments for cases experiencing R/M NPC by the China National Medical Products Administration in 2021. However, due to the high cost and variety of treatment options, the promotion of chemo-immunotherapeutics in the treatment of R/M NPC remains controversial. Therefore, we performed a cost-effectiveness assessment of the two newly approved treatment strategies to assess which treatments provide the greatest clinical benefits at a reasonable cost.

Methods: A cost-effectiveness analysis and network meta-analysis network meta-analysis was conducted based on the JUPITER-02 and CAPTAIN-first Phase 3 randomized clinical trials. A Markov model was expanded for the evaluation of the effectiveness and cost of TGP, CGP, and GP chemotherapy with a 10-years horizon and measured the health achievements in quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and life-years (LYs). We constructed a treatment strategy and other parameters based on two clinical trials and performed one-way and probabilistic sensitivity experiments for the evaluation of the uncertainty in the model.

Results: For the model of patients with treatment-R/M NPC, TGP was associated with a total cost of $48,525 and 2.778 QALYs (4.991 LYs), leading to an ICER of $15,103 per QALY ($10,321 per LY) compared to CGP. On comparing the GP chemotherapy, we found TGP and CGP incurred substantial health costs, resulting in ICERs of $19,726 per QALY and $20,438 per QALY, respectively. The risk of adverse events (AEs) and the price of the drugs had significant impacts on the ICER. At the assumed willingness-to-pay (WTP) threshold of $35,673 per QALY, there were approximately 75.8 and 68.5% simulations in which cost-effectiveness was achieved for TGP and CGP, respectively.

Conclusion: From the Chinese payer's perspective, TGP is more possible to be a cost-effective regimen compared with CGP and GP for first-line treatment of patients with R/M NPC at a WTP threshold of $35,673 per QALY.

Keywords: recurrent or metastatic nasopharyngeal carcinoma, toripalimab, camrelizumab, gemcitabine and cisplatin, cost-effectiveness

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a prevalent malignant tumor of the head and neck with high-incidence foci, and unique geographical distribution mainly distributed in southern China and Southeast Asia. According to the World Health Organization's International Agency for Research on Cancer, 40% of global NPC cases occur in China (Torre et al., 2015). Approximately 10% of new cases are metastatic patients, while another 15–30% of locally advanced NPC patients will develop locally recurrent or disseminated disease following treatment for locally advanced NPC (Lee et al., 2015; Yang et al., 2015; Tan et al., 2016). Cases experiencing recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) have a poor prognosis, with a median overall survival (OS) of only 20 months (Zhang et al., 2016).

Platinum-based regimens have been considered standard first-line chemotherapies for R/M NPC. In 2016, a phase 3 randomized controlled study (GEM20110714) confirmed that gemcitabine plus cisplatin (GP) was more efficient compared with fluorouracil plus cisplatin (PF) for the first-line treatment of R/M NPC [progression-free survival (PFS), hazard ratio (HR), 0.55; 95% confidence interval (CI), 0.44 to 0.68; $p < 0.0001$]. Although the adverse events (AEs) in the GP and PF groups were different, the overall safety was controllable. This trial was a milestone in determining the first-line treatment preference for R/M NPC. lthough its clinical benefit is limited, as the median PFS is only 7 months (Zhang et al., 2016). Thus, novel therapeutic strategies are essential for this group of patients.

Since the 21st century, immune checkpoint inhibitor (ICI) has gradually attracted the attention of tumor community (Glisch et al., 2020; Singh et al., 2020; Watson et al., 2020; Luo et al., 2021). And studies have increasingly confirmed the effectiveness of these immunotherapies for malignant tumors (Ferris et al., 2016; Burtness et al., 2019; Paz-Ares et al., 2019; Schmid et al., 2020; Colombo et al., 2021; Hua et al., 2021; Jiang et al., 2021; Paz-Ares et al., 2021; Zhou et al., 2021). Toripalimab and carrellizumab are humanized high-affinity PD-1 monoclonal antibodies showing good clinical effectiveness and safety as first-line therapies for R/M NPC. In September 2015, the Incyte Corporation reached an agreement with Hengrui Pharmaceutical Co. to purchase the overseas rights to carrellizumab for $795 million USD. Breakthrough therapy designation for Triplel was granted by the US Food and Drug Administration (FDA) for NPC treatment in September 2020. In JUPITER-02 (NCT03581786), a phase 3 study, toripalimab plus GP (TGP) significantly improved PFS compared with GP chemotherapy (median, 11.7 vs. 8.0 months; HR, 0.52; 95% CI, 0.36 to 0.74; $p = 0.0003$) (Mai et al., 2021). In CAPTAIN-first (NCT03707509), a phase 3 study, camrelizumab plus GP (CGP) extended PFS significantly compared with GP chemotherapy (median, 9.7 vs. 6.9 months; HR, 0.54; 95% CI, 0.39 to 0.76; $p = 0.0002$). Overall survival (OS) in both groups was immature, and preliminary data suggested that patients receiving carrilizumab combined with chemotherapy tended to have improved survival (median OS, NR vs. 22.6 months; HR, 0.67; 95% CI, 0.41–1.11) (Yang et al., 2021a). Based on these data, CGP and TGP were approved as first-line treatment options for cases experiencing R/M NPC by the National Medical Products Administration of China and the Chinese Society of Clinical Oncology and included in the protocols for NPC interventions, version2021[1,2].

Although these treatment options have brought clinical benefits, the high cost and variety of ICIs means an analysis of their economics and efficacy is urgently essential to appraise which recently confirmed regimen presents the most clinical benefits at reasonable expenses and is more suitable for promotion. Therefore, the target of our study was to appraise the effectiveness and potential economic implications of TGP and CGP as first-line treatments for Chinese patients with R/M NPC from the Chinese citizen's perspective.

MATERIALS AND METHODS

We conducted a network meta-analysis and cost-effectiveness analysis based on two phase 3 clinical trials. Details of the network meta-analysis methods are given in the **Supplementary Material**. Cost-effectiveness analysis is guided by the Economic Assessment Report Standard Statement (CHEERS) checklist (**Supplementary Table S1**) and the details of its methods are presented below.

Model Structure

A Markov model with three exclusive health states was structured to demonstrate the possible consequences under evaluation: PFS, progressive disease (PD), and death (**Supplementary Figure S2**). Patients with R/M NPC were investigated and randomly assigned to receive one of three treatments in our study. In the PD state, patients deemed likely to gain clinical benefit received capecitabine (Martinez-Trufero et al., 2010), otherwise they were assigned to receive best supportive care (BSC) until death (National Comprehensive Ca, 2021).

The Markov cycle length was set at 6 weeks, with a 10-years horizon, based on the treatment regimen and expected survival time of R/M NPC patients. All costs, as well as health outcomes,

[1]http://www.csco.org.cn/cn/index.aspx Accessed, 2021.
[2]https://www.nmpa.gov.cn Accessed, 2021.

were discounted by 3% annually (Ding et al., 2021). We chose the total expenses, quality-adjusted life-years (QALYs), life-years (LYs), and incremental cost-effectiveness ratios (ICERs) as primary endpoints with a willingness-to-pay threshold of $$35,673 per QALY (3 × capita gross domestic product of China in 2020) (Xiao et al., 2017). The simulation process was carried out on TreeAge Pro 2020 (TreeAge Computer program, Williamstown, MA, United States, https://www.treeage.com) and part of the statistical analysis was implemented in R (version 4.1.1, Available: http://www.rproject.org).

Patients and Treatment

Based on two randomized controlled trials (RCTs) and the published literature, we hypothesized that patients with R/M NPC were male, 50 years old, 65 kg in weight, 164 cm in height, and had a body surface-area of 1.72 m^2 (Liu et al., 2020; Yang et al., 2021a; Mai et al., 2021). We randomly assigned these patients to three groups: 1) a TGP group, which was treated with toripalimab (240 mg on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1) every 3-weeks cycle for six cycles, succeeded by toripalimab only on day 1 of every 3-weeks cycle as maintenance (for a maximum of 2 years of treatment); 2) a CGP group, which was treated with camrelizumab (200 mg on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1) every 3-weeks cycle for six cycles, succeeded by camrelizumab only on day 1 of every 3-weeks cycle as maintenance (for a maximum of 2 years of treatment); and 3) a GP group, which was treated with gemcitabine (1,000 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1) every 3-weeks cycle for six cycles, succeeded by placebo only on day 1 of every 3-weeks cycle as maintenance. Because, after disease development, follow-up treatment options for R/M NPC cases are generally restricted, and given that capecitabine chemotherapy was often used for follow-up treatment and specific drugs used for subsequent treatment were not specified in the JUPITER-02 and CAPTAIN-first clinical trials reports, we modeled that the patients received only capecitabine chemotherapy as follow-up treatment. Respectively, 32, 34, and 62% of patients in the TGP, CGP, and GP groups received subsequent chemotherapy. Treatment regimens and dosages were followed as detailed in the above clinical trials (Martinez-Trufero et al., 2010; Yang et al., 2021a; Mai et al., 2021). Specific usage details are listed in **Supplementary Table S4**.

Model Survival and Transition Estimates

The survival outcomes were extracted from the curves of Kaplan-Meier (KM) of OS and PFS generated in the original JUPITER-02 and CAPTAIN-first trials using GetData Graph Digitizer (version 2.26; http://www.getdata-graph-digitizer.com/index.php). Based on these outcomes, transition probability (TP) between health states, death probability, and fitted long-term survival data were estimated. We evaluated five parametric survival models of fitness for the time-to-event data, including Weibull, Gompertz, exponential, log-logistic, and log-normal distributions. We selected the Weibull distribution as a survival model for PFS and PD according to the Bayesian information criterion and Akaike information criterion, the clinical rationality, and a visual inspection of the degree of similarity between the KM curves and 10-years extrapolated survival curves. The Surveillance, Epidemiology, and End Results data in the published literature indicated that log-normal and log-logistic distribution appeared not to fit with the reality of the long-term survival rate (Latimer, 2013). More details are shown in **Supplementary Figure S4** and **Supplementary Table S5**. For the GP chemotherapy group, we used a network meta-approach to reconstruct the OS and PFS data at the individual patient level in both groups based on the JUPITER-02 and CAPTAIN-first trials. It is worth noting that we used the Weibull distribution for all treatment groups and obtained two parameters, scale (λ) and shape (γ), using the R software This study employed Hoyle's suggested methodology (Hoyle and Henley, 2011) (**Table 1**).

Utilities and Cost Inputs

Utility was used to reflect the weight of the patients' quality of life in the natural background of the disease on a scale of 0 (death) to 1 (total health). We regarded utility scores of 0.65 and 0.52 for PFS state and PD state, accordingly, as published by Jin et al. (2020). We assessed the impact of the deterioration of the quality of life contingent on clinical events as the disutility multiplied by the incidence of severe AEs (Tringale et al., 2018) (**Table 1**).

We only considered direct costs from the Chinese social perspective and converted to US dollars as of the 2021 conversion rate. The Chinese Yuan was converted into USD using the following exchange formula: 1US $ = CNY 6.4. The costs were calculated for medicines, administration (Lang et al., 2020), tumor imaging (Yang et al., 2020), laboratory tests (Yang et al., 2020), BSC (Xin et al., 2020), and management of severe AEs (assuming that Aes emerged only once in the PFS and PD states) (Guan et al., 2019; Lang and Dong, 2020; Lang et al., 2020; Li et al., 2020) (**Table 1**). Grades 3 to 4 Aes with an incidence rate of ≥5% in either group or with significantly different rates between groups were estimated in the calculation. In addition, due to the different reimbursement rates of medical insurance in different regions of China, we excluded preferential policies in the cost input.

Sensitivity Analysis

We executed univariable sensitivity assessments to indicate the uncertainty and impact of the parameters among the treatment alternatives using the available evidence. Univariable sensitivity analysis evaluated specific parameters in JUPITER-02 and CAPTAIN-first trials and 20% variation from baseline values (Ding et al., 2021). Probabilistic sensitivity analysis was performed to characterize the current decision uncertainties. A Monte Carlo simulation was conducted 10,000 times employing scatterplot and acceptability curves on the cost-effectiveness plane to examine the probability of being cost-effective.

We pooled the HR and 95% CI for the OS and PFS of each treatment group in the two RCTs based on indirect comparisons and used R computer program (version 4.1.1, http://www.r-project.org) for comparative analysis. However, as only one RCT involved a pairwise comparison of individuals, and due to the lack of a dataset to assess heterogeneity across the trials, we

TABLE 1 | Model parameters: baseline values, ranges, and distributions for sensitivity analysis.

Parameters	Baseline Value	Range		Reference	Distribution
		Minimum	Maximum		
Survival					
Weibull survival model of OS of GP	Scale = 0.0004758	—	—	(6, 7)	—
Weibull survival model of PFS of GP	Shape = 2.3,014,344 Scale = 0.011275 Shape = 1.991,263	—	—		—
Weibull survival model of OS of TGP	Scale = 0.0016292	—	—	(6)	—
Weibull survival model of PFS of TGP	Shape = 1.6,248,844 Scale = 0.010542 Shape = 1.663,938	—	—		—
Weibull survival model of OS of CGP	Scale = 0.005613	—	—	(7)	—
Weibull survival model of PFS of CGP	Shape = 1.319,492 Scale = 0.011551 Shape = 1.762,665	—	—		—
Risk for main AEs in GP group					
Risk of neutropenia	0.471	0.377	0.565	(6, 7)	Beta
Risk of anemia	0.412	0.330	0.494	(6, 7)	Beta
Risk of thrombocytopenia	0.342	0.274	0.410	(6, 7)	Beta
Risk of leucopenia	0.636	0.509	0.763	(6, 7)	Beta
Risk of lymphopenia	0.129	0.103	0.155	(6, 7)	Beta
Risk for main AEs in TGP group					
Risk of leucopenia	0.616	0.493	0.739	(6)	Beta
Risk of neutropenia	0.575	0.460	0.690	(6)	Beta
Risk of anemia	0.473	0.378	0.568	(6)	Beta
Risk of thrombocytopenia	0.329	0.263	0.395	(6)	Beta
Risk of lymphopenia	0.089	0.071	0.107	(6)	Beta
Risk of hyponatremia	0.089	0.071	0.107	(6)	Beta
Risk of hypokalemia	0.068	0.054	0.082	(6)	Beta
Risk of pneumonia	0.103	0.082	0.124	(6)	Beta
Risk for main AEs in CGP group					
Risk of neutropenia	0.24	0.19	0.29	(7)	Beta
Risk of anemia	0.09	0.07	0.11	(7)	Beta
Risk of thrombocytopenia	0.06	0.05	0.07	(7)	Beta
Risk of leucopenia	0.06	0.05	0.07	(7)	Beta
Risk of neutrophil count decreased	0.06	0.05	0.07	(7)	Beta
Risk of febrile neutropenia	0.06	0.05	0.07	(7)	Beta
Risk of hyponatraemia	0.06	0.05	0.07	(7)	Beta
Utility and disutility					
Utility PFS in first-line treatment	0.65	0.520	0.780	(16)	Beta
Utility PD	0.52	0.416	0.624	(16)	Beta
AEs disutility for GP	0.0069	0.0055	0.0083	(17)	Beta
AEs disutility for TGP or CGP	0.0070	0.0056	0.0084	(17)	Beta
Drug cost, $/per cycle					
Toripalimab	659.4	527.52	791.28	Local Charge	Gamma
Camrelizumab	888.3	710.64	1,065.96	Local Charge	Gamma
Gemcitabine	860.9	688.72	1,033.08	Local Charge	Gamma
Cisplatin	332.1	265.68	398.52	Local Charge	Gamma
Capecitabine	128.0	102.40	153.60	Local Charge	Gamma
Cost of AEs, $					
GP	1,940	1,552	2,328	(18, 21–23)	Gamma
TGP	1,980	1,584	2,367	(18, 21–23)	Gamma
CGP	2,246	1,797	2,695	(18, 21–23)	Gamma

(Continued on following page)

TABLE 1 | (*Continued*) Model parameters: baseline values, ranges, and distributions for sensitivity analysis.

Parameters	Baseline Value	Range		Reference	Distribution
		Minimum	Maximum		
Laboratory per cycle	216.4	173.12	259.68	(19)	Gamma
Tumor imaging per cycle	231.1	184.80	277.20	(19)	Gamma
Administration per cycle	106.2	84.96	127.44	(18)	Gamma
Best supportive care per cycle	157.6	126.08	189.12	(20)	Gamma
Body surface area (meters2)	1.72	1.38	2.06	(13)	Gamma
Discount rate	0.03	—	—	(11)	—

Abbreviation; OS, overall survival; PFS, progression-free survival; GP, gemcitabine and cisplatin; TGP, toripalimab plus gemcitabine and cisplatin; CGP, camrelizumab plus gemcitabine and cisplatin; AEs, adverse events.

developed a fixed-effect model (Rücker and Schwarzer, 2015). Therefore, the frequency method was employed for the comparison of the comparative effectiveness of various schemes. The HR of OS and PFS, and the corresponding 95% Cis and *p*-values, were evaluated, and the *p*-value of each result was used for ranking, where a higher value indicated higher success.

RESULTS

Network Meta-Analysis

A database search identified 187 records through a database search, and two phase III randomized clinical trials (JUPITER-02 and CAPTAIN-first) involving 552 patients were included in the meta-analysis (**Supplementary Figure S4** and **Supplementary Table S3**). In examining the JUPITER-02 trial, 289 patients received TGP or GP; In the JUPITER-02 trial, 263 patients received either CGP or GP treatment. The risk of bias is shown in **Supplementary Figure S5**.

Baseline Results

For patients with R/M NPC with a 10-years horizon, TGP presented an additional 0.148 QALYs (0.240 Lys) at an increased cost of $2,232 compared with CGP, leading to an ICER value of $15,103 per QALY ($10,321 per LY). A comparison of the two chemo-immunotherapies and GP chemotherapy showed that the addition of toripalimab and camrelizumab to first-line GP chemotherapy yielded 1.108 and 0.960 QALYs (2.015 and 1.799 Lys), respectively. Due to the QALY improvement, TGP and CGP involve higher medical costs than GP chemotherapy, resulting in ICERs of $19,726 and $20,438 per QALY ($10,842 and $10,904 per LY), respectively (**Table 2**).

TABLE 2 | Baseline results.

Parameters	TGP	CGP	GP
LYs	4.991	4.751	2.976
QALYs	2.778	2.630	1.670
Total cost $	48,525	46,293	26,680
ICER $/LY	10,842[a]	10,904[a]	—
	10,321[b]		
ICER $/QALY	19,726[a]	20,438[a]	—
	15,103[b]		
WTP $/QALY		37,653	

[a]*Compared to GP.*
[b]*Compared to CGP.*
Abbreviation: TGP, toripalimab plus gemcitabine and cisplatin; CGP, camrelizumab plus gemcitabine and cisplatin; GP, gemcitabine and cisplatin; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

Sensitivity Analysis Results

The outcomes of the one-way sensitivity assessment showed a high sensitivity to the risk of thrombocytopenia for TGP (ranging from 26.3 to 39.5%, with the ICER raising from -$7,598 per QALY to $38,195 per QALY). Other significant influencing factors such as the cost of the ICI, the utility of the PFS, and the incidences of anemia and neutropenia. Other factors considered in the analysis of sensitivity, for instance, the cost of chemotherapy drugs and Aes, had little impact on the ICER (**Figure 1**).

As demonstrated in the curve of cost-efficiency acceptability, the probability that the strategy of TGP is cost-efficient increased as the WTP for additional QALY rose (**Figure 2**). GP chemotherapy was the optimal strategy when WTP was less than$30,000/QALY. When WTP was greater than or equal to, $30,000/QALY TGP was found to be the optimal strategy. The scatter plots demonstrated that, at a WTP threshold of $35,673 per QALY, the TGP and CGP strategies were cost-effective in 75.8 and 68.5% of the simulations (**Supplementary Figure S6**).

An indirect comparison of the data revealed that TGP (HR, 0.60; 95% CI, 0.364–0.998 and HR, 0.52; 95% CI, 0.363–0.746) led to meaningful statistical enhancements in OS and PFS in comparison to GP. No statistically meaningful discrepancies in OS and PFS were detected across the two chemo-immunotherapy regimens. The best treatment achievements were indicated by the *p*-values (for individual outcomes), where higher values indicated the treatment was more successful. Among the overall populations, the regimen with peak *p*-values for OS and PFS was TGP ($p = 0.80$ and $p = 0.78$), followed by CGP ($p = 0.66$ and $p = 0.72$), and GP ($p = 0.04$ and $p = 0.0002$), respectively. The findings of the indirect comparisons and the *p*-values for the OS and PFS of each regimen are illustrated in **Figure 3**.

DISCUSSION

Over the past decade, immunotherapy has become one of the most important breakthroughs in cancer treatment (Sharon et al., 2014). PD-1 blocking antibody has good therapeutic effects on recurrent or metastatic head and neck cancer (R/M HNC), but there have been few corresponding economic evaluations of R/M HNC. The cost-effectiveness of pembrolizumab for R/M HNC patients demonstrated its cost-effectiveness compared to standard treatments in both China, the United States, and Argentina (Liu et al., 2019; Wurcel et al., 2021). A cost-effectiveness study by Robert et al. demonstrated that nivolumab was more cost-effective compared to chemotherapy in cases experiencing R/M HNSCC in the US (Haddad et al., 2020). In addition, network meta-analysis and cost-effectiveness analysis of R/M HNSCC patients in the US found that using nivolumab or pembrolizumab was more cost-effective based on WTP thresholds and patient weight (Pei et al., 2021). However, NPC is a type of HNC, and so far, there have been no cost-effectiveness analyses of immunotherapy for these patients; thus, a cost-effectiveness analysis of R/M NPC is crucial.

Individuals undergoing cancer treatment face a wide range of treatment options, but they and the societies they belong to face increasing economic burdens due to limited medical resources and high treatment prices. Economic assessment is a direct and theory-based approach that measures both the costs and outcomes in view of individual and social choices. Using the Markov model, we executed the first cost-effectiveness assessment of R/M NPC treatments from the Chinese citizens perspective and assessed the cost and efficacy of TGP, CGP, and GP chemotherapies at a WTP of $35,673 per QALY. Through our study, we found that TGP and CGP treatments resulted in an additional cost of $21,846 and $19,613, resulting in 1.108 and 0.960 QALYs compared to GP, respectively, which are clearly below the threshold for WTP. And ICER was significantly lower than the threshold of WTP. In addition, after comparing the two schemes, the ICER for TGP was deemed to be $15,103/QALY. Therefore, this cost-effectiveness study conducted for cases with R/M NPC in China demonstrated that TGP is the more efficient first-line treatment strategy and achieves the highest cost-effectiveness compared to CGP and GP.

The robustness of the model was verified through a sensitivity analysis of the model parameters. The most influential parameters in this model were the risk of thrombocytopenia from TGP and CGP, followed by the cost of toripalimab and camrelizumab. We found that the incidence of thrombocytopenia from TGP decreased by more than 15%, and the price of toripalimab decreased by more than 30% while that of camrelizumab rose by more than 30%, allowing TGP to dominate CGP economically. Because changing other parameters had no substantial effect on our results, mitigating drug-induced AEs and reducing the price of ICIs were considered the most practical measures for first-line TGP and CGP treatment

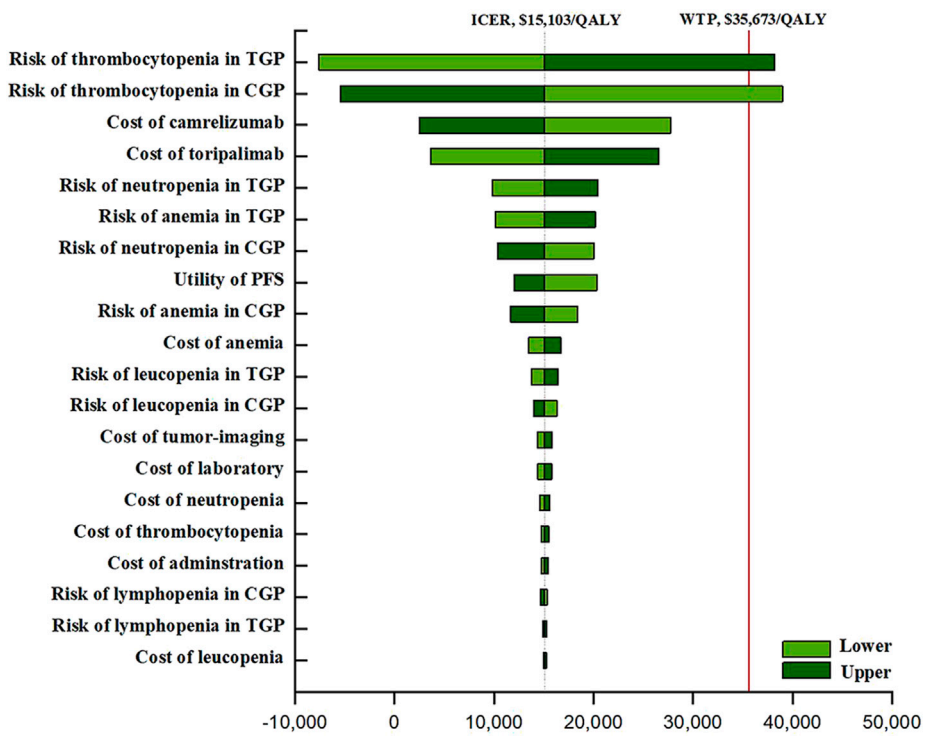

FIGURE 1 | The one-way sensitivity analyses. Abbreviation: TGP, toripalimab plus gemcitabine and cisplatin; CGP, camrelizumab plus gemcitabine and cisplatin; GP, gemcitabine plus cisplatin; PFS, progression-free survival; BSC, best supportive care.

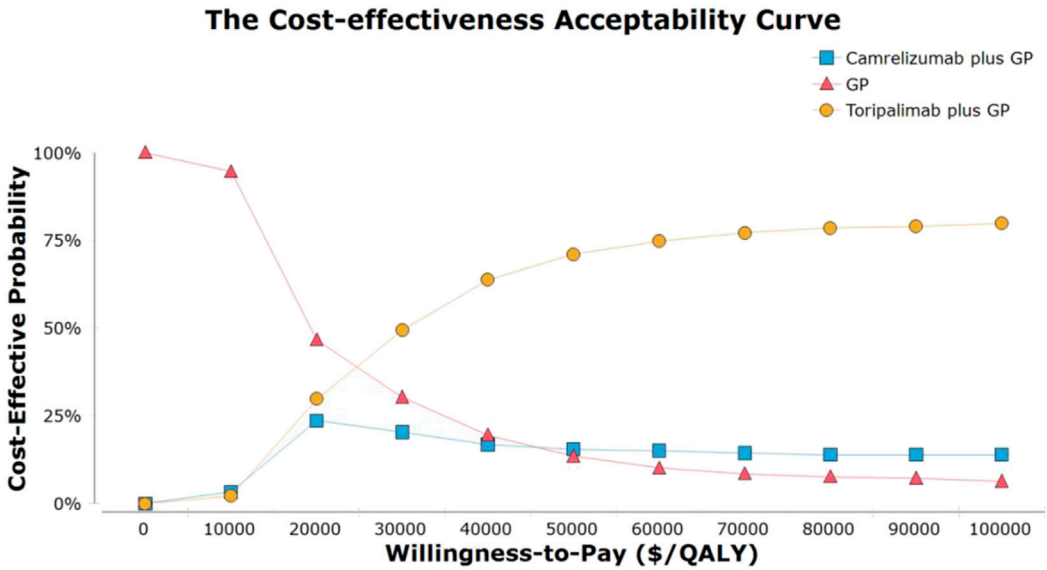

FIGURE 2 | The cost-effectiveness acceptability curves for the toripalimab plus gemcitabine and cisplatin, camrelizumab plus gemcitabine and cisplatin. Abbreviation: GP, gemcitabine plus cisplatin.

Overall population			
TGP	0.96 (0.589 to 1.573)	**0.52 (0.363 to 0.746)**	0.78
0.90 (0.443 to 1.828)	**CGP**	0.54 (0.407 to 1.102)	0.72
0.60 (0.364 to 0.998)	0.67 (0.407 to 1.102)	**GP**	0.0002
0.80	0.66	0.04	**P-Score**

FIGURE 3 | The pooled HR; 95%CI and *p*-values for OS (lower triangle) and PFS (upper triangle) of the network meta-analysis; significant results are in bold. Abbreviation: TGP, toripalimab plus gemcitabine and cisplatin; CGP, camrelizumab plus gemcitabine and cisplatin; GP, gemcitabine plus cisplatin; OS, overall survival; PFS, progression-free survival.

to become absolutely cost-effective. It is worth noting that real-world evidence and many clinical studies have shown that grade 3/4 thrombocytopenia in chemo-immunotherapy is most likely to be caused by the chemotherapy. The incidences of grade 3/4 thrombocytopenia in NPC patients treated with GP chemotherapy alone and immunotherapy alone were over 10% and almost 0%, respectively (Zhang et al., 2016; Zhang et al., 2019; Yang et al., 2021a; Yang et al., 2021b; Mai et al., 2021). In clinical practice, if severe thrombocytopenia occurs during the treatment of NPC patients given chemo-immunotherapy, we first adjust the dose of chemotherapy to reduce its incidence, then reduce the ICER of the treatment regimen.

For a new drug to be approved by government and used correctly and widely in clinical situations, we need to rely on using clinical survival benefits, regional economic factors, and predictive markers to make judgements. For example, plasma Epstein-Barr virus deoxyribonucleic acid (EBV-DNA) levels have a substantial prognostic influence in cases with NPC. A retrospective analysis of 210 patients with NPC revealed a worse relapse-free survival rate (79.3%; $p < 0.0001$) and poorer OS (86%; $p = 0.0003$) in cases who were given high pretreatment EBV-DNA levels (Wang et al., 2013). A meta-analysis involving 22 investigations and 8,128 NPC cases showed that patients with high levels of EBV-DNA had a five to six times higher risk of death and metastasis than patients with low levels (Qu et al., 2020). However, programmed cell death ligand-1 (PD-L1) expression confirmed to be a proper biomarker for predicting the clinical effectiveness and prognosis of ICIs in HNC (Li et al., 2017; Cao et al., 2019; Huang et al., 2021). Li and others'

retrospective analysis proved that the 5-years OS and PFS of 120 nasopharyngeal carcinoma patients were 87.5 and 70.1%, respectively (Li et al., 2017). Another retrospective analysis showed a PD-L1 expression of 0%, 1–5%, 5–49%, and ≥50% in 154 NPC patients and 5-years OS and PFS of 75.5 and 85.7%, 72.7 and 72.7%, 55.9 and 68.3%, and 24.8 and 35%, respectively (Cao et al., 2019). Another meta-analysis suggested that high or positive expression of PD-L1 in head and neck squamous cell carcinoma (HNSCC) has a good predictive effect for OS at 6 and 12 months [relative risk (RR), 1.30; 95% CI, 1.02 to 1.65; $p = 0.03$; RR, 1.31; 95% CI, 1.05 to 1.62; $p = 0.01$] (Huang et al., 2021). In addition to the above two main biomarkers of clinical efficacy and prognosis, many studies have also indicated that the expression of epidermal growth factor receptor, Ki-67, vascular endothelial growth factor, and BRAF may also be good predicting biomarkers for NPC patients (Cheng et al., 2018; Cao et al., 2019; Chen et al., 2020; Li et al., 2021). Unfortunately, the JUPITER-02 and CAPTAIN-first studies lacked OS data for these two major prognostic markers, and PD-L1 expression was not grouped in CAPTAIN-first, hence, these could not be analyzed. The biomarkers that might lead specific patients to benefit from immuno-chemotherapy need to be confirmed through further research, which may make personalized treatment possible.

Some limitations were also evident in this study. First, an indirect comparison between first-line TGP and CGP was performed using network meta-analysis. Because we assumed no difference in patient characteristics between the two studies, there is potential uncertainty regarding the accuracy. Second, due to the short follow-up period of the two clinical trials, it was necessary to extrapolate the survival curve to obtain complete survival outcomes. The survival data will change over time, and the model will become more stable as more mature data becomes available. However, for now, this is an unavoidable limitation in our model. Third, to simplify the calculation, we assumed that follow-up treatment in the three groups only involved capecitabine chemotherapy, with the highest probability in the two studies, and ignored the other treatment options. On this basis, the analysis may have underestimated the cost of PD. However, sensitivity assessment demonstrated that changing the cost of capecitabine had little effect on the modelled results. Finally, considering that immunotherapy-related AEs are rare (the incidence was less than 10% in the two studies) and the cost of their treatment is quite high, we overlooked their administrative costs, which may overestimate the benefit of chemo-immunotherapy. However, including the cost of AE cases associated with immunotherapy will help to more accurately assess the overall cost of treating AEs using chemo-immunotherapy.

Conclusively, our achievements explain that TGP regimens could be more cost-efficient than GP and CGP regimens in China at a WTP threshold of $35,673 per QALY. It is necessary to provide patients the most efficacious treatment at the lowest cost, and the findings may help clinicians select the most appropriate drugs for patients and develop policies for medical reimbursement.

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

YZ, KL, DD, KW, and XT designed experiment. YZ, KL, DD, KW, and XL performed the experiments. YZ, KL, DD, and XT analyzed the data. XT contributed analysis tools and funding. YZ, KL, DD, KW, XL, and XT wrote the manuscript. YZ and KL contributed equally to this article. All authors have read and approved the manuscript.

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.858207/full#supplementary-material

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Knowledge on Multi-Drug Resistant Pathogens, Antibiotic Use and Self-Reported Adherence to Antibiotic Intake: A Population-Based Cross Sectional Survey From Pakistan

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Objective: Surveying public awareness of antibiotic use and antibiotics can identify factors relevant to the design of effective educational campaigns. The aim of this study was to evaluate the knowledge, attitudes, and practices related to antibiotic use and multidrug-resistant pathogens in the general population in Pakistan.

Research Design and Methods: Cross-sectional survey was conducted, using a 60 itemed structured questionnaire and recruited individuals by convenient sampling from the general population in the four provinces of the country. Descriptive statistics were used to evaluate the responses and the chi squared statistic was used to assess differences between groups.

Results: The response rate was 87.6% (6,684 out of 7,631 individuals). Half of the respondents had received at least one prescription of antibiotics in the 6 months preceding the survey. Knowledge about antibiotic use, (39.8%) individuals scored above the mean (≥3) showed good knowledge about antibiotic use. Urban residents and male showed significant higher knowledge ($p < 0.001$) about antibiotic use. Approximately 50% of the respondents correctly answered the question about antibiotic resistance. Of the 3,611 received antibiotics, 855 (23.7%) were indicated for cough, 497 (13.8%) for a sore throat, 335 (9.3%) for ear ache, 665 (18.4%) for a burning sensation during urination, 667 (18.4%) for wounds or soft tissue inflammation. MDR pathogen was perceived as an important topic by (4,010) 60.1% of respondents.

Conclusion: Participants were aware of the problem of multidrug-resistant pathogens and understood the responsibility of each individual to avoid the spread of these infectious agents.

Keywords: knowledge, antibiotic use, multi-drug resistant pathogens, population-based, adherence

INTRODUCTION

The development of antimicrobial resistance (AMR) is a major public health concern in Pakistan (Bilal et al., 2021; Gillani et al., 2021) and worldwide (Aslam et al., 2018) AMR causes longer hospital stays, increased mortality, and substantial economic and intangible losses (Gillani et al., 2021). The rise in AMR has been positively associated with inappropriate handling and unnecessary use of antibiotics (Bilal et al., 2021), Several factors such as the physicians' knowledge gap about current antibiotic recommendations inappropriate diagnosis, availability of antibiotic without prescription, incomplete antibiotic course and insufficient patient education by healthcare providers, overuse of antibiotics in livestock cause antimicrobial resistant at population level (Dhingra et al., 2020; Murray et al., 2022). Adherence to antibiotic treatment is essential in ensuring the therapeutic effects and to preventing the development of AMR (Aslam et al., 2018).

In some developing nations, Gram-negative bacteria are a major cause of neonatal sepsis (Yadav et al., 2018; Wen et al., 2021), and these microorganisms have developed increasing multidrug resistance (MDR) over the past decades (Uddin et al., 2021a) because of inappropriate and indiscriminate antibiotic use, easy availability, lack of regulations regarding antibiotic use, poor sanitation, and unsuccessful infection control in maternity wards. The appearance of a bacterial strain that is resistant to most available antibiotics is a major concern in Pakistan (Afzal, 2017; Gillani et al., 2017; Bhatti, 2020; Uddin et al., 2021b).

A considerable number of studies have shown that the general population plays a key role in spreading the AMR due to lack of awareness about antibiotics among population in Pakistan (Ching et al., 2019; Saleem et al., 2019). The World Health Organization has stated that appropriate awareness among both the public and healthcare providers is the key to averting AMR (WHO, 2014). Decreased antibiotic use could be achieved via multifaceted educational interventions to inform healthcare practitioners and the public of the harm of antibiotic overuse (Teixeira Rodrigues et al., 2019). Also, public's current knowledge evaluation about antibiotics and the development of AMR could help to design policies and campaigns addressing these problems (Kosiyaporn et al., 2020). Few studies have focused on knowledge among the general population in Pakistan regarding antibiotic use (Akhund et al., 2019; Gillani et al., 2021) and none have focused on MDR. We therefore, conducted a study on knowledge of MDR pathogens in this population. The aim of study was to evaluate the knowledge, attitudes, and practices related to antibiotic use and multidrug-resistant pathogens in the general population in Pakistan.

METHODS

Study Area

We sampled all four provinces of Pakistan (Punjab, Sindh, Khyber Pakhtunkhwa, and Baluchistan). The provinces consist of divisions, districts, tehsils (administrative areas containing towns), and villages. Three districts were randomly selected from Punjab and Sindh and two each from Khyber Pakhtunkhwa and Baluchistan. From each target district, we selected one city and one village. City was conveniently selected by the availability of data collectors. **Figure 1** illustrates the cities and villages selected and the corresponding numbers of respondents.

Study Participants and Recruitment

We performed a cross-sectional survey in the four provinces of Pakistan. We used convenient sampling and try to collect data from maximum participants during May to November, 2020. Total 7,631 participants approached in the study during this time frame. Participants who were Immigrants, individuals over 80 or under 18 years, and persons with cognitive impairment (N = 479), participants initially participated in the study and during study refused to continue the study due to personal issues (lack of time, information sharing hesitation and others) (N = 219), and missing data from survey (N = 379) were excluded from the study. Finally, sample of 6,684 participants was included in the study. (**Figure 2**). Individuals were approached in shopping malls and in pharmacies, educational institutions, bus stations, train stations, and households. Self-administered questionnaires were filled in and collected. Interviews were conducted with individuals who were not literate. Individuals were made aware of the purpose of this study.

Training of Data Collectors

Sixteen data collectors were trained to conduct the research in the provinces. Most data collectors were pharmacy students in their final year of study, who were supervised by teachers from the local university. Training covered the following aspects: 1) presenting a concise introduction of the study rationale to respondents; 2) conducting face-to-face interviews; 3) coping with difficulties in data collection, such as lack of cooperation. The training lasted 3 days and included a demonstration by the primary researcher.

Questionnaire

The knowledge, attitudes, and practices regarding antibiotic use covered four topics: 1) exposure to antibiotics, evaluated by two questions about symptoms and prescription in the preceding 6 months. 2) Knowledge about antibiotics, evaluated by responses to seven statements related to correct identification of antibiotics and to opinions regarding antibiotic use in general. 3) Attitudes and practices related to antibiotic use, assessed by seven items concerning how participants generally obtained antibiotics and whether they were concerned about antibiotic resistance. 4) Whether participants requested antibiotics for personal use, how they used antibiotics, and whether they developed side effects during use (six items). The questionnaire used in this study differed in its contents from those of previous studies (Akhund et al., 2019; Gillani et al., 2021). The second part of the questionnaire addressed MDR pathogens: 1) awareness of MDR pathogens and past exposure (seven items). 2) Knowledge about MDR pathogens, assessed by questions and statements about infection routes, spread, and treatment of MDR pathogens (five items). 3) Attitudes about MDR pathogens, assessed by

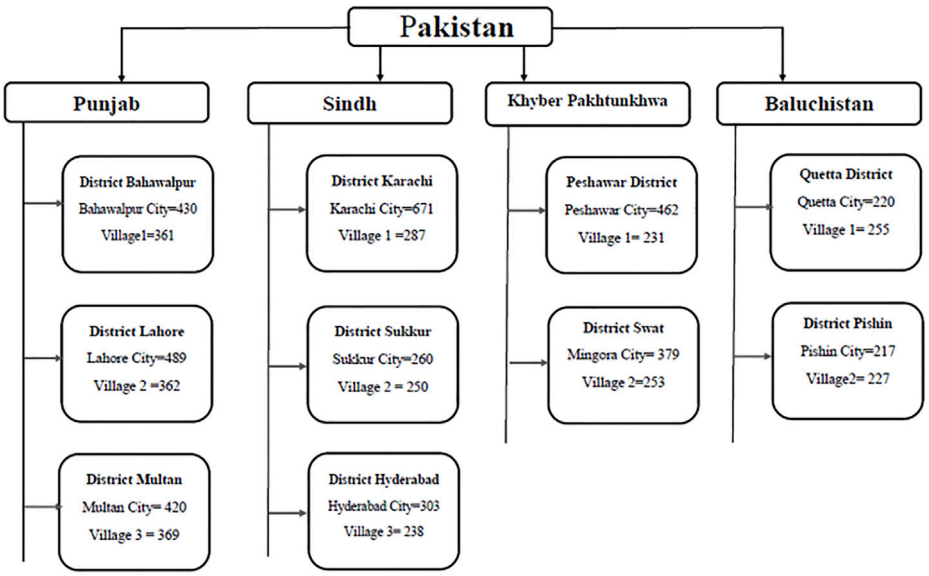

FIGURE 1 | Selection of study area.

asking participants about their feelings with respect to contracting an MDR organism, about MDR pathogens as a public health problem, and their opinion regarding who is responsible for the control of their spread (10 items). 4) Reaction to close contact with an infected person, assessed using two case scenarios. The case scenarios were presented to assess how participants would deal with carriers of MDR pathogens.

Case 1: Let us suppose that your neighbor, an elderly person residing alone, requires some help and you have been shopping for him for a couple of months. After a hospital stay, he tells you that he has become infected with a hospital-acquired pathogen. How would you behave with him/her?

Case 2: Let us suppose that your coworker, with whom you share an office and some office items, tells you after a hospital stay that she has become infected with a hospital-acquired pathogen. How would you behave with him/her?

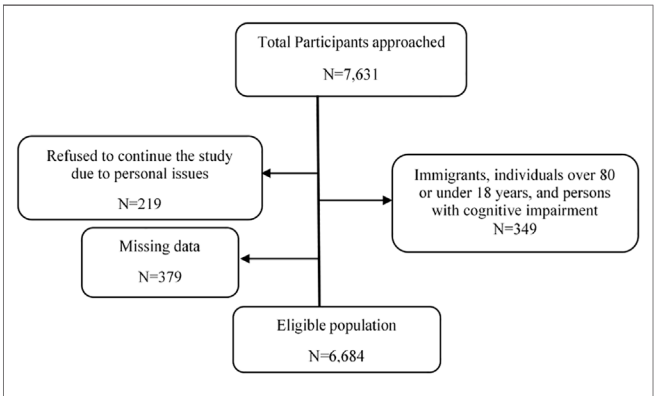

FIGURE 2 | Fears of individuals regarding MDR pathogen.

Each case scenario was associated with eight statements, and response options were "strongly agree," "agree," "somewhat disagree," and "disagree."

In addition, demographic information (age, sex, education, locality, and marital status) was also collected and included in the analysis. The questionnaire was modified slightly from a previous study (Akhund et al., 2019) according to our study protocol and translated in to national language. tResponses were back-translated into English. Construct validity and content validity of questionnaire was established by extensive literature either the designed tool was measuring the actual research question which we want to measure. Face validity was ensured when expert researchers looked at the items in the measuring tool and gave their expert opinions. Designed questionnaire was reviewed and evaluated by the research committee of four professors of pharmacy background to assess appropriateness of each question to be measure. After discussion with researchers their expert feedback was used to edit the instrument accordingly. Internal consistency was measure by Cronbach's alpha. Cronbach's alpha of questionnaire was 0.768 showed the reliability of research tool was good. Before the start of data collection, a pilot study was conducted in each area to check the accuracy of the wording and comprehensiveness. The data obtained in the pilot study were not included in the final analysis.

Data Analysis

Descriptive analysis was performed for the demographic variables. To analyze the knowledge about antibiotics, each correct response was awarded one point. For a positive question, the responses "strongly agree" or "agree" were calculated as one point and "do not know," "disagree," or "strongly disagree" were calculated as zero. For a negative question, "disagree" or "strongly disagree" were calculated as one point and "strongly agree" or "agree" and don't know were

TABLE 1 | Demographic details.

Variable	Number (%)
Age (Mean ± SD) (years)	
32.97 ±10.8	
Gender	
Male	4,746 (71.0)
Female	1938 (29.0)
Residence	
Rural	2,833 (42.4)
Urban	3,851 (57.6)
Education	
Primary or below	1749 (26.2)
Secondary school	1,338 (20.0)
High school	1,558 (23.3)
College/university	1,267 (19.0)
Post graduation or above	772 (11.5)
Marital Status	
Single	3,439 (51.5)
Married	3,245 (48.5)
Monthly Household Income (RS)	
<15,000	2,398 (35.9)
15,000–3,000	2099 (31.4)
30,001–50,000	1,047 (15.7)
>50,000	1,140 (17.0)
Province	
Punjab	2,431 (36.4)
Sindh	2009 (30.1)
KPK	1,325 (19.8)
Baluchistan	919 (13.7)

calculated as zero. A cumulative score of the seven knowledge items on antibiotics and the four items on MDR was derived in the same manner. The cut point of ≥3 is considered to be good knowledge for the knowledge about antibiotic as it was also chosen in the previous studies that those who scored more than mean were considered in good range. A complete questionnaire is subjected to the analysis those with the missing data were excluded in screening phase. Percentages for each item were calculated and the chi squared statistic was used to check significant differences between demographic groups. $p < 0.05$ was considered significant.

Ethics Approval

The research was carried out in accordance with the tenets of the Declaration of Helsinki and was approved by the Medical Research Ethics Committee of Xi'an Jiaotong University, Shaanxi, China, approved reference number (XJTMD11-2020). Respondents who were literate provided a signed consent form and for those who were not literate, the data collector signed the form on their behalf after explaining the content of the form.

RESULTS

General Characteristics of the Respondents

Out of 7,631 individuals who were approached for the study, 6,684 (87.6%) completed questionnaire items on antibiotic use and MDR pathogens. The mean age (± standard deviation) of the respondents was 32.97 (10.8) years, 4,746 (71.0%) were male, 772 (11.5%) had education above post-graduation and 2,833 (42.4%) resided in rural areas (**Table 1**).

Knowledge About Antibiotics and MDR Pathogens

The mean (± standard deviation) of the knowledge score of antibiotic use was 2.51 (1.80) and 2,260 (39.8%) individuals scored above the mean (≥3). Few participants provided correct answers to the questions about antibiotics, and those tended to be urban residents and male showed significant higher knowledge ($p < 0.001$). Approximately half of the respondents correctly answered the question about antibiotic resistance. **Supplementary Table S1** lists details about respondents and antibiotic use and **Supplementary Table S2** responds to the answers of the participants regarding the attitude. The mean (± standard deviation) of the MDR knowledge score was 1.98 (1.86). Almost one third (32.7%) of participants correctly answered the question regarding whether MDR pathogens could only infect them in a hospital, and tended to be urban residents and male. **Supplementary Table S3** lists details about respondents and MDR pathogens. **Supplementary Tables S1, S2, S3** are presented in supplementary material.

Exposure to Antibiotics and MDR Pathogen

Fifty-four percent of respondents (3,611) reported that they were prescribed antibiotics within the preceding 6 months, with a significantly higher proportion of participants from Sindh (1,274 or 35.3%) than Khyber Pakhtunkhwa (13.1%, $p < 0.001$). Of the 3,611 who received antibiotics, 855 (23.7%) were indicated for cough, 497 (13.8%) for a sore throat, 335 (9.3%) for ear ache, 665 (18.4%) for a burning sensation during urination, 667 (18.4%) for wounds or soft tissue inflammation, and 677 (18.5%) for other reasons. Almost two thirds (2,332 or 64.5%) of those who were prescribed antibiotics stopped the therapy before completion, because 433 (18.6%) felt better, 544 (23.3%) were worried about side effects, 78 (3.3%) experienced a side effect, 455 (19.5%) forgot to take the medication, 211 (9.0%) experienced "too much stress," and 611 (26.2%) for other reasons. Almost two thirds 4,211 (63%) of all participants had heard of MDR pathogens, 7.3% 488)

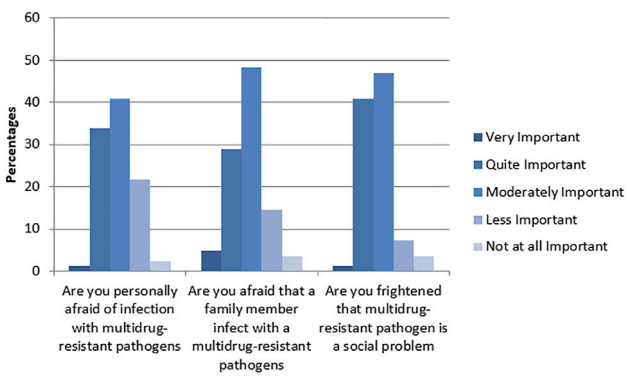

FIGURE 3 | Fears of individuals regarding MDR pathogen.

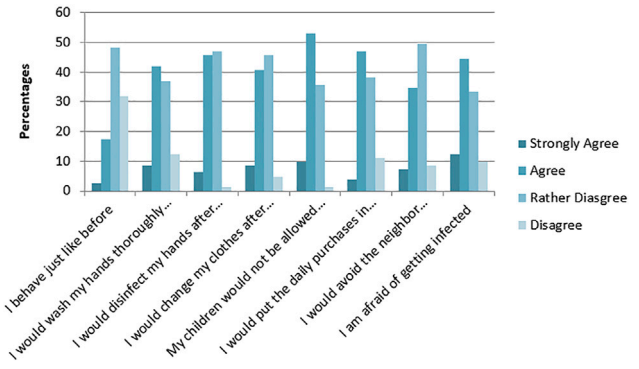

FIGURE 4 | Response to case scenario one.

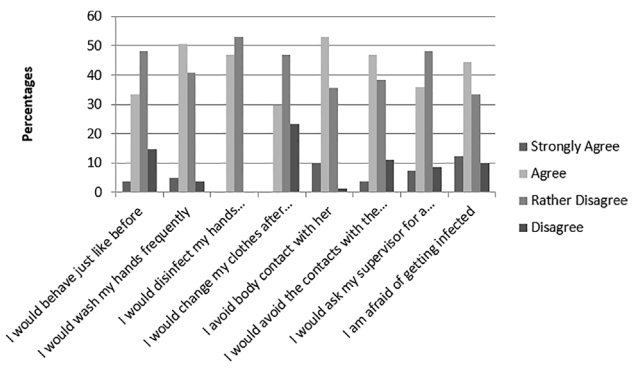

FIGURE 5 | Responses to case scenarios 2.

reported that they knew an individual who had tested positive for an MDR pathogen, and 12% (802) reported that they themselves had tested positive for an MDR pathogen once in their lifetime. **Figure 3** illustrates the fears of respondents regarding MDR pathogens.

Attitudes and Practices Regarding Antibiotic Use and MDR Pathogens

Almost half of the participants (47.6% or 3,181) reported sharing medications with family members and 35.8% 2,393) reported that they had antibiotics at home to use when necessary. MDR pathogen was perceived as an important topic by (4,010) 60.1% of respondents (**Table 2**). In terms of the responsibility to halt the spread of MDR pathogens in the healthcare sector, 30.9% (2065) of the participants thought that it rested with healthcare workers, 2,239 or 33.5% thought that it was the responsibility of everyone, and 1,430 or 21.4% believed that political administrators were responsible for halting the spread. Responsibility for reductions in antibiotic use in livestock breeding was attributed to farmers (23.6% or 1,564), political administrators (1,430 or 21.4%), and consumers (795 or 11.9%). One quarter of respondents 1,678 (25.1%) agreed that they would be willing to spend more money on meat if this could reduce antibiotic use in livestock (**Table 3**)

Case Scenarios

The first scenario involved an aged neighbor hospitalized with an MDR pathogen infection and the second scenario involved a coworker testing positive for an MDR pathogen. For the first scenario, half of the respondents demonstrated good hygiene practices: 50.6% would wash their hands, 51.8% would disinfect their hands, 49.3% would change clothes after interacting with the neighbor, and 41.8% would avoid the neighbor completely (**Figure 4**). For the second scenario, 55.6% would wash their hands, 46.9% would disinfect their hands, 43.2% would avoid the coworker completely, and 29.6% would change clothes after interacting with the coworker (**Figure 5**).

DISCUSSION

In this study, we assessed the knowledge and opinions of the general public in Pakistan about antibiotic use and MDR pathogens by interviewing the participants. Individuals showed poor knowledge of antibiotic use and poor medication adherence. Similarly, knowledge about MDR pathogens was scant, but fear of the effects of MDR pathogens was more pronounced.

More than half had been prescribed antibiotics in the past 6 months, a lower percentage reported for the United Kingdom (38%) and Germany (Holstiege et al., 2020). The main indications for prescription in the present study were cough and sore throat, similar to the indications cited in a report from Germany (Holstiege et al., 2020) and a previous study in Pakistan (Gillani et al., 2021). Upper respiratory infections are most

TABLE 2 | Causes you think important for distributions of MDR pathogens.

Statement	Very important	Quite important	Moderately important	Less important	Not important	Don't know
Improper antibiotic intake in population	410 (6.1)	1,403 (21.0)	829 (12.4)	745 (11.1)	825 (12.3)	2,472 (37.0)
Improper use of antibiotics in livestock breeding	409 (6.1)	1,234 (18.5)	663 (9.9)	742 (11.1)	743 (11.1)	2,893 (43.3)
Lacking hygiene in medical sector in general	409 (6.1)	1811 (27.1)	1,075 (16.1)	745 (11.1)	826 (12.3)	1818 (27.1)
Lacking hand hygiene from medical healthcare workers	83 (1.2)	249 (3.7)	744 (11.1)	1,481 (22.2)	2,145 (32.1)	1982 (29.7)
Lacking hand hygiene in society	497 (7.4)	577 (8.6)	662 (9.9)	1,401 (21.0)	1,402 (21.0)	2,145 (32.1)
Lacking bed capacity in hospitals	409 (6.1)	904 (13.5)	497 (7.4)	580 (8.7)	743 (11.1)	3,551 (53.1)
Too less effective medicaments	402 (6.0)	1,653 (24.7)	826 (12.4)	745 (11.1)	745 (11.1)	2,315 (34.6)

TABLE 3 | Different stakeholders' role to control the antibiotic resistance.

Statement	Totally agree	Agree	Rather disagree	Disagree	Don't know
Politicians are responsible for reducing the use of antibiotics in livestock breeding	477 (7.1)	953 (14.3)	1830 (27.4)	1,591 (23.8)	1833 (27.4)
Farmers are responsible for reducing the use of antibiotics in livestock breeding	479 (7.1)	1,033 (15.5)	1988 (29.7)	1830 (27.4)	1,354 (20.3)
Consumers are responsible for reducing the use of antibiotics in livestock breeding	793 (11.9)	0 (0.0)	2,228 (33.3)	1751 (26.2)	1912 (28.6)
I am willing to spend more money for meat (comparable with costs for organic products) if this leads to reducing the use of antibiotics	239 (3.6)	1,437 (21.5)	1,669 (25.0)	1,511 (23.6)	1828 (27.3)
The following three questions concerns who is responsible to limit the spread of antibiotic resistant pathogen on the healthcare system					
Each individual has a responsibility, to correctly take antibiotics, to reduce the spread of multidrug-resistant pathogens	639 (9.6)	1,595 (23.9)	1,430 (21.4)	1,431 (21.4)	1,589 (23.8)
Doctors and health care staff are responsible for reducing /combating spread of multidrug-resistant pathogens in the healthcare system	555 (8.3)	1,510 (22.6)	1912 (28.6)	1,435 (21.5)	1,272 (19.0)
Politicians are responsible for reducing/combating spread of multidrug-resistant pathogens in the healthcare system	478 (7.1)	954 (14.3)	1991 (29.8)	1,430 (21.4)	1831 (27.4)

commonly caused by viruses, and international health agencies recommend restrictive measures in antibiotic use so as to prevent AMR (Shaikhan et al., 2018; Gulliford et al., 2019). The knowledge scores for antibiotic use were poor, lower than scores in the previous study in Pakistan (Gillani et al., 2021) but similar to those of studies in other developing nations (Seid and Hussen, 2018; Teixeira Rodrigues et al., 2019).

In the present study, 63% of participants had heard about MDR pathogens, lower than the percentage reported by a study in Germany (94.9%) and in Scotland (86%) (Raupach-Rosin et al., 2019; Tonna et al., 2019). Very few of our respondents reported having been diagnosed with MDR pathogens (12%) or knowing someone infected with an MDR pathogen (7.3%), unlike the 42.7% reported to be acquainted with a person diagnosed with MDR pathogen in Germany or the 32.0% reported to be acquainted with a person diagnosed with methicillin-resistant *Staphylococcus aureus* in Scotland (Raupach-Rosin et al., 2019; Tonna et al., 2019).

We did not find a significant difference in antibiotic use scores between urban and rural residents, in contrast with the previous study in Pakistan (Gillani et al., 2021) or with outcomes reported by a study in China (Wang et al., 2019), both of which reported poor knowledge of antibiotic use among rural residents. Also, it was observed in the study from Croatia where urban parents were more aware (Farkaš et al., 2019) In addition, we did not find significant differences in our study population in terms of education level and knowledge, in contrast with findings from the study in Germany (Raupach-Rosin et al., 2019). Our study however suggested the gender significant difference in most of the knowledge items which is in consistent with the previous results in Italy (Bianco et al., 2020). This suggests that information for the general public should be tailored for comprehensibility. Gaps in specific knowledge about the implications of MDR pathogens and existing treatment options have been observed before (Tonna et al., 2019; McClelland et al., 2022). Hence, targeting information to the population and using appropriate media are essential for increasing the public's knowledge of proper antibiotic use and MDR pathogens.

More than half of the participants reported that they were personally concerned about infection with a MDR pathogen, but the answers to the case scenarios illustrated that the majority of individuals exhibited reasonable and non-stigmatizing behavior toward carriers of MDR pathogens in their vicinity. This finding is remarkable, considering that more than half of the participants had stated that they were fearful of contracting MDR pathogens. The percentage of respondents that reported they would avoid the infected person was higher than that reported by Raupach-Rosin and colleagues (Raupach-Rosin et al., 2016). A large number of respondents considered healthcare personnel and political administrators responsible for controlling MDR pathogens, similar to a finding reported previously (Gilbert and Kerridge, 2019).

Strengths and Limitations

The strength of our study is the comparably large sample and the fact that the study population was sampled from the general public. However, because the knowledge of antibiotics and MDR pathogens was assessed by closed-ended questions, respondents may have selected the most favorable answers rather than accurate ones, and therefore, a qualitative approach might be more suitable to reveal misconceptions. Our study faced some limitations as well such as we selected the districts randomly and targeted the cities, village and participants from the city conveniently. Also, that participants may have given socially desirable answers, rather than actual practices.

CONCLUSION

General knowledge about antibiotic use and MDR pathogens was poor in the population we sampled. However, there was a high awareness about antibiotic resistance as a public health problem, although only a few respondents reported to have been personally affected by MDR. Therefore, information about the implications of MDR pathogens should be made available for the general public. Information campaigns about correct antibiotic use could increase knowledge, thereby improving appropriate practices in antibiotic use and resistance in both humans and livestock. The data in this study provide new information and may serve as the basis for development of interventional programs and policies.

Recommendations

We recommend strict government policies should be implemented at hospital level and community pharmacy level to prescribe and dispense antibiotics in the presence of qualified physician and pharmacist. Standard guidelines and proper trainings should be provided to physicians and other health care providers to promote the safe prescribing of antibiotics to avoid the antimicrobial resistance. Community based interventions and programs should be initiated to increase the awareness about antibiotic resistant among general population. Government should increase the awareness and initiate the campaigns on electronic media for safe use of antibiotic in general population. Collective efforts of government, stakeholders, health care providers, patients, researchers, pharmaceuticals companies, policy makers and drug regulatory bodies will help to combat the life threatening scenario of antimicrobial resistant around the globe.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research Ethics Committee of Xi'an Jiaotong University, Shaanxi, China (XJTMD11-2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HA, AG, WJ conceptualized the study. HA, AG, HA, SG, JA and AA collected the data. HA and AG analyzed the data. HA, AG, and RA wrote the initial draft. YF supervised the whole study.

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SUPPLEMENTARY MATERIAL

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Immune Checkpoint Inhibitors Plus an Anti-VEGF Antibody as the First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis and Cost-Effectiveness Analysis

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Background: Sintilimab + a bevacizumab biosimilar (IBI305) (SB) and atezolizumab + bevacizumab (AB) have been approved for the treatment of unresectable hepatocellular carcinoma (HCC). At present, oncologists and their patients remain indecisive on their preferred treatment regime. Therefore, assessing their efficacy *via* a network meta-analysis and determining their comparative cost-effectiveness is necessary.

Objective: To evaluate the cost-effectiveness of SB and AB compared with sorafenib alone for the treatment of unresectable HCC.

Materials and Methods: The data used in our analysis were obtained from patients in ORIENT-32 and IMbrave150 phase III randomized clinical trials. A Bayesian network meta-analysis and cost-effectiveness analysis that included 1,072 patients were performed in this study. A partitioned survival model was applied to the patients with unresectable HCC. The model was designed with a 15-year time horizon, 1-month cycle, and 5% discount rate for costs and outcomes. In China, an incremental cost-effectiveness ratio (ICER) value of less than $33,500 (three times the GDP per capita in 2020) per quality-adjusted life-year (QALY) is considered cost-effective. The influence of parameter uncertainty on the results was verified by one-way deterministic sensitivity analysis and probability sensitivity analysis. Furthermore, scenario analyses of the patient assistance program (PAP) were conducted to explore the cost-effectiveness of SB and AB.

Results: For the model of 1,072 patients, treatment with SB produced an additional 0.617 QALYs compared with sorafenib, resulting in an ICER of $39,766.86/QALY. Similarly, treatment with AB produced an additional 0.596 QALYs compared with sorafenib, resulting in an ICER of $103,037.66/QALY. The probability sensitivity analysis showed that when the willingness-to-pay (WTP) threshold was $33,500/QALY, the cost-effectiveness of SB and AB was 15.4 and 0.4%, respectively. However, in the scenario analyses, the probability of SB and AB regimens being cost-effective was 65.4 and 15.8%, respectively, at a WTP of $33,500/QALY.

Conclusion: The findings from our study showed that sintilimab + a bevacizumab biosimilar is a cost-effective regimen compared with sorafenib as the first-line therapy for unresectable HCC in China at a $33,500 WTP threshold if sintilimab PAP is considered. However, the atezolizumab + bevacizumab regimen is not cost-effective whether atezolizumab PAP is considered or not.

Keywords: network meta-analysis, unresectable hepatocellular carcinoma, HCC, cost-effectiveness, immune checkpoint inhibitors plus an anti-VEGF antibody

1 INTRODUCTION

Primary liver cancer is the fourth leading cause of cancer-related death worldwide. In 2018, an estimated 781,631 deaths occurred globally and 368,960 deaths occurred in China, accounting for approximately 50% of the deaths worldwide (Bray et al., 2018; Valery et al., 2018). Hepatocellular carcinoma (HCC) accounts for approximately 80% of liver cancers and has a great impact on society and the economy (Perz et al., 2006). Unfortunately, only 30–40% of patients are diagnosed at an early stage and receive effective treatment (Forner et al., 2018). Over the past decade, new therapeutics have significantly improved the resectability of liver metastases and prolonged survival in advanced unresectable HCC. Such therapies include sorafenib and lenvatinib as first-line treatments, and regorafenib, cabozantinib, and ramucirumab as second-line treatments (Kong et al., 2020).

Liver cancer is often complicated by liver inflammation that exacerbates this condition. The combination of anti-PD-1 and anti-PD-L1 monotherapy or in combination with molecular targeted therapy, other immunomodulators, or cytotoxic chemotherapy has contributed to the progress in this area (Finn et al., 2020a; Finn et al., 2020b; Yu et al., 2020; Yau et al., 2020; Ren et al., 2021; Yau et al., 2022). Reliable predictors of immune checkpoint inhibitor (ICI) response are essential to allow appropriate stratification and selection of HCC patients to obtain more benefits from immunotherapy (Rizzo and Ricci, 2022). Of these, combined anti-vascular endothelial growth factor (anti-VEGF) and immunotherapies are expected to resolve the issues associated with the immunosuppressive tumor microenvironment of HCC (Fukumura et al., 2018).

Two phase III clinical trials [ORIENT-32 (Ren et al., 2021) and IMbrave150 (Finn et al., 2020a)] have shown a survival advantage of ICIs combined with anti-VEGF therapy compared with the standard treatment (sorafenib) for unresectable HCC. In the ORIENT-32 trial, sintilimab + a bevacizumab biosimilar (IBI305) (SB) may improve the overall survival (OS) [hazard ratio (HR) 0.57, 95% confidence interval (CI) (0.43–0.75)], and the median progression-free survival (PFS) time of patients was 4.6 months. In the IMbrave150 trial, atezolizumab + bevacizumab (AB) led to a higher OS rate (HR 0.58, 95% CI (0.65–0.98)], and the median PFS time in AB was 6.8 months.

AB has been approved by the US Food and Drug Administration (FDA) and the China National Medical Products Administration (NMPA) for the up-front treatment of patients with unresectable or metastatic HCC on May 29, 2020, and October 28, 2020, respectively (Genentech, 2022; Roche, 2022). However, because the ORIENT-32 trial only recruited Chinese patients, the SB regimen was only approved by NMPA for the first-line treatment of patients with unresectable or metastatic HCC on June 25, 2021 (The drug approval, 2022) and no other countries approved this regimen.

Thus, ICIs combined with an anti-VEGF antibody opened a new age for the unresectable HCC. Hence, from the perspective of the Chinese healthcare system, we examined the cost-effectiveness of two schemes (SB and AB vs. sorafenib) in the first-line therapy of unresectable HCC.

2 MATERIALS AND METHODS

The patient baseline characteristics of ORIENT-32 and the IMbrave 150 trials are given in **Supplementary Table S1**. The ORIENT-32 trial (NCT03794440) started in February 2019 and confirmed the efficacy and safety of SB in advanced or unresectable HCC. The IMbrave150 trial (NCT03434379) started in March 2018 and confirmed the efficacy and safety of AB in metastatic advanced or unresectable HCC.

In this study, we used the method of cost-effectiveness analysis (CEA). In the CEA, decision-making is based on an incremental analysis. An incremental analysis compares the costs and results of the intervention with those of the comparator. The intervention will become the strictly dominant treatment scheme when it has a lower cost and better outcome than the comparator. In contrast, the interventions will be strictly subordinated to the treatment scheme when it has a higher cost and poorer outcome compared with the comparator. In circumstances where the intervention treatment scheme has a higher cost and better outcome than the comparator, the incremental cost-effectiveness ratio (ICER), that is, the ratio of the difference in costs to the difference in outcomes between the two regimens, needs to be calculated. If the ICER is smaller than or equal to the threshold value, the intervention is a more cost-effective choice than the comparator; if the ICER is larger than the threshold value, the intervention is not a cost-effective choice compared with the comparator (Liu et al., 2020). Quality-adjusted life-years (QALYs) are recommended as indicators for the outcome measurement. The formula for ICER is as follows (Cai et al., 2019):

$$\mathrm{ICER} = (C_A - C_B)/(\mathrm{QALY}_A - \mathrm{QALY}_B) = \Delta C/\Delta \mathrm{QALY},$$

where C_i and QALY_i represent the patient's overall cost and effectiveness of treatment (i = A) or comparator (i = B).

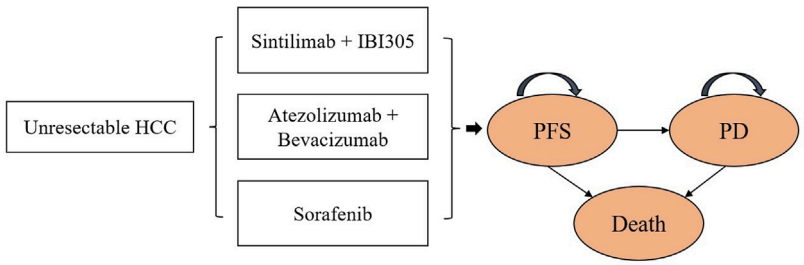

FIGURE 1 | Partitioned survival model. HCC, unresectable hepatocellular carcinoma; PFS, progression-free survival; PD, progressive disease.

2.1 Network Meta-Analysis

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for eligible publications, selecting manuscripts published up to June 25, 2021. The Clinicaltrials.gov database was also searched. The search terms used were, "Atezolizumab," "Sintilimab," "Pembrolizumab," "Novoliumab," "Camrelizumab," "Durvalumab," "Toripalimab," "Tislelizumab," and "Unresectable hepatocellular carcinoma" as medical subject keywords. The details of the filters are shown in **Supplementary Figure S1**. Multiple reports of the same clinical trial and trials which did not contain a control group, or those which were non-randomized or included other interventions, were excluded from this analysis.

We implemented the Bayesian network meta-analysis in R, version 4.0.5, with the package of "gemtc" to obtain the HRs for OS and PFS between SB, AB, and sorafenib. The pooled HRs for OS and PFS were used for the cost-effectiveness analysis. The risk of bias for the clinical trials was assessed using RevMan, version 5.4. Owing to the lack of data to assess inter-trial heterogeneity, we applied a fixed-effects model for the analysis (Su et al., 2020).

2.2 Model Structure

A partitioned survival model of unresectable HCC was exploited in Microsoft Excel to calculate the healthcare costs and health outcomes of the following three strategies: SB, AB, and sorafenib. The model included three health states: progression-free survival (PFS), progressive disease (PD), and death (**Figure 1**).

In the cost-effectiveness analysis, we compared the cost-effectiveness of SB and AB against sorafenib (reference strategy). The model cycle length was 1 month and the time horizon was 15 years. Both costs and utilities were discounted at a rate of 5% per year (Liu et al., 2020). We measured the overall costs, QALYs, life-years (LYs), and ICERs of the test therapies and references. The willingness-to-pay (WTP) threshold for China was $33,500 per QALY (three times the GDP per capita in 2020). The initial state is assumed to be PFS and death is assumed to be the absorbing state.

2.3 Efficacy Estimates

Efficacy should be based on the best available evidence. For newer drugs, clinical efficacy data from a randomized controlled trial (RCT) are preferred when available and applicable (Liu et al., 2020). The co-primary endpoints of ORIENT-32 and IMbrave150 were OS and PFS, respectively, as assessed by an independent review facility using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Finn et al., 2020a; Ren et al., 2021). To construct the survival model, the GetData Graph Digitizer (version 2.26) was used to extract graphic data from the K–M curves (OS and PFS curves) of the two trials (ORIENT-32 and IMbrave150). Fitting of the parameter model requires time-event individual patient data (IPD) using the approach suggested by Guyot et al. (2012) By fitting the IPD, the parametric regression model method was chosen among the gamma, Gompertz, Weibull, exponential, log-normal, and log-logistic distributions, based on the Akaike information criterion (AIC) value. The reproduced digitized Kaplan–Meier (KM) curves are shown in **Supplementary Figures S2, S3**. We pooled the virtual IPD in the sorafenib arm of the two clinical trials and fitted the OS and PFS data by log-logistic and log-normal distributions according to the outcomes of the goodness of fit of the AIC statistic (**Supplementary Figure S4**). The final parametric model is shown in **Supplementary Table S2**. The model-fitted K–M curves are shown in **Supplementary Figure S5**.

2.4 Clinical Inputs

Based on the ORIENT-32 and IMbrave 150 trials, sorafenib was prescribed at a dose of 400 mg orally, twice daily (Finn et al., 2020a; Ren et al., 2021). Patients in the SB group received 200 mg of sintilimab and 15 mg/kg of IBI305 intravenously every 3 weeks, and tumor assessments were conducted by contrast magnetic resonance imaging (MRI) or computed tomography (CT) at the baseline and every 6 weeks until week 48, and then every 12 weeks (Ren et al., 2021). Patients in the AB group were administered 1,200 mg atezolizumab and 15 mg/kg bevacizumab intravenously every 3 weeks, and tumor assessments were assessed by MRI or CT at the baseline and every 6 weeks until week 54, and then every 9 weeks thereafter (Finn et al., 2020a). The drug dosages were calculated using an average weight of 60 kg (Wen et al., 2021). The SB and AB treatments were continued until unacceptable toxicity or disease progression occurred, or until 2 years of follow-up. Treatment with sorafenib was continued until unacceptable toxicity or disease progression was observed. The percentages of SB, AB, and sorafenib patients receiving second-line therapy were 29, 35, and 57%, respectively (Finn et al., 2020a; Ren et al., 2021). Regorafenib (a tyrosine kinase inhibitor) was approved as a second-line treatment for patients in whom first-line treatment was ineffective (Bruix et al., 2017).

TABLE 1 | Input parameters of the model.

Parameter	Baseline value	Lower limit	Upper limit	Distribution	Source
Survival model of sorafenib					Finn et al. (2020a); Ren et al. (2021)
Log-logistic OS survival model	shape = 1.577 scale = 11.477	ND	ND	ND	Model fitting
Lognormal PFS survival model	meanlog = 1.2942 sdlog = 0.8621	ND	ND	ND	Model fitting
HR for OS (SB vs. sorafenib)	0.570	0.43	0.75	Lognormal	Network meta-analysis
HR for PFS (SB vs. sorafenib)	0.570	0.47	0.70	Lognormal	Network meta-analysis
HR for OS (AB vs. sorafenib)	0.580	0.42	0.79	Lognormal	Network meta-analysis
HR for PFS (AB vs. sorafenib)	0.600	0.47	0.76	Lognormal	Network meta-analysis
Drug cost (per month)					
Sintilimab	1168.16	934.52	1401.79	Gamma	Chinese drug (2021)
IBI305	2141.14	1712.91	2569.37	Gamma	Chinese drug (2021)
Atezolizumab	6738.57	5390.86	8086.29	Gamma	Chinese drug (2021)
Bevacizumab	2773.50	2218.80	3328.20	Gamma	Chinese drug (2021)
Sorafenib	1756.55				
Second-line therapy (per month)	2232.41	1785.93	2678.89	Gamma	Chinese drug (2021)
Percentage receiving second-line treatment					
SB group	29%	23.2%	34.8%	Beta	Ren et al. (2021)
AB group	35%	28%	42%	Beta	Finn et al. (2020a)
Sorafenib	57%	45.6%	68.4%	Beta	Finn et al. (2020a); Ren et al. (2021)
Test of AB (per month)	179.53	143.62	215.44	Gamma	Wen et al. (2021)
Test of SB (per month)	179.53	143.62	215.44	Gamma	Assumed equal to Test of AB (per month)
Test of sorafenib (per month)	167.56	134.05	201.07	Gamma	Wen et al. (2021)
Cost of follow-up in PFS (per month)	114.00	91.20	136.80	Gamma	Hou and Wu (2020)
Cost of follow-up in PD (per month)	210.00	168.00	252.00	Gamma	Hou and Wu (2020)
AEs cost (per event)					
Hypertension	16.50	13.20	19.80	Gamma	Wu et al. (2012)
Proteinuria	147.40	117.92	176.88	Gamma	Wu et al. (2012)
Nausea	56.60	45.28	67.92	Gamma	Wu et al. (2012)
Thrombocytopenia	4536.20	3628.96	5443.44	Gamma	Wu et al. (2012)
Diarrhea	188	150.4	225.6	Gamma	Hou and Wu (2020)
Palmar-plantar erythrodysesthesia syndrome	15	12	18	Gamma	Hou and Wu (2020)
AST	357.00	285.60	428.40	Gamma	Hou and Wu (2020)
ALT	357.00	285.60	428.40	Gamma	Hou and Wu (2020)
Health utility					
PFS state	0.76	0.61	0.91	Beta	Rabin and de Charro (2001)
PD state	0.68	0.54	0.82	Beta	Rabin and de Charro (2001)
Disutility due to AEs (grade ≥ 3)	0.16	0.13	0.19	Beta	Amdahl et al. (2016)
Death state	0.00	0.00	0.00	Beta	

OS, overall survival; PFS, progression-free survival; PD, progressive disease; HRs, hazard ratios; AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; SB, sintilimab plus a bevacizumab biosimilar (IBI305); AB, atezolizumab plus bevacizumab; ND, not determined.

TABLE 2 | Incidence of adverse events.

Grade ≥3 AEs	SB	AB	Sorafenib
Hypertension	0.14	0.152	0.088
Proteinuria	0.05	0.03	0.012
Nausea	0.01	0.003	0.018
Thrombocytopenia	0.08	0.033	0.006
Diarrhea	0.02	0.018	0.038
Palmar-plantar erythrodysesthesia syndrome	0	0	0.103
AST	0.02	0.07	0.053
ALT	0.01	0.036	0.021

ALT, alanine transaminase; AST, aspartate transaminase; AEs, adverse events; SB, sintilimab plus a bevacizumab biosimilar (IBI305); AB, atezolizumab plus bevacizumab.

The analysis included grade three or four adverse events (AEs) with greater clinical influence in the ORIENT-32 and IMbrave 150 trials: hypertension, proteinuria, nausea, thrombocytopenia, diarrhea, palmar-plantar erythrodysesthesia syndrome, increased aspartate aminotransferase, and increased alanine aminotransferase (Finn et al., 2020a; Ren et al., 2021).

2.5 Cost Inputs

In this study, we only considered direct medical costs, including the drug costs of sintilimab, atezolizumab, bevacizumab, and its similar, test costs, grade three or four AEs costs, follow-up costs, and subsequent costs after disease progression (**Table 1**) (Wu et al., 2012; Hou and Wu, 2020; Chinese drug, 2021; Wen et al., 2021). The drug costs were estimated from the local bid-winning price (Chinese drug, 2021). The incidence rates of major grade three or four AEs for different treatments are shown in **Table 2**. All costs were converted into US dollars using the exchange rate: $1 = ¥6.49.

The costs of managing AEs per event in China were extracted from the published literature (Wu et al., 2012; Hou and Wu, 2020). We assumed that AEs occurred during the first model cycle.

Because of the high price of PD-1 and PD-L1, they are not affordable for many patients in China, and the sintilimab and atezolizumab patient assistance program (PAP) has been implemented for Chinese patients. In this program, sintilimab is paid for by the patients for the first two cycles, followed by donations for two cycles by Innovent Biologics (the producer of sintilimab); if the patients are still alive, they pay for the next five cycles, with the remaining cycles being funded by Innovent Biologics. Atezolizumab is paid for by the patients for the first two cycles, followed by donations for three cycles by F. Hoffmann-La Roche (the producer of atezolizumab); if the patients are still alive, they pay for the next two cycles, followed by donations for the remaining cycles by F. Hoffmann-La Roche. Therefore, the impact of PAP was evaluated using a scenario analysis.

2.6 Utilities Estimates

The utility score, ranging from 0 to 1, reflects the level of social functioning and physical, mental, and disease-related health states, where 0 represents the worst health status or death, and 1 represents the best health status. The utility estimates of PFS and PD states associated with advanced HCC were 0.76 and 0.68, respectively (**Table 1**) (Rabin and de Charro, 2001). Disutility values of grade three or four AEs were considered in the analysis (**Table 1**) (Amdahl et al., 2016). We assumed that AEs occurred during the first model cycle. Duration-adjusted disutility was subtracted from baseline PFS utility.

2.7 Sensitivity Analyses

In the sensitivity analysis, we conducted a series of uncertainty analyses of the variables listed in **Table 1**. The variables in this study included costs, utilities, hazard ratios (HR, from the network meta-analysis), proportion of patients, and probability.

One-way deterministic sensitivity analyses (DSAs) were performed by varying a single input to assess the robustness of the model results. The model parameters were varied by 95% CI if such information was reported in the source or varied by ± 20% from the base case values if the information was unavailable (**Table 1**) (Wen et al., 2021).

Probabilistic sensitivity analysis (PSA) was implemented using 1,000 Monte Carlo simulations. In each iteration, the model parameters were randomly extracted from the prescriptive distributions. The log-normal distribution was set for the variables of hazard ratio parameters, gamma distribution was set for the variables of cost parameters, and beta distribution was set for variables such as proportion of patients, probability, and utility value. The results are presented as a cost-effectiveness acceptability curve (CEAC).

In addition, one-way DSA and PSA were used to assess PAP scenarios.

3 RESULTS

3.1 Network Meta-Analysis

Through a database search, 296 records were screened, and two phase III randomized clinical trials (ORIENT-32 and IMbrave150) with 1,072 patients were included in the network meta-analysis. A model schematic for the network meta-analysis is shown in **Supplementary Figure S6**. In the ORIENT-32 trial, 571 patients were administered SB (N = 380) or sorafenib (N = 191); in the IMbrave150 trial, 501 patients were administered AB (N = 336) or sorafenib (N = 165). The risk of bias is shown in **Supplementary Figure S7**. From the indirect comparisons of the network meta-analysis, both SB (HR 0.57, 95% CI, 0.43–0.75) and AB (HR 0.58, 95% CI, 0.42–0.79) could lead to great improvements in OS compared with sorafenib-related survival. The HRs for PFS of SB and AB, when compared with the sorafenib treatment, were 0.57 (95% CI, 0.47–0.70) and 0.60 (95% CI, 0.47–0.76), respectively.

TABLE 3 | Results of the base-case analysis.

Strategy	Cost ($)	LYs	QALYs	ICER
Sorafenib	18,567.66	1.59	1.11	
SB	43,109.99	2.47	1.73	39,766.86
AB	79,965.01	2.45	1.71	103,037.66

SB, sintilimab plus a bevacizumab biosimilar (IBI305); AB, atezolizumab plus bevacizumab; QALYs, quality-adjusted life years; LYs, life-years; ICER, incremental cost-effectiveness ratio.

3.2 Cost-Effectiveness Analysis

3.2.1 Base-Case Analyses

For the model of 1,072 patients, SB treatment produced an additional 0.617 QALYs compared with sorafenib, resulting in an ICER of $39,766.86/QALY, and AB treatment produced an additional 0.596 QALYs compared with sorafenib, resulting in an ICER of $103,037.66/QALY (**Table 3**).

3.2.2 Sensitivity Analyses

In this study, the results shown in the tornado diagram are the ICER values (**Figure 2**). The results indicated that the HRs of OS for both SB and AB regimens against sorafenib were the most sensitive parameters, and consequently, these had the most prominent impact on ICERs. When comparing SB with sorafenib, the results were also sensitive to the utility of PD and the price of the bevacizumab biosimilar, while the HRs of PFS and the price of atezolizumab were sensitive when AB was compared with sorafenib. As a result, the ICER value of SB versus sorafenib was less than the WTP threshold of $33,500 per additional QALY when the lower boundary of the HR (0.43) for OS was used or when the price of bevacizumab biosimilar and sintilimab was discounted by 50%. However, regardless of how the parameters changed, the ICER value of AB versus sorafenib therapy was not within the WTP ($33,500/QALY) threshold.

In the PSA, CEAC (**Figure 3**) showed that the probability of SB therapy being cost-effective was 16% compared with sorafenib at a WTP threshold of $33,500/QALY, and the corresponding probability of AB was less than 1% when compared with sorafenib. The incremental cost-effectiveness scatterplot is shown in **Figure 4**.

3.3 Scenario Analysis

Because of the high price of PD-1 and PD-L1, they are not affordable for many patients in China; therefore, sintilimab and

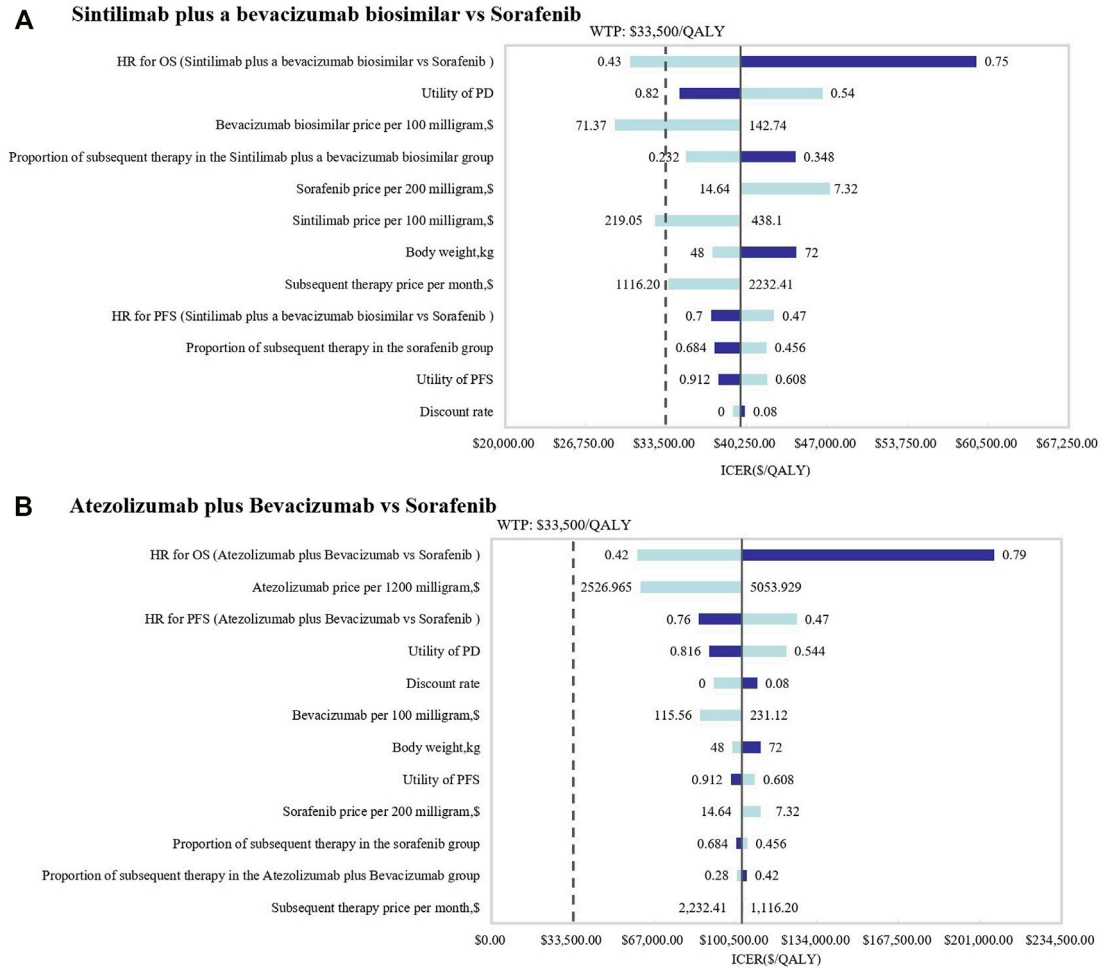

FIGURE 2 | Tornado diagrams of one-way deterministic sensitivity analyses. One-way deterministic sensitivity analyses of **(A)** SB and **(B)** AB in comparison with sorafenib.

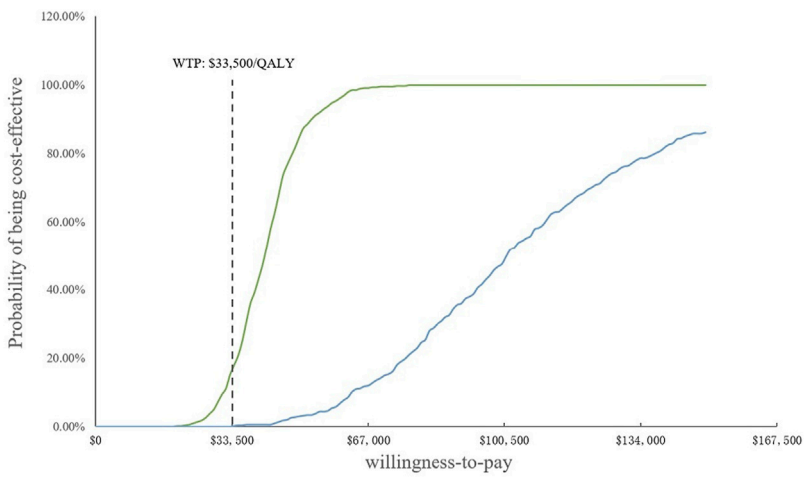

FIGURE 3 | Cost-effectiveness acceptability curves. WTP, willingness-to-pay; QALY, quality-adjusted life year.

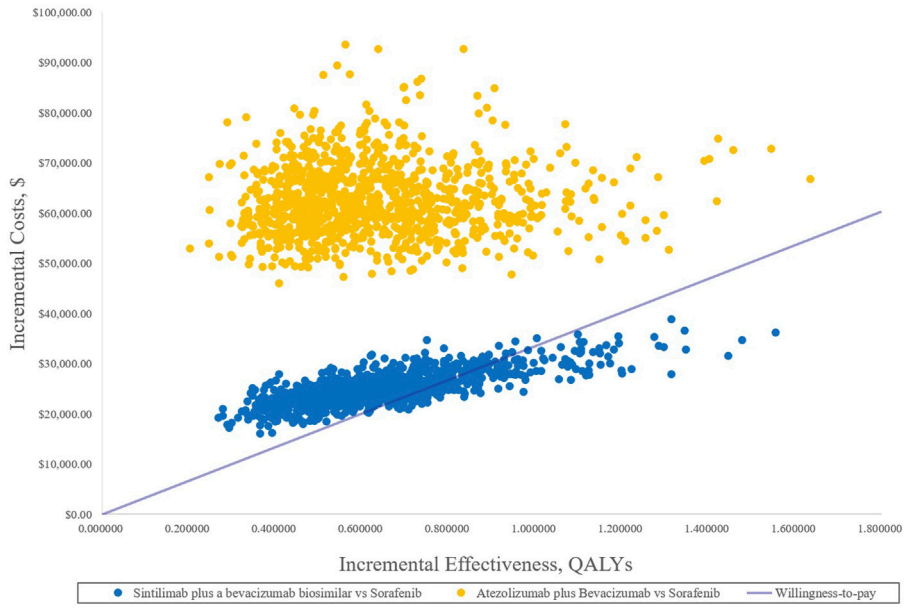

FIGURE 4 | Incremental cost-effectiveness scatterplots. QALYs, quality-adjusted life years.

atezolizumab PAP were implemented for Chinese patients. The specific scheme is described in the methodology (2.3.2). The one-way DSA of scenario analysis revealed that the HRs of the OS of both SB and AB regimens against sorafenib were the most sensitive parameters, and the ones which had the most prominent influence on the ICERs. When SB versus sorafenib, the results were also sensitive to the price of the bevacizumab biosimilar and the proportion of subsequent therapy in the SB regimen, while the HRs of PFS and the price of atezolizumab were sensitive when AB versus sorafenib. The results are shown in the tornado diagram in **Figure 5**. The CEAC of the scenario analysis (**Figure 6**) showed that the likelihood of SB and AB regimens being cost-effective was 76.2 and 30.4%, respectively, compared with sorafenib at a WTP threshold of $33,500/QALY. The incremental cost-effectiveness scatterplot is shown in **Figure 7**.

4 DISCUSSION

Two phase III clinical trials (ORIENT-32 and IMbrave150) revealed a survival advantage of ICIs plus anti-VEGF drugs compared with the standard treatment (sorafenib) for unresectable HCC (Finn et al., 2020a; Ren et al., 2021). At present, there has been no head-to-head clinical trial of SB and AB for the treatment of unresectable HCC. Therefore, in this study, the two treatments were indirectly compared by a network meta-analysis; in addition, a cost-effectiveness comparison between the regimes was conducted. To the best of our knowledge, this is the first study to explore the cost-effectiveness of SB and AB compared with sorafenib for the treatment of unresectable HCC.

In this study, we adopt a partitioned survival model. Before selecting the model, we looked for pharmaco-economic literature and found that more researchers have used the Markov model for unresectable HCC (Zhang et al., 2016; Cai et al., 2020; Wen et al., 2021). However, the Markov model needs to assume and estimate the transition probability. A partitioned survival model does not need to calculate the transition probability; it can be directly derived from the partitioned survival model, which is simpler and easier to calculate and is closer to the actual observed data (Hoyle et al., 2011). The partitioned survival model has been increasingly applied to the pharmaco-economic evaluation of advanced cancer treatments.

Considering the rising medical costs, value-based oncology is worthy of our attention. SB and AB are the leading therapies in the immunotherapy pipeline and have received considerable attention. Our study found that compared with sorafenib, SB improved the effectiveness by 0.617 QALYs, resulting in an ICER of $39,766.86/QALY, and the treatment of AB produced an additional 0.596 QALYs compared with sorafenib, resulting in an ICER of $103,037.66. The ICERs of both SB and AB, compared with sorafenib, exceeded the WTP threshold ($33,500/QALY). In the scenario analysis, we considered PAP, and found that the ICER of SB versus sorafenib ($28,539.82/QALY) was lower than the WTP threshold ($33,500/QALY). However, the ICER of AB versus sorafenib ($40,524.30/QALY) was still higher than the WTP when considering PAP.

In the IMbrave150 trial, compared with sorafenib, AB had a significant effect in patients with unresectable HCC without systemic treatment. However, many scholars have carried out a pharmaco-economic evaluation of AB in the treatment of unresectable HCC, and most of the findings were similar to ours, and showed that AB was not a cost-effective first-line choice for unresectable HCC; however, extreme cost-cutting may change the results (Hou and Wu, 2020; Wen et al., 2021). In the ORIENT-32 trial, SB showed a significant OS and PFS

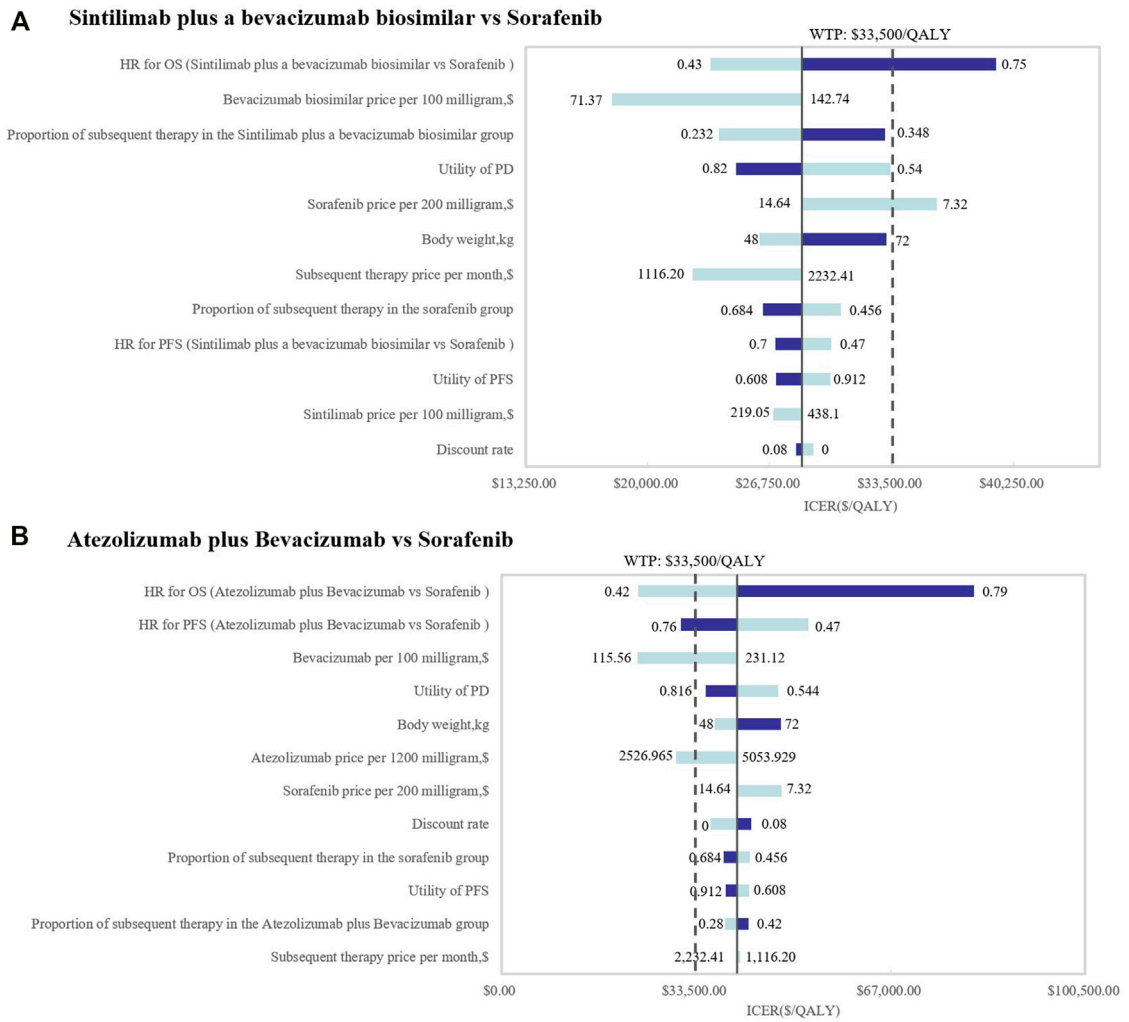

FIGURE 5 | Tornado diagrams of the scenario analysis. One-way deterministic sensitivity analyses of **(A)** SB and **(B)** AB in comparison with sorafenib in the scenario analysis. OS, overall survival; PFS, progression-free survival; HR, hazard ratios; PD, progressive disease; ICER, incremental cost-effectiveness ratio; SB, sintilimab plus a bevacizumab biosimilar (IBI305); AB, atezolizumab plus bevacizumab; WTP, willingness-to-pay; QALY, quality-adjusted life year.

benefit in patients with unresectable HCC. Through the analysis of HR for OS and PFS by network meta-analysis, we found that SB exhibits a slight advantage over AB in terms of curative effect. In terms of cost, the cost of SB is relatively low; therefore, SB is a cost-effective therapeutic regimen if PAP is considered.

Although both are ICIs, there was a huge gap in the cost between sintilimab and atezolizumab because of the following reasons: first, by considering the affordability of Chinese patients, the first price of sintilimab is relatively lower than atezolizumab because sintilimab is first approved by the Chinese government. Second, high reimbursed prices for new cancer medicines, certainly in Europe, have been enhanced by the emotive nature of cancer (Haycox, 2016; Godman et al., 2021). Meanwhile, the notion is that the US federal government is prohibited by law from negotiating drug prices as a result of the 2003 Medicare Prescription Drug, Improvement and Modernization Act (Workman et al., 2017). In addition, there can be high profitability for new cancer medicines as seen before they lose their patents (Godman et al., 2019). Therefore, the high requested/expected prices for new medicines for cancer and orphan diseases mean these two areas dominate new medicines being researched (Global, 2022). The sensitivity analysis also showed that the cost of atezolizumab had a significant impact on the model results, which led to the cost-effectiveness results in China. Thus, when the unit cost of atezolizumab decreased by 80%, the ICER for AB decreased to close to $33,500/QALY.

Our study has some limitations. First, the populations selected in the two RCTs were different: the ORIENT-32 trial recruited participants from the Chinese population and the IMbrave150 trial recruited globally. The survival information of patients by nationality was not presented in the RCT results. Moreover, owing to the lack of head-to-head experimental data, the network meta-analysis could not perform an inconsistency

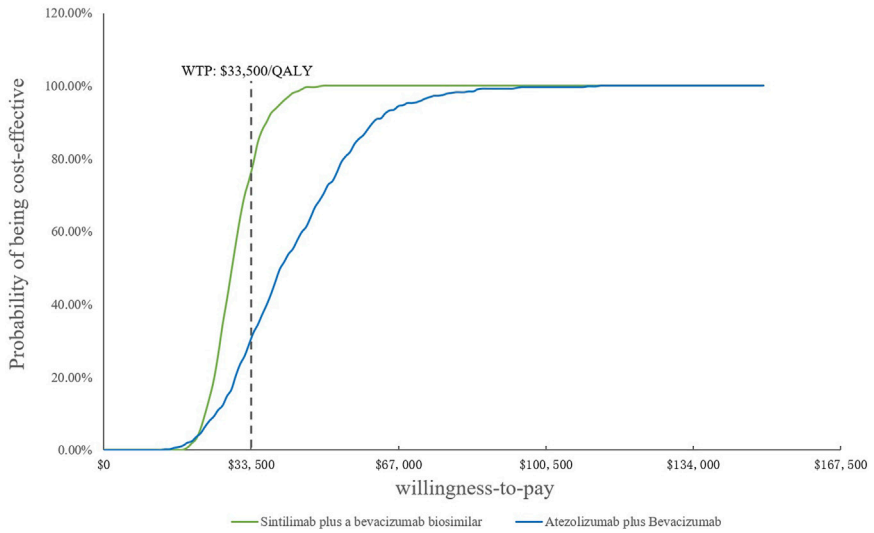

FIGURE 6 | Cost-effectiveness acceptability curves of the scenario analysis. WTP, willingness-to-pay; QALY, quality-adjusted life year.

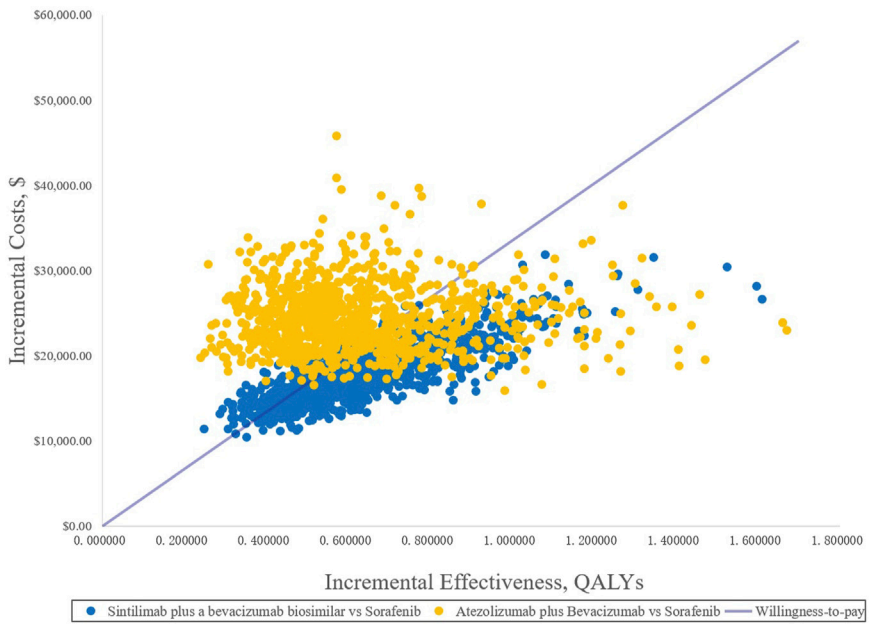

FIGURE 7 | Incremental cost-effectiveness scatterplots of the scenario analysis. QALYs, quality-adjusted life years.

test, so the data might be biased. Second, because SB was approved only in China, the results of this study should be carefully explained when the results are transferred to other regions. Third, our study only included the costs and disutilities of grade three or four AEs, and ignored the costs and disutilities of AEs below grade 3. Fourth, this study extracted the utility values of PFS and PD status from the published literature, which will affect the arithmetic of the clinical efficacy. Fifth, the IPD used in our model was simulated using the algorithm recommended by Guyot et al. (2012). It is generated by time-event data, which deviate slightly from the actual individual patient data. Finally, we did not check the economic outcomes in subgroups, such as the age of the patients, which may have an impact on the results.

5 CONCLUSION

In summary, the findings from our study showed that sintilimab + a bevacizumab biosimilar is a cost-effective regimen compared

with sorafenib as the first-line therapy for unresectable HCC in China at a $33,500 WTP threshold if sintilimab PAP was considered. However, the atezolizumab + bevacizumab regimen is not a cost-effective tactic, regardless of whether atezolizumab PAP is considered.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

LL, BW, and DD were involved in the design of the study. SY, YC, LT, and YH collected the data. SY and YC performed the meta-analysis. DD, BW, and LL performed the economic analysis. LL, BW, and DD wrote the first draft of the manuscript, which was critically revised by LL, SY, YC, LT, YH, BW, and DD. All authors have approved this version for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.891008/full#supplementary-material

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Appropriateness and Associated Factors of Stress Ulcer Prophylaxis for Surgical Inpatients of Orthopedics Department in a Tertiary Hospital: A Cross-Sectional Study

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Background: Stress ulcer prophylaxis (SUP) prescribed in patients admitted to surgical wards with a low risk of stress-related mucosal disease (SRMD) accounted for a considerable proportion of improper use of proton pump inhibitors (PPIs). This study aimed to analyze the appropriateness of SUP prescribing patterns and identify its associated factors in the orthopedics department of a tertiary hospital in the Northwestern China.

Methods: In this cross-sectional study, information regarding the demographic and clinical characteristics of 1,200 fracture inpatients who underwent surgical operations from January 2020 to August 2021 were collected from medical records. Established criteria were used to assess the appropriateness of the prescribing pattern for SUP, and the incidence of inappropriate SUP medication was calculated. Logistic regression analyses were used to identify factors associated with inappropriate SUP medication.

Results: Approximately, 42.4% of the study population was interpreted as inappropriate prescription of SUP. A total of 397 (33.1%) patients received SUP without a proper indication (overprescription), and the incidence of inappropriate SUP medication was calculated to be 43.11 per 100 patient-days. In addition, 112 (9.3%) inpatients for whom SUP was indicated did not receive SUP (underprescription). PPIs were prescribed in 96.1% of the inpatients who used acid suppression therapy (AST), and intravenous PPIs accounted for 95.3% thereof. In a multivariate logistic regression analysis, age above 65 years and prolonged hospitalization were associated with overprescription of SUP. Increased number of drugs excluding PPIs, the concurrent use of systemic corticosteroids, comorbidity of hypertension, and unemployed or retired status in inpatients were associated with a reduced likelihood of overprescription for SUP.

Abbreviations: SUP, stress ulcer prophylaxis; SRMD, stress-related mucosal disease; PPIs, proton pump inhibitors; AST, acid suppression therapy; SU, stress ulceration; ICU, intensive care unit; ASMs, acid suppressive medications; NSAIDs, non-steroidal anti-inflammatory drugs; DDD, defined daily dose; DDDs/100 PDs, defined daily doses per 100 patient-days; H_2RAs, histamine-2-receptor antagonists

Conversely, prolonged hospitalization, the concurrent use of systemic corticosteroids or anticoagulants, and unemployed status in inpatients were positively associated with underprescription of SUP.

Conclusion: There was a high prevalence of inappropriate SUP prescription among noncritically ill inpatients of fracture who underwent surgical operations. We delineated the associated factors with inappropriate SUP medication, which indicated that more information was required for clinicians about rationality and efficiency of their prescribing practices. Effective intervention strategies should be executed by clinical pharmacists to reduce improper SUP medication.

Keywords: stress ulcer prophylaxis, surgical inpatients, orthopedics department, proton pump inhibitors, clinical pharmacists

INTRODUCTION

Proton pump inhibitors (PPIs) have become one of the most commonly prescribed medicines, and its consumption continues to increase in recent years worldwide. There is definite evidence that PPIs are being overused in hospitalized patients. Between 25% and 70% of hospitalized patients receive PPIs without an appropriate indication. This means that almost £2 billion worldwide is unnecessarily spent on PPIs every year (Forgacs and Loganayagam, 2008). The inappropriate use of PPIs could not only lead to an increased risk of adverse drug reactions and bodily damage due to the unnecessary use of drugs but also increase the financial burden on patients and healthcare systems. Stress ulceration (SU) is a form of hemorrhagic gastritis, which may occur in patients who have experienced major stressful events in the case of multiple traumas, major surgery, multiple organ failure, heat injury, or sepsis (Anderberg and Sjödahl, 1985). Stress-related mucosal disease (SRMD) is most commonly observed in patients of the intensive care unit (ICU), and prophylaxis against SU should be restricted to such patients while exhibiting a relatively high rate of bleeding and not be routinely recommended in noncritically ill surgical and medical patients (ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999). Despite the recommendation, the current status is that more than 22%–88% of hospitalized patients outside the ICU still receive stress ulcer prophylaxis (SUP) without being in risk of developing SRMD or subsequent gastrointestinal bleeding, which represents one of the main reasons for the improper use of PPIs (Heidelbaugh and Inadomi, 2006; Nasser et al., 2010; Issa et al., 2012; Bardou et al., 2015; Savarino et al., 2018). Prior studies have demonstrated that improper SUP medication has been more commonly prescribed in patients admitted to surgical wards, among which orthopedic and general surgeons have prescribed the most PPIs (Mayet, 2007; Craig et al., 2010; Bez et al., 2013; Villamañán et al., 2015; Wijaya et al., 2020).

Inpatients who experience anxiety due to trauma, pain, and starvation during surgical operations are at a higher risk of developing SRMD or subsequent gastrointestinal bleeding. Therefore, SUP is recommended in urgent surgery, complicated procedures, and reoperations (Cook et al., 1994). PPIs could help reduce ulcer-related mortality and the length of hospital stay in elderly patients with femoral neck fractures with a high risk of SU (Singh et al., 2016). However, the perioperative risk of developing gastrointestinal bleeding has been reported to be only roughly 4% (Lalmohamed et al., 2013), while the frequency of nosocomial bleeding occurred in only 0.3% of the patients outside the ICU (Herzig et al., 2011). Considering the extremely low risk of bleeding and the increased risk of adverse events, while lacking direct evidence that SUP medication is beneficial for low-risk patients, the prevention of gastrointestinal bleeding routinely in surgical patients outside the ICU is often inappropriate and unnecessary (ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999; Cook and Guyatt, 2018).

So as to promote the rational use of medication and reduce medical costs, the Chinese authorities have taken various measures in recent years. Adjuvant drugs with high prices, larger consumption, and unconfirmed therapeutic effects in their clinical application have been defined as the Key Monitoring Drugs in China. The National Health and Family Planning Commission of the People's Republic of China (NHFPC) has developed management measures for the Key Monitoring Drugs from 2015. As one of the most commonly prescribed medications, PPIs were included in the list of Key Monitoring Drugs developed by the Health and Family Planning Commission of Anhui, Sichuan, Qinghai, JiangXi, and Shanxi Province from 2015 to 2019. In August 2021, the National Health Commission of the People's Republic of China indicated that management of PPIs must be scheduled because of abnormally large consumption and the current situation of irrational utilization in hospitals, which meant management targeted at these drugs for improvement had been scheduled. In China, studies have pointed out that SUP without indication account for the majority of inappropriate PPIs prescriptions (Lei, 2017; Luo et al., 2018). Through prescription analysis, we already know from the available publications that inappropriate SUP medication in surgery patients, in particular, patients of the orthopedics department, seems to be more serious (Ma et al., 2018). Between 28.7% and 100.0% of surgical inpatients in the orthopedics department received SUP, but 32.4%–65.8% of inpatients received this therapy without indications (Ruan et al., 2015; Chu et al., 2017; Ma et al., 2018; Yao et al., 2019). To promote

the proper prophylactic use of PPIs, the "Consensus Review for SUP and Treatment" was published in 2015 in China and then updated in 2018 (Bo et al., 2018). To further standardize doctors' prescription behavior of PPIs, the first guideline for the clinical use of PPIs was issued by the National Health Commission of the People's Republic of China in 2020 (National Health Commission of the People's Republic of China, 2020).

Although the non-indicated use of acid suppressive medications (ASMs) was commonplace in China, little is known about the SUP prescribing practice for surgery inpatients and its associated factors. Therefore, it is necessary to explore the current situation of SUP prescribing pattern among surgery inpatients, with the goal of providing a basis for future PPIs stewardship in China. We had a testable hypothesis that the prevailing inappropriate prescribing pattern of SUP was high among surgical inpatients of the orthopedics department. The primary objective of this study was therefore to assess the appropriateness of SUP medication for fracture patients who underwent surgical operations in the orthopedics department of a tertiary hospital, including their eligibility, medication choices, and the routes and durations of SUP dosing. The demographic and clinical factors associated with the inappropriate prescription of SUP were clarified for further designing effective interventions to improve the rational utilization of PPIs.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional study was conducted in a tertiary teaching hospital located in the Shaanxi province of Northwestern China. The hospital had around 1,300 beds in all and 60 beds in the orthopedics department.

Study Population and Sample Size

The inclusion criteria for participants were inpatients aged ≥12 years who 1) underwent surgical operations in the orthopedics department from January 2020 to August 2021 because of fractures and 2) had a hospital stay length of >3 days. The exclusion criteria were 1) a history of peptic ulcers or gastrointestinal bleeding within 1 year prior to admission; 2) ASMs prescription for the treatment of gastrointestinal diseases such as ulcers, esophagitis, dyspepsia, gastroesophageal reflux disease, or epigastric pain within 1 month prior to admission; 3) new onset of gastrointestinal disease during hospitalization; 4) admission to the ICU or being transferred from or to the ICU halfway; and 5) death during hospitalization.

The minimum number of participants was calculated applying the following formula: $n = z^2\, p(1\text{-}p)/d^2$, where n is the sample size, z is the coefficient of confidence interval (1.96), p is the prevalence rate, and d is the error margin of prevalence (3% p). Based on previously published data, SUP for inpatients who underwent surgical operations in the orthopedics department was estimated to be 57.9% (Ruan et al., 2015; Chu et al., 2017; Ma et al., 2018; Yao et al., 2019). As a result, a minimum sample size of 1,041 inpatients was required based on the above assumptions.

An initial sample size of 1,331 inpatients who underwent surgical operations because of fracture from January 2020 to August 2021 was selected randomly with a standard computer selection program. A total of 131 inpatients were excluded from the analysis according to the criteria shown above, and thus 1,200 inpatients were finally recruited in this study (**Figure 1**). Only the first admission was included for patients admitted multiple times during the study period. SUP was defined as the treatment with at least one dose of ASMs initiated in inpatients without any clear indication or any relevant symptom recorded in the medical records. The details of the types of fractures in the patients of our study are provided in the supplementary file (**Supplementary Tables S1, S2**).

Criteria Establishment

Based on published evidence-based guidelines and previous literature for the clinical practices of SUP, we established the criteria to evaluate the appropriateness of SUP medication. The claimed SUP indication group was subclassified as 1) meeting the criteria for SUP indication or 2) meeting the criteria for drug-induced ulcer prophylaxis (**Figure 1**). SUP medication was judged to be appropriate if the surgical inpatient had one major or at least two minor risk factors (Cook et al., 1994; ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999; Bez et al., 2013; Bo et al., 2018; National Health Commission of the People's Republic of China, 2020) (**Table 1**). Since nonsteroidal anti-inflammatory drugs (NSAIDs) were required for pain management, anticoagulants for deep vein thrombosis prophylaxis and the concomitant use of ulcerogenic medicine for comorbidities and acknowledged risk factors for drug-related ulcer prophylaxis were also established (García Rodríguez and Jick, 1994; Bhatt et al., 2008; Lanza et al., 2009; Bez et al., 2013) (**Table 2**). The prescription of ASMs was considered appropriate if the above risk factors were present.

Data Collection

The sociodemographic and medical variables were collected from the hospital information system (HIS) by reviewing the electronic medical records. Sociodemographic information of inpatients included data on age (years), gender (male or female), current smokers (yes or no), alcohol consumption (yes or no), occupational status (employed, unemployed, or retired), place of residence (urban or rural), and health insurance (insured or uninsured). The data extracted from the medical records included the following variables: diagnosis at admission, comorbidity conditions (hypertension, diabetes mellitus, coronary artery disease, and osteoporosis), total number of comorbidities, complications (limb vein thrombosis, respiratory infection, urinary infection, and bedsore), admission/discharge date, length of hospital stay (days), name and duration of surgical operations, pertinent laboratory data, number of drugs excluding PPIs during hospitalization, and adverse drug reactions during hospitalization. ASMs prescription for inpatients included information on generic names, drug specifications, units, total doses, manufacturers, ASMs concerning routes, and frequencies and durations of administrations. Co-medications potentially influencing the prescription pattern of ASMs were also reviewed to identify the associated factors of SUP, including

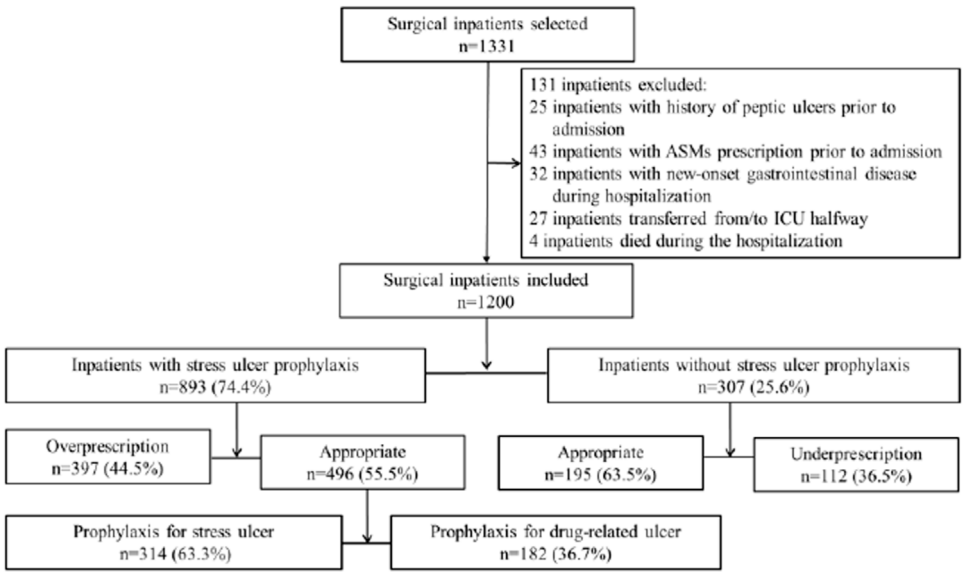

FIGURE 1 | Flow diagram demonstrating inpatient selection and subclassification. The selection and subclassification process for the inpatients who participated in the study is demonstrated. An initial sample size of 1,331 inpatients was selected randomly using a standard computer selection program, and 131 inpatients were excluded according to the criteria determined, and thus 1,200 inpatients were finally recruited in this study. The study inpatients were initially divided into subgroups on the basis of SUP prescription receivers or non–SUP prescription receivers, and then categorized into four groups through ascertaining if the indication was in accordance with the criteria determined. The inpatients who received SUP appropriately were subclassified into two groups according to the criteria determined, of which one met the criteria for SUP indication, while the other met the criteria for drug-induced ulcer prophylaxis.

TABLE 1 | Risk factors for stress ulcer (Cook et al., 1994; ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999; Bez et al., 2013; Bo et al., 2018; National Health Commission of the People's Republic of China, 2020).

The presence of one major risk factor from the following:
1 Respiratory failure: mechanical ventilation >48 h
2 Coagulopathy: platelet count <50,000/mm^3 (50 × 10^9/L), international normalized ratio >1.5, or partial thromboplastin time >2.0 times the control value
3 Experiencing surgical operation for more than 3 h
4 Head injury with a Glasgow Coma Score of ≤10 or an inability to obey simple commands
5 Thermal injury involving >35% of the body surface area
6 Partial hepatectomy
7 Hepatic or renal transplantation
8 Multiple traumas with the Injury Severity Score of ≥16
9 Acute renal failure or hepatic failure
10 Traumatic brain injury or spinal cord injury
The presence of at least two minor risk factors of the following:
1 Sepsis
2 Occult or overt bleeding for ≥6 days
3 Corticosteroid therapy (>250 mg/d hydrocortisone or equivalent daily)

antiplatelet agents (aspirin, clopidogrel, and prasugrel), anticoagulants (warfarin, low-molecular heparin, rivaroxaban, and apixaban), systemic corticosteroids (hydrocortisone, dexamethasone, and methylprednisolone), and NSAIDs (celecoxib, flurbiprofen, ibuprofen, aceclofenac, parecoxib, loxoprofen, ketochromate tromethamine, and diclofenac). Five branded and generic PPIs were available as both oral and intravenous preparations in our hospital when this study was conducted. The defined daily dose (DDD) of PPIs taken by the participants was identified according to the Anatomical and Therapeutic Classification (ATC) code A02BC (**Table 3**).

Outcome Measurements

Our primary outcome variable was the appropriateness evaluation of SUP prescribing patterns for fracture patients who underwent surgical operations in the orthopedics department. Factors influencing inappropriate prescription of SUP were analyzed as another end point in our study.

TABLE 2 | Risk factors for drug-related ulcer (García Rodríguez and Jick, 1994; Bhatt et al., 2008; Lanza et al., 2009; Bez et al., 2013).

Risk factor
1 High-dose NSAID therapy (ibuprofen >1,500 mg daily, diclofenac >100 mg daily, or mefenamic acid >1,250 mg daily)
2 Concomitant NSAID use with antiplatelet agents (including low-dose aspirin), corticosteroids, or anticoagulants
3 Age >65 years, concomitant use of NSAID
4 Concomitant anticoagulant use with antiplatelet agents
5 Dual antiplatelet therapies
6 Age ≥60 years, concomitant corticosteroid use with antiplatelet agents

Statistical Analysis

The collected data were analyzed to assess the appropriateness of ASMs prescription and identify the associated factors of inappropriate SUP medication. The appropriateness of SUP medication was determined according to the criteria listed above. Patients were initially divided into subgroups on the basis of SUP prescription receivers or non–SUP prescription receivers and were then categorized into four groups through ascertaining if the indication was in accordance with the abovementioned criteria: those who received SUP appropriately, those who received SUP without a proper indication (overprescription group), those who were appropriate non–SUP prescription receivers, and those for whom SUP was indicated for but did not receive SUP (underprescription group). Inappropriate dosage of ASMs was noted but was not included in the over- or underprescription groups. The defined daily doses per 100 patient-days (DDDs/100 PDs) were used for measuring the consumption of PPIs for SUP. ASMs prescription of the overprescription group were counted as inappropriate. Based on a previous study (Masood et al., 2018), incidence of inappropriate SUP medication was evaluated, which was calculated as the inappropriate patient-days divided by total patient-days receiving prescription of ASMs and then converted to incidence per 100 patient-days. To identify factors associated with inappropriate SUP medication, patients receiving overprescription and appropriate prescription of SUP were compared. Similarly, patients receiving underprescription were compared with non–SUP prescription receivers.

The skew continuous variables of demographic and clinical data are presented as median (interquartile range) after normality test. Categorical variables are presented as frequency (percentages). Differences in demographic and clinical data were evaluated using the Mann–Whitney test or Pearson chi-squared test as appropriate. After the univariate models were estimated for each predictive variable, the multivariate logistic regression models were used to investigate independent factors associated with the inappropriate prescription of SUP. All analyses were performed using the SPSS V25.0 Statistical Software Package for Windows. The level of statistical significance was set to 0.05.

TABLE 3 | Proton pump inhibitors available in our hospital.

Drug	DDD (mg)	ATC code
Omeprazole	20	A02BC01
Rabeprazole	20	A02BC04
Lansoprazole	30	A02BC03
Esomeprazole	30	A02BC05
Pantoprazole	40	A02BC02

RESULTS

Characteristics of Study Participants

A total of 893 inpatients with ASMs prescription for SUP had a median age of 45 (58, 70) years and the majority (50.3%) were female; 307 inpatients without ASMs prescription for SUP had a median age of 49 (33, 62) years and the majority (59.9%) were male.

Appropriateness of Stress Ulcer Prophylaxis Prescribing Patterns

SUP medication was prescribed to 893 inpatients (74.4%) of the study population, and the consumption of PPIs was 57.90 DDDs per 100 patient-days (PDs). A total of 509 inpatients (42.4%) of the study population were interpreted as having received an inappropriate prescription of SUP, of which 397 (33.1%) and 112 (9.3%) were interpreted as having received overprescription and underprescription of SUP, respectively. The incidence of inappropriate SUP medication was calculated to be 43.11 per 100 patient-days. PPIs were prescribed to 96.1% of the inpatients using acid suppression therapy, in whom intravenous PPIs accounted for 95.3%. Pantoprazole was prescribed in 46.7% of the inpatients who were prescribed PPIs, followed by omeprazole (29.7%), lansoprazole (13.2%), and esomeprazole (10.4%). Rabeprazole was not prescribed. Cimetidine injection was the only histamine-2-receptor antagonist (H_2RAs) prescribed in our study. Only 35 inpatients received cimetidine injection, while 17 inpatients received PPIs injection followed or preceded by cimetidine injection sequentially. The mean duration of SUP medication was 3.65 ± 3.24 days a total of 496 inpatients (41.3%) were judged to meet the criteria for appropriate SUP, of whom 182 (36.7%) received prophylaxis against drug-related ulcer and 314 (63.3%) received prophylaxis against SU. Patients who received surgical operation for more than 3 h accounted for almost two-thirds of the 314 inpatients with appropriate indications for prophylaxis against SU (**Figure 1**). ASMs prescription patterns for SUP are shown in **Table 4**.

Associated Factors of Inappropriate Stress Ulcer Prophylaxis Medication

Demographic and clinical variables of inpatients with ASMs prescription for SUP are shown in **Table 5** and those of inpatients without ASMs prescription for SUP are shown in **Table 6**.

When compared with inpatients who received SUP appropriately, nine factors were significantly associated with overprescription of ASMs for SUP practice ($p < 0.05$): age above 65 years, alcohol consumption, unemployed status, living in urban areas, comorbidity of coronary artery disease, complications, the concurrent use of anticoagulants, systemic

TABLE 4 | ASMs prescription patterns for SUP.

Appropriate prescription for SUP	Routes of administration		Duration of administration (days)	DDDs/100 PDs of PPIs
	Intravenous	Oral		
Yes	490	6	3.74 ± 3.13	55.93
No[a]	396	1	3.54 ± 3.37	60.23
Total	886	7	3.65 ± 3.24	57.90

[a]*This indicates the overprescription group.*

TABLE 5 | Demographic and clinical characteristics of inpatients with ASMs prescription for SUP.

Characteristics	Total (*n* = 893)	Appropriate (*n* = 496)	Overprescription (*n* = 397)	*p*-value
Age (years)				0.001
Median (Q_1, Q_3)	45 (58, 70)	56 (45, 67.5)	61 (46, 73)	
≤44	213 (23.8)	122 (24.6)	91 (22.9)	<0.001
45–64	357 (40.0)	223 (45.0)	134 (33.8)	
≥65	323 (36.2)	151 (30.4)	172 (43.3)	
Gender				0.725
Female	449 (50.3)	252 (50.8)	197 (49.6)	
Male	444 (49.7)	244 (49.2)	200 (50.4)	
Current smokers				0.342
No	737 (82.5)	404 (81.5)	333 (83.9)	
Yes	156 (17.5)	92 (18.5)	64 (16.1)	
Alcohol consumption				0.039
No	790 (88.5)	429 (86.5)	361 (90.9)	
Yes	103 (11.5)	67 (13.5)	36 (9.1)	
Occupational status				<0.001
Employed	255 (28.6)	105 (21.2)	150 (37.8)	
Unemployed	453 (50.7)	286 (57.6)	167 (42.1)	
Retired	185 (20.7)	105 (21.2)	80 (20.1)	
Residence				0.009
Rural	473 (53.0)	282 (56.9)	191 (48.1)	
Urban	420 (47.0)	214 (43.1)	206 (51.9)	
Health insurance				0.143
No	303 (33.9)	158 (31.9)	145 (36.5)	
Yes	590 (66.1)	338 (68.1)	252 (63.5)	
Comorbidity conditions				
Hypertension	225 (25.2)	128 (25.8)	97 (24.4)	0.639
Diabetes mellitus	111 (12.4)	58 (11.7)	53 (13.4)	0.456
Coronary artery disease	130 (14.6)	55 (11.1)	75 (18.9)	0.001
Osteoporosis	76 (8.5)	44 (8.9)	32 (8.1)	0.666
Number of comorbidities	0 (0, 1)	0 (0, 1)	1 (0, 2)	0.003
Complications	127 (14.2)	53 (10.7)	74 (18.6)	0.001
Concurrently used drugs				
Anticoagulants	531 (59.5)	279 (56.3)	252 (63.5)	0.029
Antiplatelet agents	24 (2.7)	16 (3.2)	8 (2.0)	0.266
Systemic corticosteroids	345 (38.6)	258 (52.0)	87 (21.9)	<0.001
NSAIDs	722 (80.9)	389 (78.4)	333 (83.9)	0.040
Number of drugs excluding PPIs				<0.001
Median (Q_1, Q_3)	19 (14, 28)	21 (15.5, 29)	16 (12, 25)	
6–14	263 (29.5)	102 (20.6)	161 (40.6)	<0.001
15–19	212 (23.7)	116 (23.4)	96 (24.2)	
20–28	217 (24.3)	141 (28.4)	76 (19.1)	
29–59	201 (22.5)	137 (27.6)	64 (16.1)	
Length of hospital stay (days)				0.172
Median (Q_1, Q_3)	10 (7, 16)	11 (8, 15)	10 (7, 16)	
3–7	230 (25.8)	111 (22.4)	119 (30.0)	0.011
8–10	224 (25.1)	131 (26.4)	93 (23.4)	
11–16	244 (27.3)	152 (30.6)	92 (23.2)	
17–54	195 (21.8)	102 (20.6)	93 (23.4)	

The data are presented as numbers (proportions) or the median (interquartile range). Bold values indicate a p*-value <0.05.*

TABLE 6 | Demographic and clinical characteristics of the inpatients without ASMs prescription for SUP.

Characteristics	Total (*n* = 307)	Appropriate (*n* = 195)	Underprescription (*n* = 112)	*p-value*
Age (years)				0.066
Median (Q_1, Q_3)	49 (33, 62)	46 (31, 61)	51.5 (36, 62)	
≤44	133 (43.3)	90 (46.1)	43 (38.4)	0.375
45–64	115 (37.5)	68 (34.9)	47 (42.0)	
≥65	59 (19.2)	37 (19.0)	22 (19.6)	
Gender				0.057
Female	123 (40.1)	86 (44.1)	37 (33.0)	
Male	184 (59.9)	109 (55.9)	75 (67.0)	
Current smokers				0.112
No	250 (81.4)	164 (84.1)	86 (76.8)	
Yes	57 (18.6)	31 (15.9)	26 (23.2)	
Alcohol consumption				0.596
No	273 (88.9)	172 (88.2)	101 (90.2)	
Yes	34 (11.1)	23 (11.8)	11 (9.8)	
Occupational status				<0.001
Employed	126 (41.0)	97 (49.7)	29 (25.9)	
Unemployed	126 (41.0)	59 (30.3)	67 (59.8)	
Retired	55 (17.9)	39 (20.0)	16 (14.3)	
Residence				<0.001
Rural	136 (44.3)	71 (36.4)	65 (58.0)	
Urban	171 (55.7)	124 (63.6)	47 (42.0)	
Health insurance				0.461
No	104 (33.9)	69 (35.4)	35 (31.2)	
Yes	203 (66.1)	126 (64.6)	77 (68.8)	
Comorbidity conditions				
Hypertension	50 (16.3)	28 (14.4)	22 (19.6)	0.227
Diabetes mellitus	18 (5.9)	12 (6.2)	6 (5.4)	0.775
Coronary artery disease	15 (4.9)	9 (4.6)	6 (5.4)	0.772
Osteoporosis	21 (6.8)	12 (6.2)	9 (8.0)	0.529
Number of comorbidities	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.370
Complications	19 (6.2)	8 (4.1)	11 (9.8)	0.045
Concurrently used drugs				
Anticoagulants	100 (32.6)	44 (22.6)	56 (50)	<0.001
Systemic corticosteroids	46 (15.0)	16 (8.2)	30 (26.8)	<0.001
NSAIDs	203 (66.1)	125 (64.1)	78 (69.6)	0.323
Number of drugs excluding PPIs				0.028
Median (Q_1, Q_3)	14 (10, 19)	13 (10, 18)	15 (12, 20.5)	
3–10	79 (25.7)	60 (30.8)	19 (17.0)	0.064
11–14	86 (28.0)	51 (26.2)	35 (31.3)	
15–19	69 (22.5)	42 (21.5)	27 (24.1)	
20–57	73 (23.8)	42 (21.5)	31 (27.7)	
Length of hospital stay (days)				<0.001
Median (Q_1, Q_3)	10 (6, 15)	8 (6, 12)	12 (8, 19)	
3–6	81 (26.4)	64 (32.8)	17 (15.2)	<0.001
7–10	94 (30.6)	68 (34.9)	26 (23.2)	
11–15	67 (21.8)	40 (20.5)	27 (24.1)	
16–65	65 (21.2)	23 (11.8)	42 (37.5)	

The data are presented as numbers (proportions) or the median (interquartile range). Bold values indicate a p-*value <0.05.*

corticosteroids or NSAIDs, number of drugs excluding PPIs, and length of hospital stay (**Table 7**). When compared with appropriate non-SUP prescription, five factors were significantly associated with underprescription of ASMs for SUP ($p < 0.05$): unemployed status, living in urban areas, the concurrent use of anticoagulants or systemic corticosteroids, number of drugs excluding PPIs, and length of hospital stay (**Table 8**).

In multivariate logistic regression analysis, age above 65 years and prolonged hospitalization were associated with overprescription of SUP. Increased number of drugs excluding PPIs, the concurrent use of systemic corticosteroids, comorbidity of hypertension, and unemployed or retired status in inpatients were associated with reduced likelihood of overprescription for SUP (**Table 7**). Conversely, prolonged hospitalization, the concurrent use of systemic corticosteroids or anticoagulants, and unemployed status in inpatients were positively associated with underprescription of SUP (**Table 8**).

There were nine cases of reversible disturbances such as nausea, headache, diarrhea, abdominal pain, constipation, flatulence, dizziness, and anaphylactic reactions documented during the study period.

TABLE 7 | Univariate and multivariate logistic regression analyses of factors associated with overprescription of ASMs for SUP.

Characteristics	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Age (years)				
≤44	1.000 (Reference)		1.000 (Reference)	
45–64	0.806 (0.570–1.138)	0.221	1.193 (0.797–1.786)	0.391
≥65	1.527 (1.078–2.164)	0.017	3.591 (2.145–6.012)	<0.001
Gender				
Female	1.000 (Reference)		1.000 (Reference)	
Male	1.049 (0.805–1.365)	0.725	1.200 (0.851–1.693)	0.299
Current smokers				
No	1.000 (Reference)		1.000 (Reference)	
Yes	0.844 (0.594–1.198)	0.343	1.076 (0.640–1.809)	0.782
Alcohol consumption				
No	1.000 (Reference)		1.000 (Reference)	
Yes	0.639 (0.416–0.980)	**0.040**	0.638 (0.350–1.163)	0.142
Occupational status				
Employed	1.000 (Reference)		1.000 (Reference)	
Unemployed	0.409 (0.299–0.560)	**<0.001**	0.457 (0.293–0.713)	**0.001**
Retired	0.533 (0.364–0.782)	0.001	0.287 (0.171–0.480)	<0.001
Residence				
Rural	1.000 (Reference)		1.000 (Reference)	
Urban	1.421 (1.090–1.853)	**0.009**	1.204 (0.791–1.833)	0.386
Health insurance				
No	1.000 (Reference)		1.000 (Reference)	
Yes	0.812 (0.615–1.073)	0.143	0.779 (0.559–1.085)	0.140
Comorbidity conditions				
Hypertension	0.930 (0.685–1.261)	0.639	0.663 (0.452–0.972)	0.035
Diabetes mellitus	1.163 (0.781–1.733)	0.456	1.035 (0.645–1.663)	0.886
Coronary artery disease	1.868 (1.282–2.721)	**0.001**	1.485 (0.934–2.359)	0.095
Osteoporosis	0.901 (0.560–1.449)	0.666	0.877 (0.511–1.506)	0.634
Number of comorbidities	1.108 (0.947–1.296)	0.199	-	
Complication				
No	1.000 (Reference)		1.000 (Reference)	
Yes	1.915 (1.309–2.802)	**0.001**	1.528 (0.984–2.372)	0.059
Concurrently used drugs				
Anticoagulants	1.352 (1.031–1.772)	**0.029**	1.008 (0.719–1.413)	0.964
Antiplatelet agents	0.617 (0.261–1.457)	0.271	0.542 (0.204–1.443)	0.220
Systemic corticosteroids	0.259 (0.193–0.348)	**<0.001**	0.316 (0.224–0.446)	**<0.001**
NSAIDs	1.431 (1.016–2.016)	0.040	1.432 (0.964–2.125)	0.075
Number of drugs excluding PPIs				
6–14	1.000 (Reference)		1.000 (Reference)	
15–19	0.524 (0.363–0.757)	**0.001**	0.602 (0.397–0.911)	**0.016**
20–28	0.341 (0.235–0.496)	**<0.001**	0.415 (0.263–0.656)	**<0.001**
29–59	0.296 (0.201–0.436)	**<0.001**	0.348 (0.205–0.590)	**<0.001**
Length of hospital stay (days)				
3–7	1.000 (Reference)		1.000 (Reference)	
8–10	0.662 (0.457–0.959)	**0.029**	0.860 (0.561–1.317)	0.487
11–16	0.565 (0.392–0.814)	**0.002**	1.209 (0.772–1.892)	0.407
17–54	0.850 (0.580–1.256)	0.406	1.838 (1.122–3.009)	**0.016**

Bold values indicate a p*-value <0.05. OR, odds ratio; CI, confidence interval.*

DISCUSSION

Our study highlights the prevalence of inappropriate SUP medication in noncritically ill fracture patients who underwent surgical operations. Approximately, 42.4% of the study population were interpreted as inappropriate prescription of SUP. The literature had revealed that 48%, 61.6%, and 69% of inpatients in the surgery department were found to be inappropriately prescribed PPIs for SUP (Nasser et al., 2010; Bez et al., 2013; Wijaya et al., 2020), which is higher than the data observed in our study. Our study indicates that approximately 33.1% of fracture patients who underwent surgical operations might not require intravenous PPIs for SUP on a routine basis, which is lower than published observations in China (Ma et al., 2018; Yao et al., 2019). The incidence of inappropriate SUP medication was calculated to be 43.11 per 100 patient-days, which is higher than 26.75 per 100 patient-days in an academic medical ICU (Masood et al., 2018). A previous study has revealed that 33% of patients who were although SUP candidates did not receive

TABLE 8 | Univariate and multivariate logistic regression analysis of factors associated with underprescription of ASMs for SUP.

Characteristic	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Age (years)				
≤44	1.000 (Reference)		1.000 (Reference)	
45–64	1.447 (0.860–2.433)	0.164	1.037 (0.522–2.058)	0.918
≥65	1.245 (0.656–2.362)	0.503	1.315 (0.463–3.737)	0.607
Gender				
Female	1.000 (Reference)		1.000 (Reference)	
Male	1.599 (0.985–2.597)	0.058	1.916 (0.963–3.814)	0.064
Current smokers				
No	1.000 (Reference)		1.000 (Reference)	
Yes	1.599 (0.893–2.865)	0.114	2.272 (0.919–5.616)	0.076
Alcohol consumption				
No	1.000 (Reference)		1.000 (Reference)	
Yes	0.814 (0.381–1.740)	0.596	0.558 (0.182–1.711)	0.308
Occupational status				
Employed	1.000 (Reference)		1.000 (Reference)	
Unemployed	3.798 (2.208–6.536)	**<0.001**	2.397 (1.075–5.346)	**0.033**
Retired	1.372 (0.672–2.804)	0.385	1.098 (0.356–3.390)	0.871
Residence				
Rural	1.000 (Reference)		1.000 (Reference)	
Urban	0.414 (0.257–0.666)	**<0.001**	0.813 (0.379–1.743)	0.595
Health insurance				
No	1.000 (Reference)		1.000 (Reference)	
Yes	1.205 (0.734–1.978)	0.461	1.059 (0.552–2.028)	0.864
Comorbidity conditions				
Hypertension	1.458 (0.789–2.695)	0.229	2.075 (0.929–4.636)	0.075
Diabetes mellitus	0.863 (0.315–2.367)	0.775	0.323 (0.082–1.268)	0.105
Coronary artery disease	1.170 (0.405–3.377)	0.772	1.103 (0.278–4.375)	0.890
Osteoporosis	1.333 (0.543–3.269)	0.531	1.220 (0.412–3.608)	0.719
Number of comorbidities	1.183 (0.830–1.687)	0.352	—	
Complication				
No	1.000 (Reference)		1.000 (Reference)	
Yes	2.546 (0.992–6.532)	0.052	1.035 (0.326–3.285)	0.954
Concurrently used drugs				
Anticoagulants	3.432 (2.082–5.658)	**<0.001**	2.427 (1.257–4.684)	**0.008**
Systemic corticosteroids	4.093 (2.114–7.924)	**<0.001**	4.548 (1.988–10.405)	**<0.001**
NSAIDs	1.285 (0.781–2.114)	0.324	1.159 (0.632–2.126)	0.632
Number of drugs excluding PPIs				
3–10	1.000 (Reference)		1.000 (Reference)	
11–14	2.167 (1.107–4.243)	**0.024**	1.346 (0.610–2.970)	0.462
15–19	2.030 (1.001–4.117)	0.050	0.830 (0.337–2.044)	0.685
20–57	2.331 (1.164–4.665)	0.017	0.394 (0.144–1.081)	0.071
Length of hospital stay (days)				
3–6	1.000 (Reference)		1.000 (Reference)	
7–10	1.439 (0.715–2.899)	0.308	1.543 (0.684–3.478)	0.296
11–15	2.541 (1.232–5.243)	**0.012**	2.029 (0.849–4.848)	0.112
16–65	6.875 (3.287–14.378)	**<0.001**	5.935 (2.302–15.300)	**<0.001**

Bold values indicate a p-*value < 0.05. OR, odds ratio; CI, confidence interval.*

ASMs (Issa et al., 2012), which is higher than 9.3% in our study. The total consumption of PPIs in our study was 60.23 DDDs/100 PDs. Therefore, efforts to reduce improper SUP medication are urgently and crucially required.

Based on recent published studies, PPIs seem to be more effective than H_2RAs for SUP (Bardou et al., 2015). PPIs were more extensively prescribed for the prophylaxis and therapy of NSAID- and aspirin-associated gastrointestinal bleeding (Bhatt et al., 2008; Lanza et al., 2009). In our study, 96.1% of the patients were prescribed PPIs, which is consistent with the current practice trends (Bo et al., 2018; Issa et al., 2012; National Health Commission of the People's Republic of China, 2020). The Food and Drug Administration has currently approved omeprazole as the only PPI for SUP in critically ill patients (Bez et al., 2013). One study indicated that lansoprazole was not recommended for SUP (Allen et al., 2004). Pantoprazole, followed by omeprazole, was the most commonly prescribed PPIs in our study. A possible explanation could be that pantoprazole was included in various surgical procedures in hospitals (Villamañán et al., 2015), and pantoprazole might be preferred in clopidogrel users for lacking inhibition of hepatic CYP 2C19 (Savarino et al., 2018). In addition, as the only PPI listed among national essential medicines of China, omeprazole should be preferred according to policy guidance of the

authorities in China. PPIs twice daily (omeprazole 20 mg, rabeprazole 20 mg, lansoprazole 30 mg, esomeprazole 30 mg, and pantoprazole 40 mg) were recommended for prophylaxis against stress ulcer according to the Chinese guidelines (Bo et al., 2018; National Health Commission of the People's Republic of China, 2020). Unfortunately, there is a lack of recommendation or consensus on PPI dose for prophylaxis against drug-related ulcer in the current literature.

Our study demonstrated the prevalence of intravenous PPIs for SUP, which occurred in approximately 95.3% of the inpatients using ASMs. Based on the published study, injections given to inpatients who have nil-by-mouth conditions or experience severe motility disorders have been considered appropriate (Wijaya et al., 2020). All the inpatients were admitted to the orthopedics ward outside the ICU in our study, most of whom could receive food intake by mouth and could be given oral therapy. In our study, 62% of the inpatients had inappropriate routes of administration including unnecessary intravenous administration when oral formulations would be more appropriate. Prior published studies have demonstrated that inappropriate routes of drug administration account for 42.7% or 45% of the preparations used (Nasser et al., 2010; Luo et al., 2018), which is lower than the observations made in our study. Another study demonstrated that the incidence of omeprazole being administered *via* inaccurate routes was 96.7% (Wijaya et al., 2020), which is higher than that observed in our study. The effectiveness of oral PPIs was similar to injectable formulations with equivalent doses but with cheaper prices and fewer complications related to intravenous administration (Nasser et al., 2010; Wijaya et al., 2020). This highlights the need for clinical pharmacists to intervene and suggest appropriate routes of drug administration for inpatients.

SUP should be started at the onset of risk factors and continued beyond the high-risk period (Allen et al., 2004; Bo et al., 2018; National Health Commission of the People's Republic of China, 2020), while prophylaxis should be discontinued when risk factors have been resolved (ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999). In our study, the mean duration of SUP was 3.65 ± 3.24 days; 246 inpatients (27.6%) had received ASMs for more than 5 days and 3 of them for up to more than 20 days. Based on the literature review, most patients received intravenous PPIs for claimed SUP indication for approximately 5 days or a mean duration of 6.3 ± 4.5 (SD) days, respectively (Lam et al., 1999; Nasser et al., 2010), which appeared to be longer than the findings in our study. This might be explained by the fact that physicians did not reassess the need for PPIs use regularly (Bez et al., 2013). In addition, due to heavy work and misunderstanding "longer duration for better effect," surgeons have always ignored or prolonged the duration of prophylaxis (Luo et al., 2018).

Age above 65 years was a predictor of overprescription for SUP in our study. This was supported by published data which states that older age was a significant variable predicting inappropriate AST use (Afif et al., 2007; Issa et al., 2012). In a large cohort of noncritically ill hospitalized patients, age >60 years was identified as an independent risk factor for nosocomial gastrointestinal bleeding (Herzig et al., 2013). Furthermore, comorbidities did increase with age, and older patients were often potentially precarious during hospitalization (Afif et al., 2007), as a result of which the use of ASMs was understandable. Nonetheless, the use of ASMs must be individualized.

Our study shows that increased number of drugs excluding PPIs was associated with a decreased risk of overprescription of ASMs for SUP, which suggests that clinicians are more cautious about prescribing ASMs for patients on multiple drug treatments. The findings in our study are inconsistent with the current literature. One study had indicated that the only independent predictor of inappropriate PPIs use was the number of medications (Voukelatou et al., 2019). Another analysis also indicated that the total number of drugs excluding PPIs was the predictor of overprescribed PPIs (Jarchow-Macdonald and Mangoni, 2013). Our study also shows that comorbidity of hypertension is associated with a decreased risk of overprescription of ASMs for SUP, which indicates that clinicians have been more cautious about prescribing ASMs for hypertension patients. According to the literature, cardiology patients were often maintained on aspirin and other anticoagulants and therefore most of these patients would actually fit the criteria for acceptable SUP use. And these patients were not associated with significant SUP misuse (Issa et al., 2012), which is consistent with our study.

Our study shows that the concurrent use of corticosteroids or anticoagulants is a predictor of underprescription of SUP. Prior studies have demonstrated PPIs underprescription and overprescription to be positively and negatively associated with systemic corticosteroids, respectively (Schepisi et al., 2016), which is consistent with our study. A study had shown that inappropriate SUP increased twofold in patients concomitantly using corticosteroids or anticoagulants (Issa et al., 2012). Furthermore, the concomitant use of anticoagulants was also a significant independent predictor of guideline-noncompliance prescribing of PPIs in another study (Eid et al., 2010).

Our results suggest that unemployed inpatients are more likely to be under-prescribed ASMs for SUP, while unemployed and retired inpatients are less likely to be overprescribed ASMs for SUP. The most likely reason for this is that economic characteristics among different populations are factors which might influence clinicians' prescribing behavior in underdeveloped regions where this study has been conducted. Because unemployed and retired inpatients tended to have lower incomes and more barriers to access affordability of drugs than employed inpatients, it is possible that the prescribers were aware of the economic situation of such inpatients and generally avoided prescribing medications for these patients. But there is little information indicative of any association of SUP medication with employment status in the available literature. The relationship between employment status and inappropriate prescription of SUP needs further research to build upon our findings in the future.

Prolonged hospitalization was found to be predictive of increased likelihood of inappropriate prescription of SUP in inpatients in our study. One study had noted that the duration of hospital stay was a significant factor for AST misuse (Issa et al.,

2012). But literature has also suggested that the proportion of correct use of ASMs has increased, while the proportion of misuse has decreased with prolonged hospitalization (Mayet, 2007), which is contrary to the results obtained in our study.

The reasons why clinicians prescribed SUP inappropriately were multifactorial. First, the fear of development of stress ulcer syndrome in non-ICU patients who were not on SUP therapy might be largely unreasonable, as the overall incidence of bleeding events seemed low (Allen et al., 2004; Hussain et al., 2010). Due to the tense relationship between doctors and patients in China, doctors had to prescribe SUP therapy for low-risk inpatients so as to protect themselves from litigation (Luo et al., 2018). The incidence of an adverse reaction related to ASMs has not been high, and for this reason, doctors have believed PPIs to be safe (Hussain et al., 2010). The incidence of serious clinical adverse reactions in adults has been low when PPIs and H_2RAs were used for a short time (ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, 1999). However, physicians must take into account the possible risk of the side effect when prescribing PPIs. Last but not the least, doctors might not have prescription awareness of the existing guidelines, and it is conceivable that SUP has been routinely prescribed to their patients (Heidelbaugh and Inadomi, 2006; Voukelatou et al., 2019).

Strengths and Limitations

To the best of our knowledge, current studies in China mainly focus on the irrational use of PPIs, and this is the first study to identify the associated factors of inappropriate SUP medication for inpatients of fracture who have underwent surgical operations in the orthopedics department. We believe that this study will help the researchers and policymakers understand the prescription behavior of clinicians comprehensively and provide effective measures for SUP management. Our study has several limitations. First, as only a single tertiary hospital was surveyed, it might create a bias due to the small size of inpatient sampling. However, we believe the findings of our study are worthy of reference for other hospitals in China. The second limitation is that differences in the incidence of SU between fracture operations of inpatients might lead to bias. This study has focused on inpatients of fracture who underwent surgical operations outside the ICU ward, and inpatients were not stratified according to the types of fracture operations, which needs to be further evaluated in future studies. Furthermore, the clinical practice guidelines for the evaluation of appropriate SUP medication in surgery patients has not been established as consensus statements. Therefore, we have established the evaluation criteria according to evidence-based recommendations.

Practical Implications

We should pay more attention to the prevalence of inappropriate prescribing patterns of SUP. The presence of patient risk factors for stress ulcer syndrome should determine the need for SUP. Institution-specific recommendations must be formulated to help clinicians identify appropriate candidates for SUP medication (Allen et al., 2004; Hussain et al., 2010). Continuous education programs for clinicians detailing evidence-based indications for SUP and the adverse reaction of AST are required to correct doctors' misunderstandings (Hussain et al., 2010; Savarino et al., 2018). The intervention of clinical pharmacists could decrease the inappropriate usage of ASMs, as well as drug expenditures and the risk of adverse events, effectively (Hussain et al., 2010; Jarchow-Macdonald and Mangoni, 2013; Buckley et al., 2015; Masood et al., 2018; Tandun et al., 2019). Clinical pharmacists could help strengthen regulation of clinical application of PPIs. For future studies, more comprehensive information on the irrational use of PPIs should be collected and drug-related problems (DRPs) should be investigated, so as to provide a reference for PPIs stewardship.

CONCLUSION

This cross-sectional observational study has confirmed that approximately 33.1% of the 1,200 inpatients of fracture who underwent surgical operations in the orthopedics department might not require intravenous PPIs for SUP on a routine basis. Additionally, the prevalence of inappropriately prescribed PPIs for SUP had increased unnecessary costs and the potential risk of adverse events. Furthermore, we delineated the associated factors with inappropriate SUP medications, which indicates the need for more information for clinicians on rationality and efficiency of their prescribing practices. Age above 65 years and prolonged hospitalization were associated with overprescription of SUP. Conversely, prolonged hospitalization, the concurrent use of systemic corticosteroids or anticoagulants, and unemployed status in inpatients were positively associated with underprescription of SUP. Effective intervention strategies should be executed by clinical pharmacists to reduce improper SUP medication and attain substantial cost savings without impairment of patient outcome.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Xi'an People's Hospital (Xi'an Fourth Hospital) (No: 20180044). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

Conceptualization: HL, NL, and XJ; data collection: HL, YZ, and XX; methodology and software: HL and YQ; supervision: XJ and

NL; original draft: HL; critical revision of the manuscript: NL, YQ, and XJ. All authors have approved the final version of the manuscript.

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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.2022.881063/full#supplementary-material

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Medicine shortages: Product life cycle phases and characteristics of medicines in short supply—A register study

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Introduction: Product life cycle refers to all phases of a product from development to active market phase and finally the phase in which products possibly exit the market. The product life cycle of medicines in short supply has not been studied in depth, although there is some indication of mature products and products with lower prices and profit margins being exposed to shortages more often. The aim of this study was to examine the product life cycle phases and characteristics of medicines in short supply as well as the features of medicine shortages in Finland from 2017 to 2019.

Material and methods: Register data on medicine shortages of human medicinal products from 2017 to 2019 was combined with timely data on marketing authorizations and reimbursement status to gain data on product life cycle phases and characteristics (e.g., the age and the reimbursement status) of medicines in short supply and the features of medicine shortages. The data were analyzed in descriptive manner using appropriate statistical testing.

Results: 3,526 shortages were reported during the 3-year study period and the number of shortages increased annually. The average duration of a shortage was 83 days and shortages affected 660 active pharmaceutical ingredients. Most often, shortages occurred with medicines affecting the nervous system, the cardiovascular system, and the genitourinary system. A majority of shortages (n = 2,689) was reported in the reimbursable medicines group, where shortages increased as the number of patients receiving reimbursements increased ($p < 0.001$). In the reimbursable medicines group, shortages most commonly involved medicines aged 15–19, 20–24, and 25–29, whereas with both reimbursable and non-reimbursable products the shortages most often occurred in medicines aged 50–54. The frequency of shortages differed between the groups ($p < 0.001$) when both age and reimbursement status were taken into account.

Conclusion: Medicine shortages are common and affect commonly used medicines. Product life cycle phase has an effect on the frequency of shortages: Reimbursable medicines and medicines exposed to changes in life cycle are more likely to face a shortage. The impacts of product life cycle on the availability of medicines and medicine shortages should be studied in more detail.

KEYWORDS

medicine shortage, product life cycle, age, reimbursement, register study

Introduction

The first medicine shortage, a shortage of insulin, was reported a century ago. Today, medicine shortages pose an increasing challenge to patient care worldwide (U.S. Food and Drug Administration 2019; Shukar et al., 2021). The causes of shortages have been studied and mitigation strategies have been developed (U.S. Food and Drug Administration 2019; Shukar et al., 2021) because medicine shortages have major impacts on patient care, the workload of health-care professionals, and even on pharmaceutical costs (Dill and Ahn 2014; Mazer-Amirshani et al., 2014; Fox and Tyler 2017; Phuong et al., 2019).

The causes of medicine shortages often remain unclear, partly due to the complexity of the issue and the plurality of the causes (Shukar et al., 2021). Earlier research has recognized supply and demand issues and regulatory issues as major determinants of shortages (Dill and Ahn 2014; Alsheikh et al., 2016; Fox and Tyler 2017; Heiskanen et al., 2017; Phuong et al., 2019; Shukar et al., 2021). Furthermore, reports and studies indicate that products with lower prices and profit margins and mature products that have lost their exclusive selling rights might be more exposed to shortages (Fox and Tyler 2017; Dave et al., 2018; U.S. Food and Drug Administration 2019; Tapanila et al., 2021), as the manufacturers' motivation to keep products in the market may be lower with less profitable medicines. A retrospective cohort study has reported the lowest priced medicines being at a substantially elevated risk of shortage (Dave et al., 2018). In part, mature products may be more exposed to shortages because the market does not reward manufacturers for investing in quality and back-up systems when it comes to mature products (U.S. Food and Drug Administration 2019). Minimizing investments might eventually lead to quality issues that potentially cause shortages. Previous findings by the United States Food and Drug Administration (FDA) define mature products as those with the median time of 35 years since first approval (U.S. Food and Drug Administration 2019). However, a uniform definition of mature products is lacking, resulting in a lack of comparative information between countries and markets.

Product life cycle refers to all development, regulatory and optimization procedures during the lifespan of a medicine (Bauer and Fischer 2000; Langedijk et al., 2016; Stevens et al., 2020; Bere 2022). Life cycle includes the pre-submission phase (including development to non-clinical and clinical testing), the evaluation phase (including marketing authorization, and price and reimbursement evaluations, negotiations, and implementation), the post-marketing authorization phase (including post-marketing authorization surveillance, and optimization of life cycle, and patent protection) and finally the market exit phase. Critical aspects in terms of availability of medicines and medicine shortages exist in each phase. However, the impacts of product life cycle on the availability of medicines and medicine shortages have not been studied in depth or published in scientific journals.

The aim of this study was to examine the product life cycle phases and characteristics of medicines in short supply as well as the features of medicine shortages in Finland from 2017 to 2019. More specifically, we studied the frequency and duration of medicine shortages, affected active ingredients and medicine groups, and if and how age and reimbursement status of the products in short supply affect the frequency of shortages. The period 2017–2019 was selected to cover the most recent years prior to the COVID-19 pandemic.

Material and methods

Context and data

The data were formed from registers held by two national authorities: Finnish Medicines Agency (Fimea) and the Social Insurance Institution of Finland (Kela). Fimea is responsible for, e.g., handling marketing authorizations, the supervision of product life cycle from classification to marketing promotion, and for collecting and reporting data on medicine shortage notifications (Finnish Medicines Agency 2022a). Kela is responsible for, e.g., social security coverage (including medicine reimbursements) of all residents regardless of age, wealth or address (Kruuti, 2021; The Social Insurance Institution of Finland 2022a). In Finland, the National Health Insurance scheme covers some of the costs of necessary prescription medicines and some over-the-counter products and basic ointments prescribed by a physician (Kruuti, 2021). Generic substitution and reference price system are in use. The reimbursement system is vital in steering rational prescribing and use of pharmacotherapies and in moderating pharmaceutical costs (Närhi and Asola 2021).

In this study, a medicine shortage accounts for a shortage notification of a human medicinal product from marketing authorization holder to the national authority, Finnish Medicines Agency (Finnish Medicines Agency 2022b). In Finland, shortage reporting is mandatory, on pain of a fine. Multiple notifications can be done for each product. In this study, the data on shortage notifications included the Anatomic Therapeutic Chemical (ATC) classification (World Health Organization 2022) of the product in short supply, the number of shortage notifications from 2017 to 2019, and the start and end dates of each shortage. For simplicity, all shortages that were active on 1 January 2017, were included in the data, even though some shortages may have emerged earlier. Correspondingly, all shortages that were active on 31 December 2019, were included, even though some shortages

may have lasted beyond the study period. Shortage notifications with unclear or incomplete ATC codes or missing start and end dates were excluded from the data. Shortage notifications did not contain information on the product name, strength, or package size.

The shortage notifications data were combined with data from Medicinal Products Database (The Social Insurance Institution of Finland 2022b). The database contains information on whether there are reimbursable products within each seven-digit ATC code (e.g., A01AA01). In this study, the term "reimbursable" is used for a medicine/ATC class in which at least one product is reimbursable, regardless of the reimbursement status of other products in the class. The term "non-reimbursable" is used when none of the products in a class are reimbursable. In the reimbursable ATC classes, the number of patients receiving reimbursements was also included in the data (The Social Insurance Institution of Finland 2022c). The number of patients that received reimbursements annually was divided into four somewhat evenly distributed categories: less than 1,000 patients (90 ATC codes of 382 reimbursable groups), 1,000–9,999 patients (111 ATC codes), 10,000–49,999 patients (103 ATC codes), and 50,000 or more patients (78 ATC codes).

The data were enriched with public data from Fimea's register on the first marketing authorization date for each seven-digit ATC code in order to calculate the age of the products (Finnish Medicines Agency 2022c). The first marketing authorizations in Finland were granted in 1964 (Palva 2015). Therefore, the classification of the product age in years is 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55 or older, based on the first marketing authorization date of the originator product of each active ingredient. The data were searched in February 2022, presenting the situation at the time.

Analysis

The data were analyzed with SPSS Statistics for Windows, Versions 27.0 and 28.0 (SPSS Inc., Chicago, IL, United States) using frequencies and percentages for descriptive analysis. Associations between variables were assessed by Kruskal–Wallis' and Mann-Whitney's U- test for independent samples and by Pearson's χ^2-test between categorical variables. p-value of <0.05 was considered statistically significant.

Ethical consideration

According to the national ethical instructions (Finnish National Board on Research Integrity 2022), this register study did not require ethical statement or permission.

Results

Characteristics of medicines in short supply and medicine shortages

During the 3-year study period, there were 3,539 shortage notifications. Thirteen notifications were excluded from the data due to incorrect or lacking information. The final data consisted of 3,526 medicine shortage notifications. On average, the number equals to more than three shortage notifications a day during the study period. The frequency of shortages increased annually: 817 shortages were reported in 2017, while the number of shortages in 2018 and 2019 were 1,112 and 1,597. Seventeen shortages had started before 2017. The majority of shortages had started in the previous year (2016), but one shortage had reportedly started already in 2015 and another in 2014. Correspondingly, 39 shortages were still active at the end of 2019. The average duration of a reported shortage was 83 days with the median of 60 days.

The most common medicine shortages involved medicines affecting the nervous system (ATC code: N, $n = 928$, 26.3% of all shortages), the cardiovascular system (C, $n = 698$, 19.8%), and the genitourinary system (G, $n = 325$, 9.2%) (Figure 1). At the three-digit level of ATC codes, medicine shortages were most common in agents acting on the renin-angiotensin system (C09, $n = 342$, 9.7% of all shortages), analgesics (N02, $n = 287$, 8.1%) and in psychoanaleptics (N06, $n = 239$, 6.8%) (Supplementary Table S1).

Shortages affected 660 active pharmaceutical ingredients. On average, five shortage notifications were made per each API (median being two notifications). Shortages were most often reported of sumatriptan (N02CC01, $n = 50$), rosuvastatin (C10AA07, $n = 48$), candesartan (C09CA06, $n = 47$) and paracetamol (N02BE01, $n = 47$).

Product life cycle phase of medicines in short supply

Medicine shortages were most common in products aged 20–24 ($n = 818$, 23.2% of all shortages), 15–19 ($n = 652$, 18.5%), and 25–29 ($n = 523$, 14.8%) (Figure 2: the number of medicine shortages according to the age of the products is shown in black bar charts). Notably, shortages were also common in products aged 50–54 ($n = 503$, 14.3%). The difference in the number of medicine shortages in different age groups was statistically significant ($p < 0.001$). In pairwise comparisons, statistically meaningful differences were most often found in comparisons between medicine groups aged 24 or younger, while meaningful differences lacked between pairwise comparisons in medicine groups aged 25 or older (Supplementary Table S2).

Medicines aged 20–24 in short supply ($N = 818$) were most commonly medicines affecting the nervous system ($n = 225$), the cardiovascular system ($n = 219$), and antineoplastic and

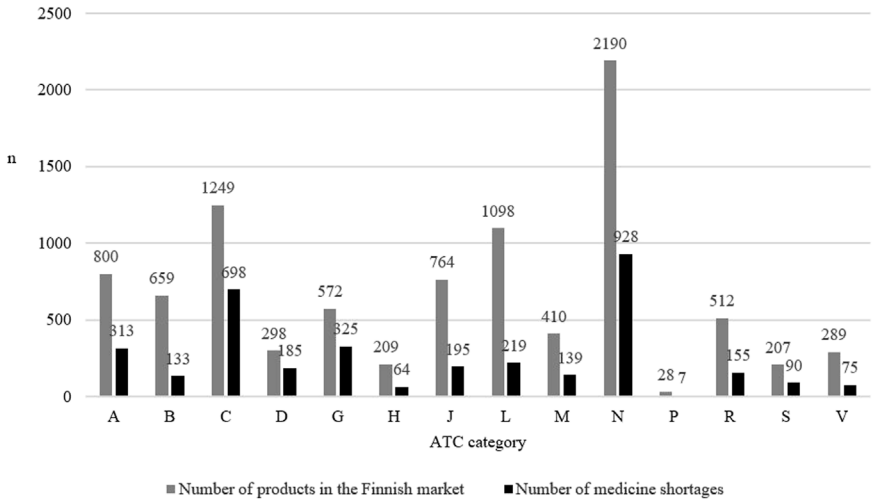

FIGURE 1
The number of products on the Finnish market in 2022 according to the Anatomic Therapeutic Chemical (ATC) category and the number of medicine shortages in Finland (*N* = 3,526) in each category from 2017 to 2019.

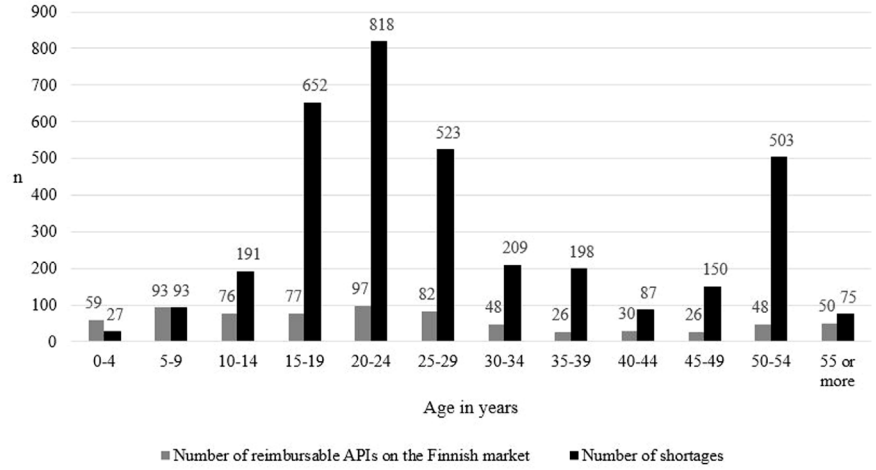

FIGURE 2
The number of reimbursable active pharmaceutical ingredients (API) marketed in Finland (*N* = 712, based on Kari et at, unpublished), and the number of medicine shortages in Finland from 2017 to 2019 (*N* = 3,526) and the age of the products calculated from the first marketing authorization date. Information on the number of APIs marketed in Finland in classes A10AB03, A10AC03, A11JC, B05AX03, C01BA03, L04AC, N05AL05 and V03AG01 was not available.

immunomodulating agents (*n* = 87) (Supplementary Table S3). In medicines aged 15–19 (*N* = 652) and 25–29 (*N* = 523), shortages typically involved medicines affecting the nervous system (*n* = 230 in medicines aged 15–19, and *n* = 140 in medicines aged 25–29), the cardiovascular system (*n* = 107 and *n* = 139), and the genitourinary system (*n* = 71 and *n* = 37). In medicines aged 50–54 (*N* = 503), shortages most often occurred in medicines affecting the nervous system (*n* = 82), alimentary tract and metabolism medicines (*n* = 76), and medicines for cardiovascular diseases (*n* = 56).

A majority of all shortages, 76% in total (*n* = 2,689), were reported in the reimbursable medicines group, while less than one fourth affected the non-reimbursable medicines (*n* = 837) (Supplementary Table S4). In the reimbursable group (*n* = 2,689), shortages were most commonly reported of medicines affecting the nervous system (ATC code N, *n* = 812), the cardiovascular

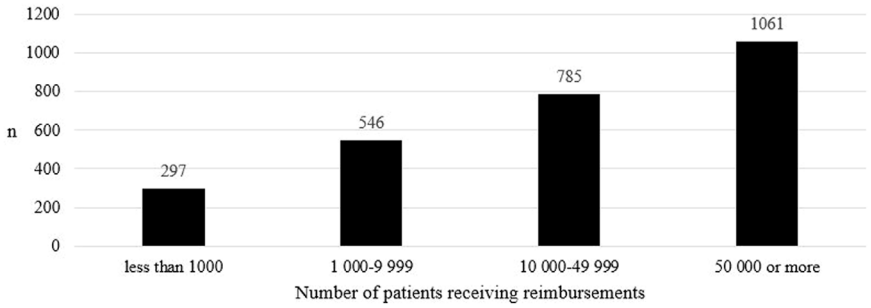

FIGURE 3
The number of medicine shortages in Finland from 2017 to 2019 in groups including at least one reimbursable product (*N* = 382) according to the number of patients receiving reimbursements in Finland in 2022.

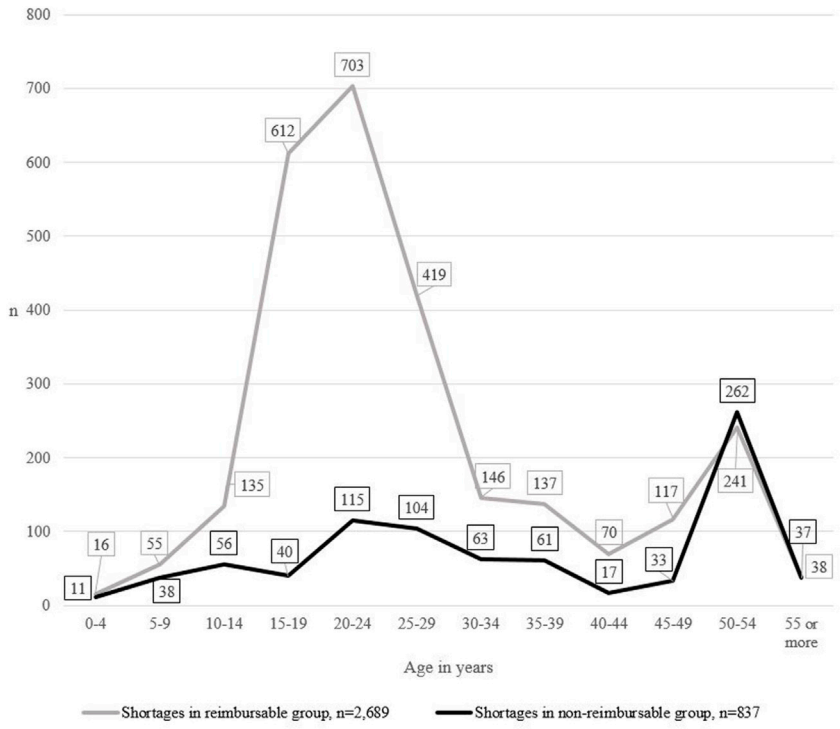

FIGURE 4
The number of medicine shortages in Finland from 2017 to 2019 (*N* = 3,526), the age of medicines in short supply and the reimbursement status of the group.

system (C, *n* = 643), the genitourinary system (G, *n* = 219), and alimentary tract and metabolism (A, *n* = 194) and immunomodulating agents (L, *n* = 176). In the non-reimbursable group, shortages most often occurred of medicines affecting the alimentary tract and metabolism (A, *n* = 119), the nervous system (N, *n* = 116), the genitourinary system (G, *n* = 106), in anti-infectives for systemic use (J, *n* = 102), and in dermatologicals (D, *n* = 63).

In the reimbursable medicines group, the number of medicine shortages increased as the number of patients receiving reimbursements increased (Figure 3). The difference in the number of medicine shortages between groups was statistically significant in all comparisons between groups ($p < 0.001$).

At the level of active pharmaceutical ingredients, at least one reimbursable product was present in a group in 382 ATC codes of

the 660 APIs affected, which accounts for 54% of all reimbursable APIs marketed in Finland (Figure 2: the number of medicine shortages is shown in black bar charts and the number of reimbursable APIs marketed in Finland in grey bar charts). In 278 ATC codes, all products were non-reimbursable.

When both the age and the reimbursement status of products were taken into account, the frequency of medicine shortages differed between the groups (Figure 4). The difference between groups was statistically significant ($p < 0.001$). In the reimbursable group, shortages peaked in products aged 15–19, 20–24, and 25–29, while shortages in the non-reimbursable group remained stable. In both groups, another, yet smaller, peak was detected in products aged 50 to 54.

Discussion

According to this study, medicine shortages are common and growing in numbers. Shortages occur of commonly used medicines, such as medicines affecting the nervous system and the cardiovascular system. These results are consistent with earlier studies conducted in Finland (Heiskanen et al., 2015; Tapanila et al., 2021) and other countries (e.g., Pauwels et al., 2014; Dave et al., 2018; Videau et al., 2019; Benhabib et al., 2020; Clark et al., 2020). Even though shortages can often be resolved with alternative, interchangeable products and patients are rarely left without medicines (Heiskanen et al., 2015; Tapanila et al., 2021), they still burden the health care system and health professionals in their daily work, resulting also to possible increase in medicine prices (Fox and Tyler 2017) and undoubtedly an increase to pharmaceutical expenditure (Blankart and Felder 2022). Our results, together with previous results, pinpoint the fact that despite extensive discussion and the implementation of mitigation strategies (e.g., Clark et al., 2020; Musazzi et al., 2020; Shukar et al., 2021), medicine shortages continue to pose a significant threat to pharmaceutical care. There is a growing need to improve the understanding of the determinants of medicine shortages and to find novel strategies to combat the issue of shortages.

To the best of our knowledge, product life cycle phases of medicines in short supply has not previously been studied in depth or published in scientific journals, and our study is the first one to report the differences in the number of shortages of products in different life cycle phases systematically. According to our results, reimbursable medicine groups are more likely to face shortages than non-reimbursable medicine groups. Furthermore, the number of shortages increases as the number of patients receiving reimbursements increases. Our results are in line with previous Finnish studies, indicating that shortages often occur of commonly used medicines (Heiskanen et al., 2015; Tapanila et al., 2021), and with a Canadian study indicating that markets with a high proportion of medicines covered by public insurance programs were more likely to face shortages (Zhang et al., 2020). In addition, our results are in line with the fact that in 2018, 60% of all products on the Finnish market were reimbursable (Ruskoaho 2018), although, in our study, the share of reimbursable medicines group in all shortages was slightly higher, 76%. Notably, according to our results, more than half of reimbursable active pharmaceutical ingredients are affected by shortages, suggesting that critical products may be exposed to shortages as well. In an earlier Finnish study, the number of critical products in shortage was lower (19%), but the study took account both products in the national mandatory reserve supplies and in the WHO Model Lists of Essential Medicines list (Tapanila et al., 2021). Regardless, to draw any further conclusions, additional research on the impacts of price and reimbursement status of products affected by medicine shortages is needed.

Our study is the first one to report statistical differences in the number of shortages of products of different age. According to this study, products aged 15–19, 20–24, 25–29, and 50–54 were most likely to face a shortage. Strikingly, products aged 15–19, 20–24, and 25–29 in short supply mainly belong to the reimbursable medicines group, while products aged 50–54 in short supply include both reimbursable and non-reimbursable products. It seems that in the reimbursable medicines group, shortages peak after the exclusive selling rights and possible additional protection have expired. Typically, this happens approximately 15–20 years after the initial patent was granted (Garattini et al., 2022). Potentially, increased (generic) competition in the market leads to lower profitability and new market positions, due to which some products temporarily exit the market causing a shortage for commercial reasons (Heiskanen et al., 2017; Shukar et al., 2021). According to Canadian studies, a majority of medicines in short supply are manufactured by generic companies (Videau et al., 2019) and markets with a single generic manufacturer are more likely to face a shortage (Zhang et al., 2020). Similarly, a Finnish study reported that medicines in short supply were most often affordable products for which there were one or more generic alternatives available in the market (Tapanila et al., 2021). Our results, together with previous findings, highlight the fact that the product life cycle, the competitive environment and the role and behavior of players in the market, and medicine shortages should be studied in more detail.

According to our study, another peak in shortages is detected in products aged 50–54. Our results are in line with a Finnish and a French study indicating that the medicines is short supply were most often older products (Benhabib et al., 2020; Tapanila et al., 2021). In the United States, reportedly, the median time since first approval of products in short supply in the United States in 35 years (U.S. Food and Drug Administration 2019), also indicating a rise in shortages of older products. In addition, statistically meaningful differences between age groups were most often found in younger medicine groups aged 24 or

under. This is logical because changes in the life cycle, such as expiration of exclusive selling rights and changes in reimbursement or competitive environment typically occur within the first 20 years of life cycle. The later phases prior to exiting the market appear to be stable, showing no statistical differences between groups. Our results, together with findings from France and from the United States, indicate that shortages might indicate a permanent exit from the market, as the use and profitability of these products may have been declining over the decades. Overall, our results on the differences in the number of shortages of products of different age support previous findings: Medicine shortages appear to occur simultaneously with changes in the life cycle, for example, when exclusive selling rights expire and in the final phase of life cycle.

The strength of this study is the novel information it provides on the impacts of product life cycle on shortages. Furthermore, the study is based on reliable and comprehensive register data from national authorities. However, this study also has limitations. In this study, we use the term "reimbursable" to refer to classes where at least one product is reimbursable. Unfortunately, the data did not include information on the reimbursement status of each individual product; instead, it only included information on whether at least one product in the class was reimbursable. In addition, the information on reimbursement status and the first marketing authorization dates was searched in February 2022, which means there might have been some changes in comparison to 2017–2019. Nonetheless, we believe that possible changes have been minor and would not have significantly affected the results. It is also noteworthy that the data of this study reflects the situation prior to the COVID-19 pandemic. We acknowledge that distinct results on the occurrence of medicine shortages have also been reported during the pandemic (e.g., American Society of Health System Pharmacists 2020). The pandemic has affected the availability of medicines and, since differences only highlight the diversity of the issue, we believe that research is needed to study the situation prior, during and after the pandemic. Overall, further research on the topic of product life cycle and medicine shortages is also needed to better understand the determinants of shortages and to gain novel mitigation strategies. Although this was a single-country study, product life cycle research in one country produces valuable information on the global impacts as well, since there is little variance between countries in, for example, product age.

Conclusion

Medicine shortages are common and involve commonly used medicines. Product life cycle phase has an effect on the frequency of shortages, as reimbursable medicines and medicines exposed to changes in life cycle, for example medicines of which exclusive selling rights expire and medicines in the final phase of their life cycle, are more likely to face a shortage. Although this study was conducted in a single country, product life cycle is likely to have similar impacts elsewhere, thus, the impacts of product life cycle on the availability of medicines and medicine shortages should be studied in more detail.

Data availability statement

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

Author contributions

Conceptualization: all. Data analysis and writing the first draft of the manuscript: KS. Critical revision of the manuscript: all. Approval of the final version of the manuscript: all. Supervision: HKo.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.943249/full#supplementary-material

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SYSTEMATIC REVIEW
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Cost-Effectiveness of Poly ADP-Ribose Polymerase Inhibitors in Cancer Treatment: A Systematic Review

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Background: PARP inhibitors have shown significant improvement in progression-free survival, but their costs cast a considerable financial burden. In line with value-based oncology, it is important to evaluate whether drug prices justify the outcomes.

Objectives: The aim of the study was to systematically evaluate PARP inhibitors on 1) cost-effectiveness against the standard care, 2) impact on cost-effectiveness upon stratification for genetic characteristics, and 3) identify factors determining their cost-effectiveness, in four cancer types.

Methods: We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library using designated search terms, updated to 31 August 2021. Trial-based or modeling cost-effectiveness analyses of four FDA-approved PARP inhibitors were eligible. Other studies known to authors were included. Reference lists of selected articles were screened. Eligible studies were assessed for methodological and reporting quality before review.

Results: A total of 20 original articles proceeded to final review. PARP inhibitors were not cost-effective as recurrence maintenance in advanced ovarian cancer despite improved performance upon genetic stratification. Cost-effectiveness was achieved when moved to upfront maintenance in a new diagnosis setting. Limited evidence indicated non–cost-effectiveness in metastatic breast cancer, mixed conclusions in metastatic pancreatic cancer, and cost-effectiveness in metastatic prostate cancer. Stratification by genetic testing displayed an effect on cost-effectiveness, given the plummeting ICER values when compared to the "treat-all" strategy. Drug cost was a strong determinant for cost-effectiveness in most models.

Conclusions: In advanced ovarian cancer, drug use should be prioritized for upfront maintenance and for patients with BRCA mutation or BRCAness at recurrence. Additional economic evaluations are anticipated for novel indications.

Keywords: cost-effectiveness, systematic review, PARP inhibitors, precision oncology, health economics, health policy

1 INTRODUCTION

The development of poly (ADP-ribose) polymerase (PARP) inhibitors represents a breakthrough in first harnessing the "synthetic lethality" concept in clinical use (Helleday, 2011; Sonnenblick et al., 2015) and kick-started the era of redefining a single tumor type for stratification into distinct diseases specific to genetic aberrations. Patients with tumor-harboring BRCA1/2 mutations or who show homologous recombination deficiency (HRD) are particularly sensitive to the effect of PARP inhibitors (O'Sullivan et al., 2014). At the time of writing, four PARP inhibitors have been approved by the U.S. Food and Drug Administration (FDA): olaparib, niraparib, rucaparib, and talazoparib (RUBRACA (rucaparib), 2020; LYNPARZA (olaparib), 2021; ZEJULA (niraparib) 2021; TELZENNA (talaparib), 2021).

Although efficacy as first-line monotherapy is as yet unproven, PARP inhibitors as maintenance therapy amplify the existing treatment effect. In advanced ovarian cancer, patients receive repeated courses of platinum-based chemotherapies with over 70% risk of recurrence until "platinum resistance" (Jiang et al., 2019; Ovarian Cancer Research Alliance, 2020). In metastatic pancreatic cancer, progression-free survival (PFS) following first-line chemotherapies last only 6 months with less than 10% of patients surviving after 5 years (Conroy et al., 2018; Rawla et al., 2019). PFS often diminishes with subsequent cycles; maintenance therapy between lines could prolong PFS and allow patient eligibility for subsequent strategies, thus enhancing survival likelihood (Evans and Matulonis, 2017). PARP inhibitors targeting ovarian cancer all demonstrated longer median PFS against placebo (olaparib, niraparib, and rucaparib: 16.6–21.0 vs. 5.4–5.5 months) in BRCAmut cohorts of recurrent platinum-sensitive cases, and in the first-line maintenance setting, olaparib and niraparib further extended PFS by 3 years and 1 year among BRCAmut and HRD-positive patients, respectively (Ledermann et al., 2012; Mirza et al., 2016; Coleman et al., 2017; Pujade-Lauraine et al., 2017; Moore et al., 2018; González-Martín et al., 2019). Patients with gBRCAmut metastatic pancreatic cancer also had longer PFS with maintenance olaparib against placebo (7.4 vs. 3.8 months) (Golan et al., 2019). Apart from maintenance, PARP inhibitors demonstrated efficacy in later lines as active treatment for gBRCAmut metastatic breast cancer (PFS extension with olaparib and talazoparib: 2.8–3 months) and gBRCAmut and/or HRD-positive metastatic castration-resistant prostate cancer (PFS with olaparib vs. placebo: 7.4 vs. 3.6 months; objective response rate with rucaparib: 43.5–50.8%) (Robson et al., 2017; Litton et al., 2018; Abida et al., 2020; Hussain et al., 2020).

Value-based oncology is thus warranted to address the cost-effectiveness of novel drugs, for which acceptable prices should be tied to justifiable patient outcomes by cost-effectiveness analyses (Neumann et al., 2021). Incremental cost-effectiveness ratio (ICER), a quotient of the cost difference between two therapeutic interventions divided by the outcome difference, denotes the incremental monetary value for an additional life-year or quality-adjusted life-year (QALY). When this falls below the willingness-to-pay (WTP) or when a strategy is both cost-saving and clinically superior (dominance), it is concluded as cost-effective. A previous literature review on the cost-effectiveness studies of PARP inhibitors focused, however, only on methodological quality and publications related to ovarian cancer (Gao et al., 2020).

Given the recently approved multiple indications in a variety of cancer types and the inconsistent genetic prerequisites for BRCA mutation and HRD status across indications, it is also questionable whether the full biomarker-guided use of PARP inhibitors would improve cost-effectiveness as they acted more profoundly on patient stratification. In this systematic review, we aimed to evaluate PARP inhibitors on 1) the cost-effectiveness against the standard of care, 2) impact on cost-effectiveness upon stratification for genetic characteristics, and 3) to elucidate the key factors that determine cost-effectiveness in the management of ovarian, breast, pancreatic, and prostate cancers.

2 METHODS AND MATERIALS

This study was conducted according to the recommended checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and benchmarked with the methodology of similar systematic reviews on medicinal cost-effectiveness (Moher et al., 2009; Verma et al., 2018; Yoshida et al., 2020).

2.1 Search Strategy and Eligibility

We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library, without language and date restriction, using the search terms: ("poly ADP-ribose polymerase inhibitors" OR "PARP inhibitors" OR "olaparib" OR "rucaparib" OR "niraparib" OR "talazoparib") and ("cost" OR "cost-effectiveness" OR "cost-utility" OR "economics") in any field, updated to 31 August 2021. Reference lists of eligible articles were checked for additional relevant articles, and other studies known to the authors were included. Eligibility criteria were trial-based, or modeling cost-effectiveness analyses published in English or Chinese language related to any of the four FDA-approved PARP inhibitors, regardless of cancer types, lines of treatment, and comparator interventions. Non-comparative studies, reviews, responses, editorials, protocols, and abstract-only articles were excluded.

2.2 Quality Assessment

Studies were assessed using the Quality of Health Economics Studies (QHES) instrument (for methodological quality) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (for reporting quality) (Ofman et al., 2003; Husereau et al., 2013). Articles which obtained a QHES score above 74 out of 100 and CHEERS score above 20 out of 24 were qualified for final data extraction and synthesis.

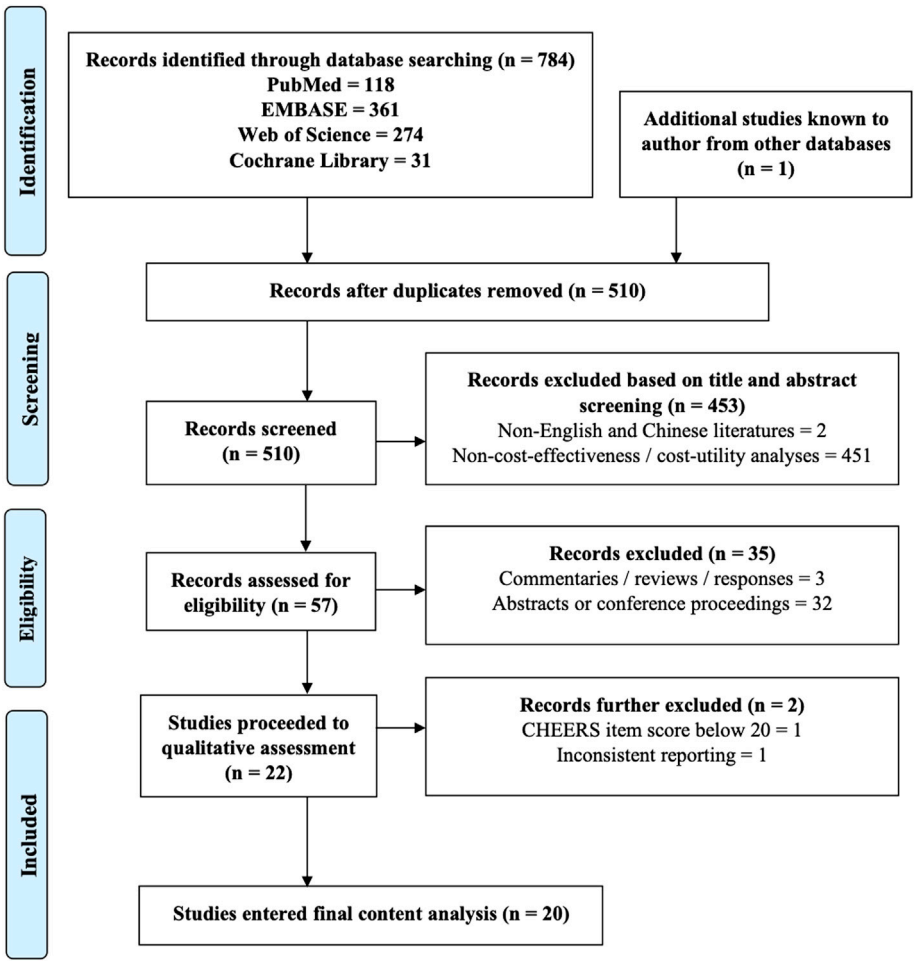

FIGURE 1 | Literature screening process based on 2018 PRISMA flow diagram.

2.3 Data Extraction and Synthesis

Data were extracted based on a pre-defined extraction framework for bibliography, methods, results, and conclusion, including ICER at base-case analysis and model impact at sensitivity analyses. All presented monetary values were converted to U.S. dollars in the year of publication. The primary outcome of interest was the ICER of PARP inhibitors compared with observation (no maintenance treatment after standard treatment), alternative PARP inhibitors, and the standard of care.

Two independent researchers (VKYC and RQY) performed literature screening and quality assessment. Data were extracted by one researcher (RQY) and cross-checked by another researcher (VKYC). All discrepancies were resolved in consensus meetings.

3 RESULTS

3.1 Study Selection and Quality Assessment

A total of 22 original full-text studies passed the initial screening for eligibility (**Figure 1**). Among them, 21 articles achieved good methodological and reporting quality (mean QHES score: 92.5/100 and a CHEERS score of 22.5/24) (**Supplementary Table S1**). One study was excluded further due to inconsistent reporting. Eventually, 20 articles proceeded into final review.

3.2 Study Characteristics

Table 1 illustrates the general characteristics of the included studies. The majority of studies were conducted in the United States (n = 13), five in Asia, and two in Europe. Most studies targeted patients with advanced ovarian cancer (n = 15), with nine focusing on recurrence and six covering new diagnosis setting. The remaining studied metastatic pancreatic (n = 2), breast (n = 2), and prostate (n = 1) cancers. Five studies investigated the role of PARP inhibitors as active treatment, 16 studies as maintenance treatment, and one covered both categories. All studies used decision modeling. The most frequently adopted time horizon was a short-term between 1 and 5 years or until disease progression (n = 10). Ten studies were set out from the payer's perspective, seven from a healthcare system

TABLE 1 | Characteristics of included studies by indication.

Study	Year	Country and perspective	PARPi role	Comparison category[a]	Comparison arms	Model	Time horizon
Recurrent advanced ovarian cancer							
Secord et al.	2013	US society	Recurrence maintenance	PARPi vs. observation Treat-all' vs. Biomarker-directed strategy	(1) *BRCA* testing followed by selective olaparib vs. observation (2) "Global olaparib" vs. *BRCA* testing followed by selective olaparib	Modified Markov model	12 months
Smith et al.	2015	US third-party payer	Recurrence maintenance	PARPi vs. observation	(1) Olaparib vs. observation (g*BRCA*mut) (2) Olaparib vs. observation (*BRCA*wt)	Decision analysis model	Not mentioned
Wallbillich et al.[b]	2016	US payer	Recurrence active treatment	PARPi vs. standard care	Genomic-guided targeted therapy[c] vs. chemotherapy for all without testing	Decision model	12 months
Institute for Clinical and Economic Review Report	2017	US healthcare system	Recurrence maintenance and recurrence active treatment	PARPi vs. observation PARPi vs. standard care	(1) Olaparib vs. placebo (g*BRCA*mut) (2) Niraparib vs. placebo (g*BRCA*mut) (3) Niraparib vs. placebo (non-g*BRCA*mut) (4) Rucaparib vs. placebo (*BRCA*mut) (5) Olaparib vs. chemotherapy (g*BRCA*mut) (6) Rucaparib vs. chemotherapy (*BRCA*mut)	Semi-Markov model	15 years
Zhong et al.	2018	US healthcare sector	Recurrence maintenance	PARPi vs. observation PARPi vs. PARPi	(1) Olaparib vs. placebo (general population) (2) Niraparib vs. placebo (general population) (3) Olaparib vs. placebo (g*BRCA*mut) (4) Niraparib vs. placebo (g*BRCA*mut) (5) Olaparib vs. placebo (non-g*BRCA*mut) (6) Niraparib vs. placebo (non-g*BRCA*mut) (7) Niraparib vs. olaparib (general population) (8) Olaparib vs. niraparib (g*BRCA*mut) (9) Niraparib vs. olaparib (non-g*BRCA*mut)	Decision tree model	Until disease progression or death
Dottino et al.	2019	US society	Recurrence maintenance	PARPi vs. observation 'Treat-all' vs. biomarker-directed strategy	(1) g*BRCA* mutation testing followed by selective niraparib vs. observation (2) g*BRCA* mutation + tumor HRD testing followed by selective niraparib vs. g*BRCA* mutation testing followed by selective niraparib (3) Treat all with niraparib vs. g*BRCA* mutation + tumor HRD testing, followed by selective niraparib	Decision analysis model	Less than 24 months
Guy et al.	2019	US payer	Recurrence maintenance	PARPi vs. observation PARPi vs. PARPi	(1) Niraparib vs. routine surveillance (g*BRCA*mut)* (2) Niraparib vs. routine surveillance (non-g*BRCA*mut)* (3) Niraparib vs. olaparib (non-g*BRCA*mut) (4) Niraparib vs. rucaparib (g*BRCA*mut) (5) Niraparib vs. rucaparib (non-g*BRCA*mut)	Decision-analytic model	Lifetime
Cheng et al.	2021	SG healthcare system	Recurrence maintenance	PARPi vs. observation 'Treat-all' vs. biomarker-directed strategy	(1) Olaparib for all patients vs. observation (2) Olaparib for g*BRCA*mut patients only vs. observation (3) Olaparib for all patients vs. olaparib for g*BRCA*mut patients only	Partition-survival model	15 years
Leung et al.	2021	TW healthcare system	Recurrence maintenance	PARPi vs. observation	(1) Olaparib vs. placebo (all patients)* (2) Niraparib vs. placebo (all patients)* (3) Olaparib vs. placebo (g*BRCA*mut)* (4) Niraparib vs. placebo (g*BRCA*mut)* (5) Olaparib vs. placebo (non-g*BRCA*mut) (6) Niraparib vs. placebo (non-g*BRCA*mut)	Decision analysis model	24 months
Newly diagnosed advanced ovarian cancer							
Armeni et al.	2020	IT National health service	First-line maintenance	PARPi vs. observation	Olaparib vs. active surveillance (*BRCA*mut)*	Markov model	50 years (lifetime)

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies by indication.

Study	Year	Country and perspective	PARPi role	Comparison category[a]	Comparison arms	Model	Time horizon
Barrington et al.	2020	US third-party payer	First-line maintenance	PARPi vs. observation	(1) Niraparib vs. observation (all patients)* (2) Niraparib vs. observation (HRD-positive)* (3) Niraparib vs. observation (*BRCA*mut)* (4) Niraparib vs. observation (HRD-positive, non-*BRCA*mut)* (5) Niraparib vs. observation (Non–HRD-positive)*	Decision analysis model	Not mentioned
Gonzalez et al.	2020	US third-party payer	First-line maintenance	'Treat-all' vs. biomarker-directed strategy	(1) Niraparib for all patients vs. biomarker-directed niraparib (2) Olaparib/bevacizumab for all patients vs. biomarker-directed olaparib/bevacizumab	Modified Markov model	28 months–45 months
Muston et al.	2020	US third-party payer	First-line maintenance	PARPi vs. observation	(1) Olaparib vs. surveillance (*BRCA*mut)*	Partition-survival model	50 years (lifetime)
Penn et al.	2020	US healthcare system	First-line maintenance	PARPi vs. observation	*BRCA*mut patients: (1) Olaparib vs. observation (2) Olaparib–bevacizumab vs. observation (3) Bevacizumab vs. observation (4) Niraparib vs. observation HRD-positive, non-*BRCA*mut patients: (5) Olaparib–bevacizumab vs. observation (6) Bevacizumab vs. observation (7) Niraparib vs. observation HRD-positive patients: (8) Olaparib–bevacizumab vs. observation (9) Bevacizumab vs. observation (10) Niraparib vs. observation	Decision tree model	2 years
Tan et al.	2021	SG healthcare payer	First-line maintenance	PARPi vs. observation	Olaparib vs. routine surveillance (*BRCA*mut)*	Partition-survival model	50 years (lifetime)
Germline *BRCA*-mutated, HER2-negative locally advanced or metastatic breast cancer							
Saito et al.	2019	JP payer	Recurrence active treatment	PARPi vs. standard care	Olaparib for *BRCA*mut patients after *BRCA* testing vs. standard chemotherapy alone	Markov cohort model	5 years
Lima et al.	2021	SP national health system	Recurrence active treatment	PARPi vs. standard care	After anthracyclines/taxanes: (1) Talazoparib vs. capecitabine After anthracyclines/taxanes and capecitabine: (2) Talazoparib vs. eribulin	Partition-survival model	43 months
Germline *BRCA*-mutated metastatic pancreatic cancer							
Wu et al.	2020	US payer	First-line maintenance	PARPi vs. observation	Olaparib vs. placebo*	Partition-survival model	Not mentioned
Zhan et al.	2020	CN society	First-line maintenance	PARPi vs. observation	Olaparib vs. placebo	Markov model	5 years
HRD-positive metastatic castration-resistant prostate cancer							
Su et al.	2021	US payer	Recurrence active treatment	PARPi vs. standard care	Patients with at least one alteration in *BRCA*1/2 and *ATM*: (1) Olaparib vs. standard care* Patients with alterations in any of 15 pre-specified genes: (2) Olaparib vs. standard care*	Partition-survival model	Not mentioned

Asterisk (*) indicates that a positive conclusion for cost-effectiveness was achieved. [a] PARPi vs. Observation = *any PARP inhibitors were compared against observation, routine surveillance, or placebo, which all mean no maintenance therapy after standard chemotherapy. PARPi vs. SOC = any PARP inhibitors were compared against standard chemotherapy or hormone therapy. Treat-all vs. biomarker-directed = an approach when any PARP inhibitors were given to all patients without genetic characterization, compared with treatment on selective patients guided by the results of genetic tests.* [b] *Wallbillich et al. study was the only group that studied the use of PARPi among platinum-resistant patients.* [c] *PARPi acted as one of the consequential treatment choices guided by the genome-based diagnostic test. Abbreviations: HRD = homologous recombination deficiency; PARPi = poly (ADP-ribose) polymerase inhibitors; SG = Singapore; US = United States; JP = Japan; IT = Italy; CN = China; TW = Taiwan; SP = Spain.*

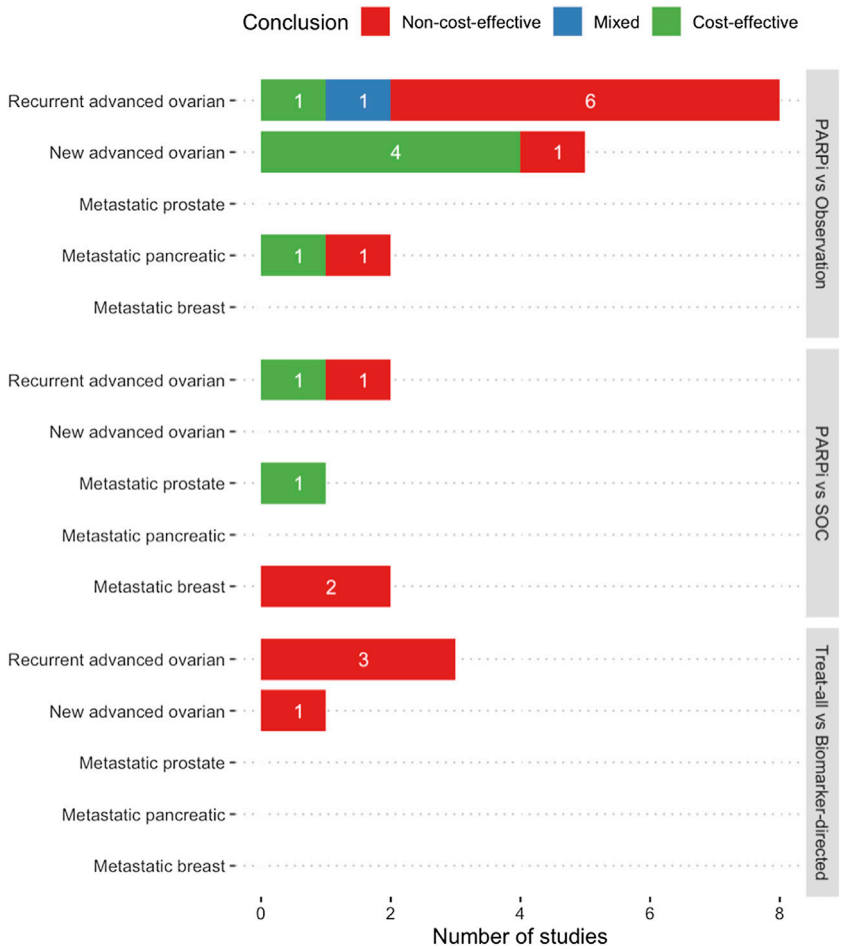

FIGURE 2 | Summary of economic evaluation outcomes of included studies (a,b). (a) Mixed conclusion indicates the presence of both positive and negative conclusion for cost-effectiveness in different comparison arms in the same study. (b) PARPi vs Observation = Any PARP inhibitors were compared against observation, routine surveillance, or placebo, which all mean no maintenance therapy after standard chemotherapy. PARPi vs SOC = Any PARP inhibitors were compared against standard chemotherapy or hormone therapy. Treat-all vs Biomarker-directed = An approach when any PARP inhibitors were given to all patients without genetic characterization, compared with treatment on selective patients guided by the results of genetic tests. Abbreviations: PARPi – PARP inhibitors, SOC – Standard of care.

perspective, and three from a societal perspective. Major comparison arms were observation (n = 15), followed by standard care (n = 5), and alternative biomarker-directed strategies (n = 2). All studies stratified patients based on BRCA mutation, but only three studies examined the effect of HRD status. **Figure 2** summarizes the economic outcomes by comparison arms, and **Tables 2–4** provide detailed economic outcomes of each included study.

3.3 Cost and Clinical Benefits of PARP Inhibitors

Overall, the maintenance strategies with PARP inhibitors generated additional 0.07–4.41 QALYs compared with observation. As active treatment, PARP inhibitors gave 0.03–0.67 QALY compared with the standard care. Clinical benefits varied across types and lines of PARP inhibitors, comparison arms, genetic characteristics, time horizon, and simulation methods of survival data. Costs varied greatly between health systems and country contexts.

3.3.1 Treating Recurrent Advanced Ovarian Cancer

PARP inhibitors were widely studied as maintenance treatment for patients with recurrent advanced ovarian cancer who were responsive to platinum-based chemotherapy. Eight studies compared PARP inhibitors against observation, with six of these concluding that they were not cost-effective. Specifically, Smith et al. (2015) determined that olaparib costs $600,552 per PF-YLS for BRCA wild-type patients, with improved ICER at $258,864 per PF-YLS when restricted to gBRCAmut patients, but this was still beyond the $50,000 WTP threshold. Zhong et al.

TABLE 2 | Details of economic evaluation outcomes of studies in recurrent advanced ovarian cancer.

Study	Comparison arms	IncreEff	IncreCost	Discount rate	ICER	WTP threshold	Conclusion
PARPi vs. observation							
Secord et al.	BRCA testing followed by selective olaparib vs. observation	0.7 months PFS†	$11,518†	None	$193,442 per PF-YLS	$100,000	Not CE
Smith et al.	Olaparib vs. observation (gBRCAmut)	6.9 months PFS	$147,477†	Not reported	$258,864 per PF-LYS	$50,000	Not CE
	Olaparib vs. observation (BRCAwt)	1.9 months PFS	$95,089†	Not reported	$600,552 per PF-LYS	$50,000	Not CE
Institute for Clinical and Economic Review Report	Olaparib vs. placebo (gBRCAmut)	0.59 QALY†	$192,114†	3% yearly	$324,116 per QALY	$50,000–150,000	Not CE
	Niraparib vs. placebo (gBRCAmut)	0.65 QALY†	$191,959†	3% yearly	$291,454 per QALY	$50,000–150,000	Not CE
	Niraparib vs. placebo (non-gBRCAmut)	0.07 QALY†	$126,966†	3% yearly	$1.9M per QALY	$50,000–150,000	Not CE
	Rucaparib vs. placebo (BRCAmut)	0.49 QALY†	$178,083†	3% yearly	$369,175 per QALY	$50,000–150,000	Not CE
Zhong et al.	Olaparib vs. placebo (general population)	0.43 PFS-LY	$122,000	None	$287,000 per PFS-LY	$100,000	Not CE
	Olaparib vs. placebo (gBRCAmut)	1.13 PFS-LYs†	$255,500†	None	$197,000 per PFS-LY	$100,000	Not CE
	Olaparib vs. placebo (non-gBRCAmut)	0.3 PFS-LY	$98,500	None	$328,000 per PFS-LY	$100,000	Not CE
	Niraparib vs. placebo (general population)	0.58 PFS-LY†	$136,800†	None	$235,000 per PFS-LY	$100,000	Not CE
	Niraparib vs. placebo (gBRCAmut)	1.29 PFS-LYs	$254,700	None	$226,000 per PFS-LY	$100,000	Not CE
	Niraparib vs. placebo (non-gBRCAmut)	0.46 PFS-LY	$116,000†	None	$253,000 per PFS-LY	$100,000	Not CE
Dottino et al.	gBRCA mutation testing followed by selective niraparib vs. observation	0.19 PF-QALY	$45,330	None	$243,092 per PF-QALY	$100,000	Not CE
Guy et al.	Niraparib vs. routine surveillance (gBRCAmut)	4.41 QALYs	$301,174	3% yearly	$68,287 per QALY	$150,000	CE
	Niraparib vs. routine surveillance (non-gBRCAmut)	2.148 QALYs	$232,598	3% yearly	$108,287 per QALY	$150,000	CE
Cheng et al.	Olaparib for all patients vs. observation	0.6627 QALY	$66,879	3% yearly	$100,926 per QALY	No fixed WTP	Not CE
	Olaparib for gBRCAmut patients only vs. observation	0.1637 QALY	$14,334	3% yearly	$87,566 per QALY	No fixed WTP	Not CE
Leung et al.	Olaparib vs. placebo (all patients)	0.46 PFS-LY	$29,805	3% yearly	$64,457 per PFS-LY	$92,943	CE
	Niraparib vs. placebo (all patients)	0.62 PFS-LY	$51,686	3% yearly	$83,581 per PFS-LY	$92,943	CE
	Olaparib vs. placebo (gBRCAmut)	1.13 PFS-LYs	$29,805	3% yearly	$26,329 per PFS-LY	$92,943	CE
	Niraparib vs. placebo (gBRCAmut)	1.29 PFS-LYs	$51,686	3% yearly	$40,005 per PFS-LY	$92,943	CE
	Olaparib vs. placebo (non-gBRCAmut)	0.29 PFS-LY	$29,805	3% yearly	$101,033 per PFS-LY	$92,943	Not CE
	Niraparib vs. placebo (non-gBRCAmut)	0.45 PFS-LY	$51,686	3% yearly	$114,859 per PFS-LY	$92,943	Not CE
PARPi vs. standard care							
Wallbillich et al.	Genomic test-guided targeted therapies vs. PLD for all without testing	0.03 QALY†	$15,345†	Not reported	$479,303 per QALY	$100,000	Not CE
Institute for Clinical and Economic Review Report	Olaparib vs. PLD + C (gBRCAmut)	0.67 QALY†	$96,864†	3% yearly	$146,210 per QALY	$50,000–150,000	CE
	Rucaparib vs. PLD + C (BRCAmut)	0.61 QALY†	$180,123†	3% yearly	$294,593 per QALY	$50,000–150,000	Not CE

(Continued on following page)

TABLE 2 | (*Continued*) Details of economic evaluation outcomes of studies in recurrent advanced ovarian cancer.

Study	Comparison arms	IncreEff	IncreCost	Discount rate	ICER	WTP threshold	Conclusion
"Treat-all" vs. biomarker-directed strategy							
Secord et al.	"Global olaparib" vs. BRCA testing, followed by selective olaparib	2.1 months PFS†	$39,822†	None	$234,128 per PF-YLS	$100,000	Not CE
Dottino et al.	gBRCA mutation + tumor HRD testing followed by selective niraparib vs. gBRCA mutation followed by selective niraparib	0.23 PF-QALY	$63,211	None	$269,883 per PF-QALY	$100,000	Not CE
	Treat all with niraparib vs. gBRCA mutation + tumor HRD testing, followed by selective niraparib	0.03 PF-QALY	$59,759	None	$2.2M per PF-QALY	$100,000	Not CE
Cheng et al.	Olaparib for all patients vs. olaparib for gBRCAmut only	0.499 QALY	$52,545	3% yearly	$105,308 per QALY	No fixed WTP	Not CE

All monetary values were converted into U.S. dollars, using specified exchange rates in publication or average exchange rates in the corresponding year of publication. CE = cost-effective; Not CE = not cost-effective. † Incremental values that were computed manually due to the lack of exact figures in original studies. Abbreviation: BRCAmut = BRCA mutation; BRCAwt = BRCA wild-type; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; IncreCost = incremental cost; IncreEff = incremental effectiveness; LY = life-year; PARPi = poly(ADP-ribose) polymerase inhibitors; PLD(+C) = pegylated liposomal doxorubicin (+carboplatin); PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; WTP = willingness-to-pay.

(2018) later expanded the comparison to both olaparib and niraparib and identified their ICERs at $287,000 and $235,000 per PFS-LYS, which dropped only slightly to $197,000 and $226,000 per PFS-LY when restricted to gBRCAmut patients. Consistent findings were noted in the Institute for Clinical and Economic Review Report, two more studies in the United States (Secord et al., 2013; Institute for Clinical and Economic Review 2017; Dottino et al., 2019), and one study in the Singaporean context (Cheng et al., 2021). The Guy group in the United States was one of the two that concluded PARP inhibitors were cost-effective in comparison to observation, with niraparib in both gBRCAmut and wild-type patients giving ICERs at $68,287 and $108,287 per QALY, albeit a questionably high WTP threshold at $150,000 (Guy et al., 2019). Another similar conclusion was drawn in Taiwan by Leung et al., which later expanded the comparison to both niraparib and olaparib. Regardless of genetic features, the ICERs accounted for 69–90% of the WTP threshold. When restricted to gBRCAmut patients only, the ICERs even dropped to between 28 and 43% of the threshold (Leung et al., 2021).

In contrast to maintenance therapies, two studies evaluated the active role of PARP inhibitors in later lines in comparison with chemotherapies in the recurrence setting, with inconsistent results. In BRCAmut patients, the Institute for Clinical and Economic Review Report deemed olaparib cost-effective versus PLD + C (pegylated liposomal doxorubicin + carboplatin) at $146,210 per QALY, in contrast to rucaparib, which was not cost-effective at $294,593 per QALY against PLD + C (Institute for Clinical and Economic Review 2017). However, the genome-guided approach with next-generation sequencing (NGS) to test all concurrent targetable mutations was not cost-effective, although it was in the context of platinum-resistant cases (Wallbillich et al., 2016).

3.3.2 Treating Newly Diagnosed Advanced Ovarian Cancer

Since 2018, PARP inhibitors have been approved for earlier use as upfront maintenance rather than waiting for relapse occurrence following successful response to first-line chemotherapy, based on genetic characteristics. Six studies investigated their value as upfront maintenance. Five studies compared PARP inhibitors against observation with four concluding them to be cost-effective. In particular, Tan et al. (2021)compared first-line olaparib maintenance with routine surveillance in the Singaporean context and demonstrated $14,470 per QALY, an ICER far below their $36,496 WTP threshold. Olaparib was similarly found to be cost-effective in Italy and the United States, with ICERs accounting for 52–69% of their WTP thresholds (Armeni et al., 2020; Muston et al., 2020). Apart from olaparib, Barrington et al. (2020) comprehensively modeled five scenarios when offering niraparib to all patients, HRD-positive-only patients, BRCAmut-only patients, HRD-positive non-BRCAmut patients, and non–HRD-positive patients; all ICERs ranged from $50,914 to $88,741 per QALY, which remained lower than the $100,000 threshold. Without applying cost and benefit discounting, Penn et al. was the only group that showed negative findings for first-line maintenance with and without adding an antiangiogenic agent. Among the ten strategies composed of olaparib-only, niraparib-only, bevacizumab-only, and olaparib and bevacizumab with and without stratification by genetic characteristics, when compared against observation, the ICERs stayed high in the range from $366,100 to $10,870,576 per PF-LYS (Penn et al., 2020).

3.3.3 Treating Metastatic Breast, Pancreatic, and Prostate Cancers

PARP inhibitors were approved for metastatic breast cancer with HER2-negative gBRCAmut patients who failed chemotherapy or

TABLE 3 | Details of economic evaluation outcomes of studies in newly diagnosed advanced ovarian cancer.

Study	Comparison arms	IncreEff	IncreCost	Discount rate	ICER	WTP threshold	Conclusion
PARPi vs. observation							
Armeni et al.	Olaparib vs. active surveillance (BRCAmut)	2.41 QALYs	$30,586	3% yearly	$12,703 per QALY; $10,654 per LY	$18,332	CE
Barrington et al.	Niraparib vs. observation (All patients)	5.6 months PFS	$918,750	Not mentioned	$72,829 per QALY	$100,000	CE
	Niraparib vs. observation (HRD-positive)	11.5 months PFS	$737,500	Not mentioned	$56,329 per QALY	$100,000	CE
	Niraparib vs. observation (BRCAmut)	11.2 months PFS	$412,500	Not mentioned	$58,348 per QALY	$100,000	CE
	Niraparib vs. observation (HRD-positive, non-BRCAmut)	11.4 months PFS	$300,000	Not mentioned	$50,914 per QALY	$100,000	CE
	Niraparib vs. observation (Non-HRD-positive)	2.7 months PFS	$268,750	Not mentioned	$88,741 per QALY	$100,000	CE
Muston et al.	Olaparib vs. surveillance (BRCAmut)	2.93 QALYs	$152,545	Not mentioned	$51,986 per QALY; $42,032 per LY	$100,000	CE
Penn et al.	Olaparib vs. observation (BRCAmut)	2.23 PF-LYS	$415,798	No discounting	$186,777 per PF-LYS	$100,000	Not CE
	Olaparib–bevacizumab vs. observation (BRCAmut)	1.48 PF-LYS	$542,708	No discounting	$366,199 per PF-LYS	$100,000	Not CE
	Bevacizumab vs. observation (BRCAmut)	0.26 PF-LYS	$130,541	No discounting	$508,434 per PF-LYS	$100,000	Not CE
	Niraparib vs. observation (BRCAmut)	0.46 PF-LYS	$489,176	No discounting	$1,069,627 per PF-LYS	$100,000	Not CE
	Olaparib–bevacizumab vs. observation (HRD-positive, non-BRCAmut)	0.86 PF-LYS	$542,708	No discounting	$629,347 per PF-LYS	$100,000	Not CE
	Bevacizumab vs. observation (HRD-positive, non-BRCAmut)	0.18 PF-LYS	$130,541	No discounting	$717,255 per PF-LYS	$100,000	Not CE
	Niraparib vs. observation (HRD-positive, non-BRCAmut)	0.46 PF-LYS	$489,176	No discounting	$1,072,754 per PF-LYS	$100,000	Not CE
	Olaparib–bevacizumab vs. observation (HRD-positive)	0.25 PF-LYS	$542,708	No discounting	$2,153,600 per PF-LYS	$100,000	Not CE
	Bevacizumab vs. observation (HRD-positive)	0.23 PF-LYS	$130,541	No discounting	$557,865 per PF-LYS	$100,000	Not CE
	Niraparib vs. observation (HRD-positive)	0.05 PF-LYS	$489,176	No discounting	$10,870,576 per PF-LYS	$100,000	Not CE
Tan et al.	Olaparib vs. routine surveillance (BRCAmut)	2.85 QALYs	$41,184	3% yearly	$14,470 per QALY	$36,496	CE
"Treat-all" vs. biomarker-directed strategy							
Gonzalez et al.	Niraparib-for-all vs. biomarker-directed niraparib	Not mentioned	$68,081	3% yearly	$593,250 per QA-PFY	$150,000	Not CE
	Olaparib/bevacizumab-for-all vs. biomarker-directed olaparib/bevacizumab	Not mentioned	$105,836	3% yearly	$3,347,915 per QA-PFY	$150,000	Not CE

All monetary values were converted to U.S. dollars, using specified exchange rates in publication or average exchange rates in the corresponding year of publication. CE = cost-effective, Not CE = not cost-effective. Abbreviation: BRCAmut = BRCA mutation; HRD = homologous recombination deficiency; IncreCost = incremental cost, IncreEff = incremental effectiveness; LYS = life-year saved; PARPi = poly(ADP-ribose) polymerase inhibitors; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; WTP = willingness-to-pay.

for HR-positive gBRCAmut patients who failed or were ineligible for endocrine therapies. Two studies investigated the cost-effectiveness of PARP inhibitor versus standard chemotherapies in these patients, and both deemed the former not cost-effective. Saito's group in Japan compared the strategy of olaparib monotherapy after positive BRCA mutation profiling to the use of capecitabine, eribulin, or vinorelbine without testing and discovered that the former costs $131,047 per QALY, which was hardly cost-effective at the WTP threshold of $89,286 (Saito et al., 2019). Regarding talazoparib, consistent findings were presented in a Spanish study by Lima and others, who obtained ICERs slightly above $280,000 per QALY in two scenarios compared with capecitabine or eribulin, which were ten-fold higher than the threshold of $23,945 (Olry de Labry Lima et al., 2021).

Olaparib, as maintenance after first-line platinum-based chemotherapy for g*BRCA*mut metastatic pancreatic cancer, a recent indication approved in 2019, was studied by two groups for its cost-effectiveness versus placebo, but the conclusions were mixed. In particular, Wu and Shi (2020) in the United States found that olaparib was cost-effective with an ICER at $191,596 per PFS-QALY, which was below the $200,000 threshold but not

TABLE 4 | Details of economic evaluation outcomes of studies in other cancers.

Study	Comparison arms	IncreEff	IncreCost	Discount rate	ICER	WTP threshold	Conclusion
Germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer							
Saito et al.	Olaparib for BRCAmut patients after BRCA testing vs. standard chemotherapy alone	0.037 QALY	$4,787	2% yearly	$131,047 per QALY	One- to three-times the GDP of Japan	Not CE
Lima et al.	Talazoparib vs. capecitabine	0.26 QALY	$65,766	Not mentioned	$287,822 per QALY	$23,945	Not CE
	Talazoparib vs. eribulin	0.26 QALY	$67,639	Not mentioned	$296,020 per QALY	$23,945	Not CE
Germline BRCA-mutated metastatic pancreatic cancer							
Wu et al.	Olaparib vs. placebo	0.483 QALY	$128,266	8% yearly	$191,596 per PFS-QALY	$200,000	CE
Zhan et al.	Olaparib vs. placebo	0.69 QALY	$23,544	3% yearly	$34,122 per QALY	$28,256	Not CE
Germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer							
Su et al.	Olaparib vs. standard care (at least one of the BRCA1, BRCA2 and ATM gene alterations)	0.063 QALY	$7,382	3% yearly	$116,903 per QALY	$150,000 per QALY	CE
	Olaparib vs. standard care (at least one of the BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L gene alterations)	0.068 QALY	$-6,950	3% yearly	Dominated	$150,000 per QALY	CE (olaparib-dominant)

All monetary values were converted to U.S. dollars, using specified exchange rates in publication or average exchange rates in the corresponding year of publication. CE = cost-effective; Not CE = not cost-effective. Abbreviation: BRCAmut = BRCA mutation; HRD = homologous recombination deficiency; IncreCost = incremental cost; IncreEff = incremental effectiveness; LY = life-year; LYS = life-year saved; MLG = month of life gained; PARPi = poly(ADP-ribose) polymerase inhibitors; QALY = quality-adjusted life year; WTP = willingness-to-pay.

the case when modeling was based on overall survival data ($265,290 per QALY). In China, Zhan et al. (2020) identified an ICER at $34,122 per QALY which did not support cost-effectiveness at the WTP threshold of $28,255, although the ICER drastically dropped to $14,563 per QALY when the drug cost was calculated based on the donation plan for ovarian cancer.

Only one study evaluated the cost-effectiveness in metastatic castration-resistant prostate cancer, owing to the recent approval in 2020. In the two scenarios modeled by Su et al. in the United States, compared with the standard care, olaparib was cost-effective when used among patients with at least one gene alteration in BRCA1, BRCA2, and ATM, with an ICER yielded at $116,903 per QALY. In the case of expanding the treatment group to patients who had alterations in any of all 15 pre-specified genes (BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B/C/D, and RAD54L) after NGS testing, olaparib turned out to be a cost-effective option (Su et al., 2020).

3.4 Worthiness of the Biomarker-Directed Treatment Strategy

In the studies that separated their analyses based on genetic characteristics, the ICERs using PARP inhibitors among only BRCAmut and/or HRD-positive patients were always lower than those among all patients, implying that the biomarker-directed treatment strategy was potentially cost-effective. Four studies directly compared the biomarker-directed strategy against "global PARP inhibitors," an approach that offers the drug to all patients, regardless of their genetic characteristics. In recurrent advanced ovarian cancer, Secord et al. (2013)concluded that "global olaparib" offered the greatest efficacy but was the costliest. In the United States and Singapore, "global olaparib" was associated with an incremental cost of $234,128 or $105,300 per progression-free life year compared with the BRCA1/2 testing stratification strategy (Secord et al., 2013; Cheng et al., 2021). However, compared with observation only, BRCA1/2 testing-directed treatment was still not cost-effective. The Dottino group demonstrated similar findings for niraparib, except that they also evaluated the addition of HRD testing alongside BRCA testing before treatment (Dottino et al., 2019). Consistently in newly diagnosed advanced ovarian cancer, Gonzalez et al. (2020) concluded that when compared with biomarker-directed treatment, adopting "global olaparib or niraparib" yielded ICERs as high as $3,347,915 per QA-PFY.

3.5 Key Cost-Effectiveness Determinants

All the articles performed sensitivity analyses to assess the factors which potentially impacted the cost-effectiveness of PARP inhibitors. Out of 20 studies, 17 highlighted that the drug price was a significant driver of the ICER (Secord et al., 2013; Smith et al., 2015; Wallbillich et al., 2016; Institute for Clinical and Economic Review, 2017; Zhong et al., 2018; Dottino et al., 2019; Armeni et al., 2020; Barrington et al., 2020; Gonzalez et al., 2020; Muston et al., 2020; Penn et al., 2020; Su et al., 2020; Wu and Shi, 2020; Zhan et al., 2020; Cheng et al., 2021; Leung et al., 2021; Olry de Labry Lima et al., 2021). In the United States system, to be cost-effective in treating recurrent ovarian cancer

among BRCAmut patients, major cost reduction to $3,000–6,400 per cycle was warranted for olaparib, niraparib, and rucaparib, which was up to 76% reduction at the WTP of $100,000 (Secord et al., 2013; Smith et al., 2015; Wallbillich et al., 2016; Dottino et al., 2019). For newly diagnosed ovarian and metastatic pancreatic cancers, 47 and 50% reduction in olaparib cost for BRCAmut patients was highlighted, respectively (Penn et al., 2020; Wu and Shi, 2020). In the Spanish context, for metastatic breast cancer, an even more drastic price cut for talazoparib to $906 per cycle (85% reduction) was warranted to reach the $23,945 threshold (Olry de Labry Lima et al., 2021). ICERs were less sensitive to the costs of chemotherapies, hospital care, general adverse event management, and molecular testing. As for clinical estimates, models were more sensitive to the hazard ratios of PFS or the ratios used to project overall survival, time-receiving maintenance treatment, and utility values at progressive disease state (Smith et al., 2015; Zhong et al., 2018; Guy et al., 2019; Saito et al., 2019; Armeni et al., 2020; Barrington et al., 2020; Su et al., 2020; Wu and Shi 2020; Leung et al., 2021).

4 DISCUSSION

PARP inhibitors marked a breakthrough in the burgeoning wave of precision oncology as they provide substantial progression-free survival benefit in a broad range of patients with actionable targets. The unbridled high costs may nonetheless hinder their presence in clinical routines; health economic studies are therefore warranted to assess priorities. This systematic review depicts several findings. First, the cost-effectiveness of PARP inhibitors varied with cancer types and lines of treatment. In most cases, they were not cost-effective as maintenance treatment for recurrent advanced ovarian cancer was compared with observation, but a stronger potential was attained when moved earlier to upfront maintenance in newly diagnosed advanced ovarian cancer. Limited evidence showed that PARP inhibitors were not cost-effective in metastatic breast cancer. The conclusions were mixed for metastatic pancreatic cancer, whilst olaparib in metastatic prostate cancer seemed to be cost-effective. Next, stratification by tumor genetic characteristics displayed an effect on ICERs, given the plummeting ICER values after confining treatment to BRCAmut- and/or HRD-only patients. Finally, drug cost was consistently highlighted in all models as a strong cost-effectiveness determinant, followed by the hazard ratio of PFS in some models. However, costs of comparator treatments, hospice care, general adverse event management, and molecular tests made minimal impact on all models.

This review serves to inform payers of the overall cost-effectiveness pattern of PARP inhibitors and key areas to intervene for resource prioritization. Although all included studies utilized registrational randomized data, the overall conclusions in the analyses are logical. In platinum-sensitive BRCAmut ovarian cancer, olaparib maintenance offered significant PFS improvement with 19.1 versus 5.5 months of placebo upon first recurrence in the landmark trial, but when the drug was moved to upfront maintenance in newly diagnosed advanced ovarian cancer, the estimated median PFS difference was numerically extended to 36 months (Pujade-Lauraine et al., 2017; Moore et al., 2018). Despite the higher cost, cost-effectiveness was reflected by the greater survival difference for earlier use along the patient's journey. This finding echoes the recent guidance from the National Institute for Health and Care Excellence in 2020 and 2021 that olaparib alone or plus bevacizumab should be recommended for first-line maintenance in Cancer Drugs Fund with managed access agreement (National Institute for Health and Care Excellence 2019; National Institute for Health and Care Excellence 2021), heralding the importance of maximizing the value of the drug by re-adjusting the treatment position of PARP inhibitors and identifying BRCA mutation and HRD early at the time of diagnosis. In all relevant articles, biomarker-directed treatment was always more cost-effective than treating all patients with PARP inhibitors, regardless of genetic features. Comprehensive genome profiling was particularly valuable in metastatic prostate cancer as the targeted use of olaparib among patients with alterations in any of the 15 pre-specified genes yielded a cost-effective option, which was concluded as a more appropriate strategy than testing for only three gene alterations, owing to a lower number needed to screen for identifying eligible patients. When a funding decision has to be made, it is important to prioritize targeted use based on genetic stratification and to select the composition of test panels prudently to maximize the value of PARP inhibitors.

Undeniably, the poor cost-effectiveness of PARP inhibitors in recurrent ovarian cancer and metastatic breast cancer remains an issue. The standard comparator in platinum-sensitive ovarian cases was wait-and-watch, which explains the tremendous incremental cost, following the introduction of an extra treatment. In the case of metastatic breast cancer, however, it was more attributed by the relatively minuscule incremental QALY as olaparib and talazoparib were compared against an effective treatment. Another contributor for both was the steep drug price, a strong determining factor identified in 85% of the studies. Taking the United States system as an example, the per month wholesale acquisition costs of PARP inhibitors for ovarian cancer ranged from $13,679 to 18,070 between 2017 and 2018 (Institute for Clinical and Economic Review 2017; Gonzalez et al., 2020). In this review, PARP inhibitors could face a radical price cut to as low as $3,000 in order to fulfill the common WTP thresholds at $100,000, but the requirement seems unrealistic since other novel targeted therapies were commonly marketed at $5,000–10,000 per month or higher (Kaplan, 2017). Price negotiation could be an alternative measure as Zhan et al. (2020) found that olaparib turned out to be cost-effective in metastatic pancreatic cancer despite off-label use if the discounted price approved in ovarian cancer could similarly be applied to pancreatic cancer (Zhan et al., 2020).

There is a disproportionate distribution of economic evidence across different indications, countries, and health systems. The majority of studies were in the United States, and the remaining studies mostly originated from other developed countries, which signify an unmet need in developing countries where cost-effectiveness or even treatment access is questionable. Next, compared with advanced ovarian cancer, fewer studies evaluated the use of PARP inhibitors in metastatic breast, pancreatic, and prostate cancers, given that the latter

indications were only approved recently. An assessment of cost-effectiveness consistency across systems was therefore less possible in these indications. Finally, owing to the lack of mature overall survival data, most studies either projected the overall survival impact based on the available PFS data or relied heavily on PF-QALY for interpretation. However, previous literature studies showed that a positive PFS correctly predicted a positive overall survival only 71% of the time (Lakdawalla et al., 2015). Since overall survival depicts the actual length of time until death, it is of greater clinical importance and accounts for any diminished effect in subsequent therapies after PARP inhibitor treatment. Therefore, further verification with mature data from trial or real-world evidence is highly encouraged as this will be critical for payers to confirm how PFS could be translated into overall survival benefit.

5 CONCLUSION

PARP inhibitors were not cost-effective as maintenance treatment for recurrent ovarian cancer but could be cost-effective if used for newly diagnosed patients. PARP inhibitor use should be prioritized for upfront maintenance and for patients with BRCA mutation or BRCAness at recurrence. Economic evidence in metastatic breast, pancreatic, and prostate cancers was less and with mixed conclusions. Drug cost is the most important determinant for cost-effectiveness. Additional economic evaluations across the globe with mature overall survival data and novel indications are anticipated.

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

VC and XL conceived the study idea and study design. VC and RY performed literature screening and data extraction and drafted the manuscript. XL supervised the study conduction. All authors interpreted the results and critically revised for intellectual content. All authors had full access to all the data in this study. All authors met the authorship criteria, approved manuscript submission, and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

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Changing Characteristics of Pharmaceutical Prices in China Under Centralized Procurement Policy: A Multi-Intervention Interrupted Time Series

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Long H, Yang Y, Geng X, Mao Z and Mao Z (2022) Changing Characteristics of Pharmaceutical Prices in China Under Centralized Procurement Policy: A Multi-Intervention Interrupted Time Series. Front. Pharmacol. 13:944540. doi: 10.3389/fphar.2022.944540

Objective: National centralized drug procurement organized by the Chinese government currently represents the largest group purchasing organization worldwide, to establish a reasonable price formation mechanism. This study aimed to evaluate the effects of centralized procurement policy on drug price and price ratio in China.

Method: Monthly drug procurement data of public medical institutions were extracted from the national procurement database, including 11 pilot cities and 36 months from January 2018 to December 2020. Centralized procured INNs (International Nonproprietary Names) (n = 25) and their alternative INNs (n = 96) were selected as study samples. Centralized procured INNs were divided into bid-winning and non-winning products according to the bidding results. Drug price, price distribution, and price ratio were measured. Multi-intervention interrupted time series analysis was performed to estimate the policy impacts in two centralized procurement periods.

Results: The price of centralized procured INNs showed an immediate drop of 44.57% (β = -0.59, p < 0.001) at the policy implementation, among which bid-winning drugs decreased by 61.71% (β = -0.96, p < 0.001). No significant change in the price level or trends was found for non-winning products and alternative drugs in the first-year procurement period (all p-values > 0.05). During the second-year procurement period, alternative drugs in four therapeutic categories detected significant increases in the price level (all p-values < 0.05). The overall coefficient of variation of price distribution exhibited upward trends after policy implementation. Among the most centralized procured INNs, the price ratio between certificated generics (generics that have passed the consistency evaluation) and original drugs declined significantly after policy intervention (p < 0.05), whereas the price ratio between uncertificated and certificated generics increased significantly (p < 0.05).

Conclusion: Chinese government-organized group purchasing resulted in prominent price reduction of bid-winning drugs. The policy observed a short-term "spillover" effect of synergistic price reduction, while the effect wore off after 1-year procurement period. The

extremely dispersed price distribution, as well as unreasonable price ratios, requires further effective price regulation means.

Keywords: centralized procurement, group purchasing, pharmaceutical price, price ratio, China

1 BACKGROUND

Universal access to affordable medicines and healthcare services despite a consistently surging medicine expenditure remains to be one of the biggest health challenges faced by all countries, and China is no exception. From 2010 to 2018, China spent 30–40% of its total health expenditure on medicines (NHC, 2020), exceeding the figures not only in the United States (12.0%), Japan (18.6%), and Korea but also in the OECD (Organization for Economic Co-operation and Development) countries, average (16.4%) (OECD, 2022). Despite years of radical commitment to a drug price reduction in China, the lack of strong purchasing/negotiation power, integrated pricing strategy, standardized pricing principles, as well as efficient financial incentives have still hindered the establishment of a rational drug-pricing mechanism for the last 2 decades (Hu and Mossialos, 2016; Jiang et al., 2021), which in turn have resulted in skyrocketing medicine expense.

In 2009, China launched its ambitious Universal Health Coverage (UHC) reform to provide all citizens equal access to basic healthcare and medicines. Since then, transparent tendering and pooled procurement have gradually become the major approach to lower drug prices in China (Mao et al., 2014). In 2015, the General Office of the State Council officially called for establishing a regional procurement model to implement centralized procurement of well-competitive essential drugs and generic drugs at the provincial level (General Office of the State Council, 2015). However, due to the significant regional variations in negotiation power, tendering standards, and the legacy of the past "drug mark-up policy", the early-stage effect of this drug price control action was below expectations (Fu et al., 2015; Zhang et al., 2019).

To improve the overall affordability of quality drugs, promote balanced demand-supply relations, and facilitate healthy competition in the drug market, in November 2018, China launched a novel National Centralized Drug Procurement (NCDP) initiative. The first pilot program of the NCDP was launched in four municipalities (Beijing, Tianjin, Shanghai, Chongqing) and seven subprovincial cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, and Xi'an) (so-called "4 + 7" procurement). The bidding results revealed that centralized procurement was successful in enhancing payers' negotiation power to maximize the average bid-winning drug price reduction by 52% (General Office of the State Council, 2019). In January 2021, China further called for the expansion of regular NCDP initiatives and adapt it as a trigger for the establishment of a rational drug-pricing mechanism (General Office of the State Council, 2021). As of February 2022, China has carried out six batches of centralized drug procurement and saved over 260 billion Chinese Yuan (CNY) on medicines for the country. With an average price reduction of 53%, the volume of the bid-winning drugs has accounted for 30% of the annual volume purchased by public medical institutions. (NHSA, 2022).

As the current largest group purchasing organization in the world, certainly, the NCDP initiative in China has generally successfully established a "buyer-cartels" to countervail pharmaceutical companies for quality drugs at lower prices (Huff-Rousselle, 2012; Xing et al., 2022). However, the policy impact on drug price change patterns and mechanisms across different countries/regions may be associated with various contextual factors (e.g., policy environment, healthcare conditions, market maturity, competitiveness, etc) and structural factors (e.g., strategy design, stakeholder dynamics, operating mechanism, affected product categories, etc). Aiming to obtain further empirical insights on the practices and impacts of NCDP policy in China, this exploratory study mainly focuses on examining the mid- to long-term price change and price relation characteristics among different categories of pharmaceutical products under centralized procurement policy.

2 LITERATURE REVIEW

2.1 Price Change

Fostering the formation of buyer monopoly through integrating purchasing power for price negotiation with seller is known as the theoretical base for the price-cutting outcome brought by centralized procurement (Huff-Rousselle, 2012). Many studies have provided evidence for such price-changing effects (Kim and Skordis-Worrall, 2017; Toulemon, 2018; Dubois et al., 2021). Dubois et al. (2021) found that centralized procurement contributed at least 15% of the drug price reductions among seven low- and middle-income countries between 2015 and 2017.

In addition, our literature review shows that price change characteristics may be associated with multiple barriers and facilitators among different pharmaceutical categories under the centralized procurement policy. Dubois et al. (2021) argued that the impact of centralized procurement mechanisms on product prices was related to the degree of market concentration or level of competitiveness, in that the higher the market concentration of products, the smaller the impact brought by the policy. Besides, the group purchase of innovative high-cost drugs in France revealed that the policy has a greater impact on oligopolistic drug prices than on monopoly prices (Toulemon, 2018). Pérez et al. (2019) mentioned that pharmaceutical enterprises might rapidly raise the product prices 1 or 2 years after initial price reduction, suggesting a need to observe the long-term effects of such policies on drug prices.

In China, Zhang et al. (2019) conducted a systematic review on the impact of the centralized drug procurement policy, in which 29% of the included studies were positive that the policy has

facilitated drug price cuts and 13.5% believed that it accelerated the progress of universal access to essential medicines. Huang et al. (2019) analyzed the impact of centralized procurement policy on drug prices of ten "4 + 7" centralized procured drugs. It was found that the price ratio of the bid-winning products compared with the international reference price (3.65) was far lower than that of the non-winning products (7.42), indicating that the price of the bid-winning product gradually cut to a rational level. Chen et al. (2020) and Wang et al. (2021) suggested that in the short run (10 months after the execution of the NCDP pilot), the marked decline in the prices of bid-winning products might have potentially driven the price cut of the non-winning products. Wang et al. (2021) found that despite that the price index for alternative medicines (i.e., drug substances that have an alternative relationship with centralized procured drugs) did not change significantly at the beginning of policy implementation, but gradually a downward trend emerged.

However, there is inadequate evidence regarding the mid- or long-term policy effect on the drug price cut in the context of centralized drug procurement policy in China. Without first deeply understanding the complex factors and triggers of drug price change (Sun et al., 2022), the country may continue to struggle with significant issues such as drug price deviation, drug rebates, inflated prices, and unstandardized procurement practice (Zhang et al., 2019). It is necessary for a more in-depth sub-group analysis to comprehensively reveal the pivotal and regularity of drug price change associated with centralized drug procurement policy in China.

2.2 Price Relations

Establishing a rational drug pricing mechanism is the fundamental means and end for the vigorous advocating of the centralized drug procurement initiative in China (Wang, 2020). Therefore, it is of great pragmatic significance to explore the impact of centralized procurement policy on drug price mechanism and price relation (price comparison relationship) in China. Drug price relation/ratio refers to the proportional relationship among prices of different pharmaceutical products in the same market within a certain period, which is known to be one key ingredient for the structure and process of drug price formation (Lu, 2018). Relevant studies on drug price relations have revealed the significance of price differences, price comparisons, and referencing prices in the establishment of a drug price mechanism (Danzon and Chao, 2000; Vieira and Zucchi, 2006; Puig-Junoy and Moreno-Torres, 2010; Dylst and Simoens, 2011).

In China, relevant research on price gaps between generic and original drugs presents the dilemma in the current drug pricing mechanism—the inconsistent quality and efficacy of domestic generic drugs compared with originators, thus hindering the effective formation of market competitiveness of generic drugs (Zhang and Hu, 2016). Efforts have been made since 2012, the Generic Consistency Evaluation (GCE) work was conducted and promoted by the National Medical Products Administration (NMPA) to ensure that marketed generic drugs became bioequivalent to their corresponding original brand-name drugs and has made great strides (State Council Information Office, 2019). Generic drugs are certified for quality and efficacy consistency through pharmacokinetics equivalence and bioequivalence trials (therapeutic equivalence trials are exempted) (Hu, 2021). Although whereafter the National Healthcare Security Administration (NHSA) reports that certificated generics are equivalent to original drugs in both clinical therapeutic efficacy and safety (i.e., therapeutic equivalence) (CCTV, 2021), nor does it seem to completely reassure prescribers and patients (He et al., 2021; Qu et al., 2021). The existence of bioequivalence with originators can theoretically improve the market competitiveness of generic drugs and promote overall price reduction, while it is not the case in China (Chen et al., 2018; Rong and Sun, 2018; Oncu et al., 2020). Li et al. (2012) reported that the price of original drugs in the selected province was 3.6 times that of generic drugs. In 2014, Zhang et al. (2016) found in a drug market survey in Shanghai that the overall price ratio of generic drugs to original drugs was 0.54, indicating the latter was about 1.85 times more expensive than that of the former. An investigation of the prices of 27 commonly used drugs in 31 provinces (Rong and Sun, 2018) found that not only the prices of both original and generic drugs in China were significantly higher than international reference prices, but also the price levels of certain generic drugs drastically varied across provinces in their drug price distribution analysis. The high price difference between generics and originators, as well as the low market share of generics were blamed to the motives of personal interests which drives physicians to prescribe expensive drugs where prices had not been cut off, thus consistency evaluation alone had not generally promoted the substitution of generics.

Recent NCDP policy adopts the GCE as the gate-keeper for qualified generic drugs to participate in the price competition with original drugs in state-wide centralized bidding. All the drugs involved in the market under centralized procurement are comparable as the policy requires that their quality and efficacy are consistent. This provides a pragmatic premise for measuring drug price relation changes. However, to the best of our knowledge, there is limited research focusing on the changes in product price differences and price relations associated with the implementation of the national centralized procurement policy in China.

In light of the abovementioned evidence and current research gaps, this study aims to apply the large-scale NCDP program data to 1) explore the direct and "spillover" effects of NCDP policy on the price-changing patterns and characteristics among the bid-winning drugs, non-winning drugs, and alternative drugs in both short- and long-term, and 2) estimate the effects of the NCDP policy on the change in drug price distribution and price relation among different pharmaceutical categories.

3 METHODS

3.1 Description of the Policy Intervention

As a pharmaceutical reform with multi-dimensional target attributes and multiple intervention measures, the NCDP

policy has been systematically elaborated on its policy practices by previous scholars (Chang, 2021; Hu, 2021; Yuan et al., 2021). In this study, we focus on the policy measures mostly directly related to drug price changes. As is well-known, improving seller's competition is an effective approach to price reduction. In the national centralized drug procurement, the Chinese government adopted the following measures to improve competition: 1) Enhancing competition between quality-assured generics and originators drugs. Only generic drugs certified for quality and efficacy consistency by NMPA (called certificated generic drugs) as well as corresponding originators are eligible to participate in NCDP. They are considered of equal quality and efficacy, and thus were assigned as the same quality level for price competition during centralized bidding (General Office of the State Council, 2019). 2) Merging dosage form and specification. The dosage forms and specifications of drugs were properly merged, and some products with "strange" specifications and dosage forms were excluded from the centralized bidding. Price competition was conducted in the unit of generic name. 3) The limited number of bid-winning enterprises. To improve the intensity of bidding, only the lowest bidder wins the bid in the first bidding of "4 + 7" pilot, and the number of bid-winner adjusted to one to three in the second bidding.

Compared with the first bidding, the core purpose of the second renewal bidding is to achieve "three stabilization" (market expectation, price level, and clinical medication) (NHSA, 2021), rather than a further significant decline in drug price. Therefore, unlike the first bidding, the organization and decision-making of the second renewal bidding were delegated from the state to pilot cities. The bid-winning enterprises of each INN in the two biddings are also different, see **Supplementary Table S1**.

In the present study, the implementation of centralized bidding results was assigned as the intervention to quantify the policy impact on drug prices. In March 2019, all public medical institutions in "4 + 7" pilot cities started carrying out the bid-winning results of the first bidding. After the end of the first 1-year procurement period, second renewal bidding was conducted and the bidding results were implemented in April 2020. Thus, the observation months (January 2018 to December 2020) were divided into three periods: 1) pre-intervention period (January 2018 to February 2019), 2) the first procurement period (March 2019 to March 2020), and 3) second procurement period (April to December 2020).

3.2 Data Sources and Samples

The data used in this study were extracted from the China Drug Supply Information Platform (CDSIP), which summarizes and maintains the drug procurement data of 31 provincial drug bidding and procurement platforms in mainland China. Procurement data extracted from CDSIP include drug name (International Nonproprietary Name, INN), drug code, the name of the medical institution, procurement date, dosage form, specification, packaging, manufacturer, unit price, procurement unit, procurement quantity, procurement expenditures, etc. The integrality and accuracy of CDSIP procurement data are largely endorsed, in that the Chinese government mandates all public medical institutions shall purchase the drugs to be used through the government-led provincial drug centralized procurement platform (General Office of the State Council, 2015). By the end of 2020, CDSIP data covered 48,205 public medical institutions in 31 provinces, including 9176 public hospitals and 39,029 public healthcare centers (Yang et al., 2022). Despite its full coverage of public medical institutions, the CDSIP is estimated to cover over 80% of drug purchasing data from national health facilities in mainland China. The procurement data from the private departments may not be included.

In this study, drug procurement data of all public medical institutions from all eleven "4 + 7" pilot cities were extracted for analysis. The scope of medicines includes centralized procured drugs and their alternative drugs, which were defined as follows:

1) Centralized procured drug refers to the INNs covered by the centralized procurement catalog, which was announced by the Joint Procurement Office (JPO) in the tender document (Joint Procurement Office, 2018a). A total of 25 INNs were procured during the "4 + 7" pilot and thus were included and defined as centralized procured INNs in this study. Furthermore, centralized procured INNs we dichotomized into bid-winning and bid-non-winning drugs according to the bidding results (Joint Procurement Office, 2018b). Drug products that won the bid in the JPO-organized centralized bidding were identified as bid-winning drugs, otherwise were bid-non-winning drugs. We also sorted centralized procured INNs into off-patent original branded products (i.e., original drugs) and generic products based on the *Catalogue of Marketed Drug in China* (NMPA, 2017). Generic drugs were further distinguished by whether had passed the GCE as of March 2019.
2) Alternative drugs were defined as the clinically substitutable drugs of the same therapeutic category with centralized procured drugs, which were not covered by the "4 + 7" centralized procurement catalog. We included alternative drugs following the list of "alternative drugs" provided by the NHSA in the *Monitoring Plan for Centralized Drug Procurement and Use Pilot Work* (NHSA, 2019a). Among them, several drugs were procured in the centralized procurement work of subsequent batches during our observation period, and thus were excluded from our sample. A total of 96 alternative drugs were included in the analysis.

Data were managed using ATC (Anatomical Therapeutic and Chemical) code. Included drugs were sorted into 12 therapeutic categories based on the ATC 2-level code: hypotensive drugs (C08/09), lipid-modifying agents (C10), antiepileptics (N03), psycholeptics (N05), psychoanaleptics (N06), antineoplastic agents (L01), antibacterials for systemic use (J01), antivirals for systemic use (J05), antidiarrheals (A07), antithrombotic agents (B01), antiinflammatory and antirheumatic products (M01), and drugs for obstructive airway diseases (R03). The detailed information on included drugs is listed in **Supplementary Table S2**.

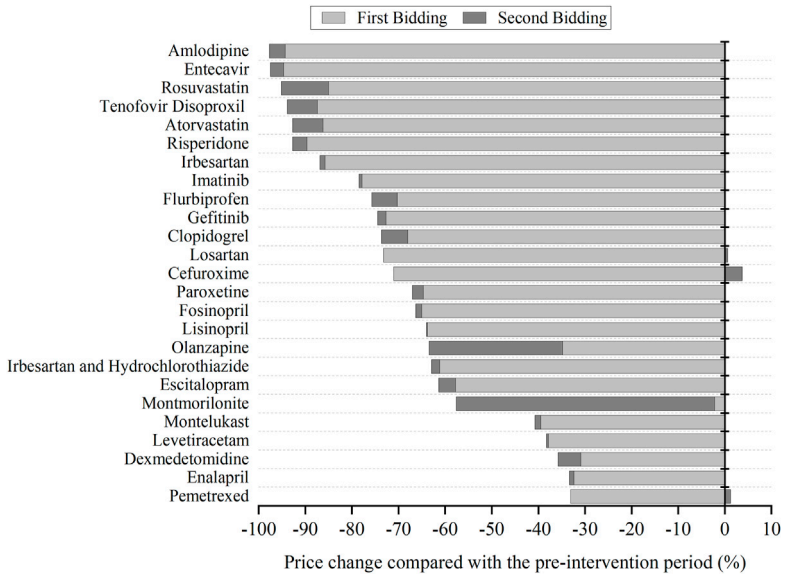

FIGURE 1 | The change of bid-winning prices for each centralized procured INN in two centralized biddings compared with the pre-intervention period.

3.3 Definition of Outcome Variables

3.3.1 Measure of Drug Price

The unit price of each procured drug was calculated based on its defined daily dosage (DDD) defined by the World Health Organization (WHO) (WHO Collaborating Centre for Drug Statistics Methodology, 2018) in absolute monetary terms (CNY). The calculation of drug price is as follows:

$$Y = \sum_{i=1}^{n} C_i \Big/ \sum_{i=1}^{n} \left(\frac{U_i P_i}{DDD_i} \times N_i \right) \quad (1)$$

where Y refers to unit price, C_i represents the cumulative procurement costs of drug product i, DDD_i refers to the DDD value of product i; U_i refers to the unit ingredient of product i; P_i refers to the packing specification of product i; N_i refers to the number of product i.

3.3.2 Measure of Price Distribution

In the present study, we described the price distribution among different drug products within the same therapeutic category. The indicators of dispersion tendency were employed including median, range, coefficient of variation (CV), etc.

3.3.3 Measure of Price Ratio

The price relation of drugs can be measured by the price ratio (PR) of different products. Following the previous studies' approach (Vieira and Zucchi, 2006; Zhang et al., 2016; Zhang and Hu, 2016), we first calculated the price ratio between generic drugs and original drugs: PR_1 = price of generic drug/price of the original drug. The difference in quality and efficacy between generic drugs and original drugs would lead to the lack of practical significance of their price comparison (Zhang et al., 2016). Therefore, we further calculated the price ratio between certificated generic drugs and original drugs: PR_2 = price of certificated generic drug/price of original drug, as well as the price ratio between uncertificated generic drugs and certificated generic drugs: PR_3 = price of uncertificated generic drug/price of certificated generic drug.

3.4 Statistical Analysis

The descriptive statistical method was first employed. To visualize the policies' effects, we graphed monthly trends in drug price of each drug category, fitting the curves of monthly moving averages. Indicators of dispersion tendency (median, range, and CV), as well as violin plots, were applied to describe the price distribution characteristics of different products.

This study applied multi-intervention interrupted time series (ITS) analysis (Ariel, 2015) to estimate the effect of centralized procurement policy in two bidding periods. The regression model was constructed as follows:

$$Y_{it} = \alpha + \beta_0 * time + \beta_1 * intervention_1 + \beta_2 * time * intervention_1 + \beta_3 * intervention_2 + \beta_4 * time * intervention_2 + \mu_{it} + \varepsilon_{it} \quad (2)$$

where Y_{it} refers to outcome variables, i.e. drug price or price ratio. *time* is a continuous variable of observation months ranging from 1 to 36. $intervention_1$ and $intervention_2$ are dummy variables of policy intervention time. $intervention_1$ was coded 1 in the first bidding period (March 2019 to March 2020), otherwise coded 0. $intervention_2$ was coded 1 in the second bidding period (April to December 2020), otherwise coded 0. μ_{it} is the fixed effect of drug products. ε_{it} refers to the random error term. α and β estimated the intercept and slope of drug price in the pre-intervention period of centralized procurement policy, respectively. β_1 and β_3 estimated the immediate level change of dependent variables at the point of implementing the first and second bidding results, respectively. β_2 and β_4 estimated the slope change of dependent variables during the first and second

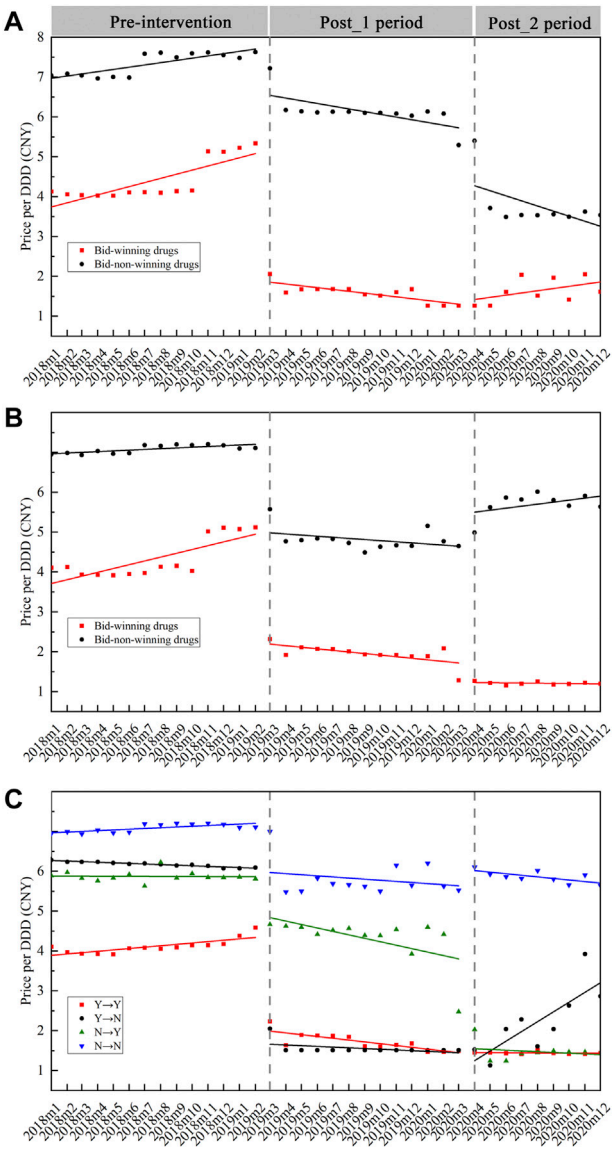

FIGURE 2 | Monthly trends in the price of bid-winning and bid-non-winning products. **(A)** Bid-winning and bid-non-winning products in the first procurement period, **(B)** bid-winning and bid-non-winning products in the second procurement period, **(C)** the cross-bidding results among two procurement periods. *Note.* DDD, defined daily dose; CNY, Chinese yuan.

procurement periods. Data were managed and analyzed in Stata version 15.0 (Stata Corp LP, College Station, TX, United States). A difference with $p < 0.05$ was considered to indicate statistical significance.

4 RESULTS

4.1 Bid-Winning Prices in Centralized Bidding

In the pre-intervention period, the median price of 25 centralized procured INNs was 7.33 CNY. After centralized bidding, the median price of bid-winning products is 1.65 CNY (first bidding) and 1.26 CNY (second bidding), respectively. The price decline of first bidding compared with the pre-intervention period ranges from 2.16 to 94.65%, with an average of 63.16%. The price decline of second bidding compared with the pre-intervention period ranges from 31.87 to 97.71%, with an average of 68.86%.

Figure 1 presents the price changes of bid-winning drugs in two centralized biddings. For most INNs, the prominent price decline occurred in the first bidding period, and then observed a slight decrease in the second bidding. For several INNs, such as Olanzapine and Montmorillonite, a significantly prominent price reduction was also observed in second bidding. Three INNs (Losartan, Cefuroxime, and Pemetrexed) observed price raising in the second bidding against the first bidding.

4.2 Price Change Under Policy Impact

4.2.1 Price Change of Bid-Winning and Bid-non-winning Products

Centralized procured INNs were divided into bid-winning and bid-non-winning products. Moreover, according to the discrepant bid-winning results in two centralized biddings, they were sorted into four categories: 1) products that won the bid in two centralized biddings, coded as Y→Y; 2) products that won the first bid but failed in the second bidding, coded as Y→N; 3) products failed in the first bidding and won the second bid, coded as N→Y; and 4) products that did not win the bid in two centralized biddings, coded as N→N. **Figure 2** graphs the monthly price trends of products in different bidding results between January 2018 and December 2020. The corresponding multi-intervention ITS results are presented in **Table 1**. In two procurement periods, the price level of bid-winning drugs significantly decreased by 61.71% ($e^{-0.96}$–1) ($\beta = -0.96$, $p < 0.001$) after first bidding and 23.97% ($e^{-0.27}$–1) ($\beta = -0.27$, $p < 0.001$) after second bidding, respectively. The price change of bid-non-winning drugs had no significance (all p-values > 0.05) in two procurement periods (**Figures 2A,B**).

For Y→Y products, the immediate price decline of 59.30% ($\beta = -0.90$, $p < 0.001$) and 10.51% ($\beta = -0.11$, $p = 0.023$) were found at the start of the first and second procurement period, respectively; the change in price slopes during two procurement periods showed no significance (all p-values > 0.05). As for Y→N products, an immediate price decline of 78.92% ($\beta = -1.56$, $p < 0.001$) was found after first bidding; the price level had no significant change after second bidding ($p > 0.05$) and showed an increasing trend during the second procurement period ($\beta = 0.16$, $p = 0.002$, 14.80% increment). With regards to N→Y products, the significant decrease in price level change ($\beta = -0.15$, $p < 0.001$, 13.93% decrease) and trend change ($\beta = -0.03$, $p = 0.001$, 2.76% decrease) were detected in the first procurement period; the price significantly decreased by 41.14% ($\beta = -0.53$, $p < 0.001$) at the start of second procurement period. For N→N products, the increase in price level and trend showed no significance (all p-values > 0.05) in the first procurement period; the decrease in price level and trend also had no significance (all p-values > 0.05) in the second procurement period (**Figure 2C**).

TABLE 1 | Multi-intervention ITS quantifying the impact of centralized procurement policy on prices of bid-winning and bid-non-winning products.

Categories	Involved INNs	Level_1		Trend_1		Level_2		Trend_2	
		β_1	*p*	β_2	*p*	β_3	*p*	β_4	*p*
First procurement period									
Bid-winning	25	−0.96	**0.000**	−0.01	0.374	−0.10	0.081	0.02	0.061
Bid-non-winning	25	−0.01	0.839	−0.01	0.230	−0.20	**0.000**	−0.001	0.952
Second procurement period									
Bid-winning	25	−0.76	**0.000**	−0.01	0.201	−0.27	**0.000**	0.01	0.321
Bid-non-winning	23	−0.12	**0.001**	−0.003	0.461	0.06	0.145	0.01	0.187
Cross-bidding results[a]									
Y→Y	22	−0.90	**0.000**	−0.01	0.334	−0.11	**0.023**	0.01	0.464
Y→N	4	−1.56	**0.000**	−0.01	0.727	0.05	0.827	0.14	**0.002**
N→Y	17	−0.15	**0.016**	−0.03	**0.001**	−0.53	**0.000**	0.01	0.653
N→N	23	−0.04	0.109	−0.003	0.385	0.01	0.730	0.001	0.798

[a]*Y→Y represents products that won the bid in two centralized biddings, Y→N represents products that won the first bid but failed in the second bidding; N→Y represents products that failed in the second bidding and won the second bid, and N→N represents products that did not win the bid in two centralized biddings.*

*INNs, International Nonproprietary Names. Bold values indicate regression coefficients with statistical significance (*p *< 0.05). Fixed effect of drug products was applied.*

4.2.2 Price Change of Centralized Procured and Alternative Drugs by Therapeutic Category

Figure 3 outlines the monthly price change of centralized procured INNs and alternative INNs from January 2018 to December 2020, stratified by therapeutic categories. The corresponding multi-intervention ITS results are summarized in **Table 2**. The overall price of centralized procured drugs significantly decreased by 44.57% (β = −0.59, p < 0.001) and 19.27% (β = −0.21, p = 0.001) at the start of the first and second procurement period, respectively. The trend change in the overall price of centralized procured drugs showed no significance during two procurement periods (all p-values > 0.05). The level and trend change in the overall price of alternative drugs had no significance in the first procurement period (all p-values > 0.05). The overall price of alternative drugs showed no significant change in the level and slope in the first procurement period (all p-values > 0.05), whereas the price level significantly increased by 7.04% (β = 0.07, p = 0.036) and decreased by 1.59% (β = -0.02, p = 0.018) in price slope in the second procurement period.

Among 12 therapeutic categories of centralized procured drugs, except for A07 (Montmorillonite) (p = 0.688), the immediate decline was detected in the price of the other 11 categories at the start of the first procurement period (all p-values < 0.001), with the decline ranging between 17.22% (N03) and 70.54% (J05). During the implementation of first bidding, the trend change significantly decreased in the price of eight therapeutic categories (C08/09, C10, N03, n05, N06, L01, J05, and B01) (all p-values < 0.05). At the start of the second procurement period, a significant decline in the price of eight categories (C08/09, C10, N06, J01, J05, A07, B01, and R03) was found (all p-values < 0.05). Four (N05, L01, J05, and M01) of the 12 therapeutic categories showed significant increments in price trends during the second procurement period (all p-values < 0.05).

In regards to alternative drugs, the immediate price change in all 12 therapeutic categories had no significance (all p-values > 0.05) at the start of first procurement period, while the price slope of four categories (C08/09, C10, N03, and B01) decreased significantly (all p-values < 0.05). At the implementation of second bidding, the immediate price increases were observed in C08/09 (β = 0.04, p = 0.010), N03 (β = 0.14, p = 0.027), and B01 (β = 0.14, p = 0.041), with the estimated increment of 3.77, 15.14, and 14.91%. The price slope of five categories (C08/09, C10, N05, N06, and J01) increased prominently during the second procurement (all p-values < 0.05).

4.3 Change of Price Distribution

4.3.1 Centralized Procured Drugs

Figure 4 presents the price distribution of centralized procured INNs among different products in three observation periods, and obvious changes in price distribution were observed after policy intervention.

For some categories, such as C08/09 (**Figure 4A**), J05 (**Figure 4H**), B01 (**Figure 4J**), and M01 (**Figure 4K**), the range of products' price distribution decreased markedly in post-intervention periods. In most categories, such as C10 (**Figure 4B**), N03 (**Figure 4C**), N06 (**Figure 4E**), L01 (**Figure 4F**), J05 (**Figure 4H**), A07 (**Figure 4I**), B01 (**Figure 4J**), M01 (**Figure 4K**), R03 (**Figure 4L**), the median and mean of price distribution decreased after policy intervention, and the distribution density moved downward. In several categories, such as C10 (**Figure 4B**), J05 (**Figure 4H**), A07 (**Figure 4I**), and R03 (**Figure 4L**), the CV of price distribution increased compared with the pre-intervention period. Overall, the medians of CV among the 12 categories were 58.51, 62.38, and 67.02% in three observation periods, respectively, indicating the ascending of dispersion degree.

4.3.2 Alternative Drugs

As shown in **Figure 5**, among alternative drugs, the price distribution of most therapeutic categories was consistent in three observation periods, indicating the little policy impact on products' price distribution. In several categories, i.e., C08/09 (**Figure 5A**), N03 (**Figure 5C**), N05 (**Figure 5D**), A07 (**Figure 5I**), B01 (**Figure 5J**), and M01 (**Figure 5K**), the CV of

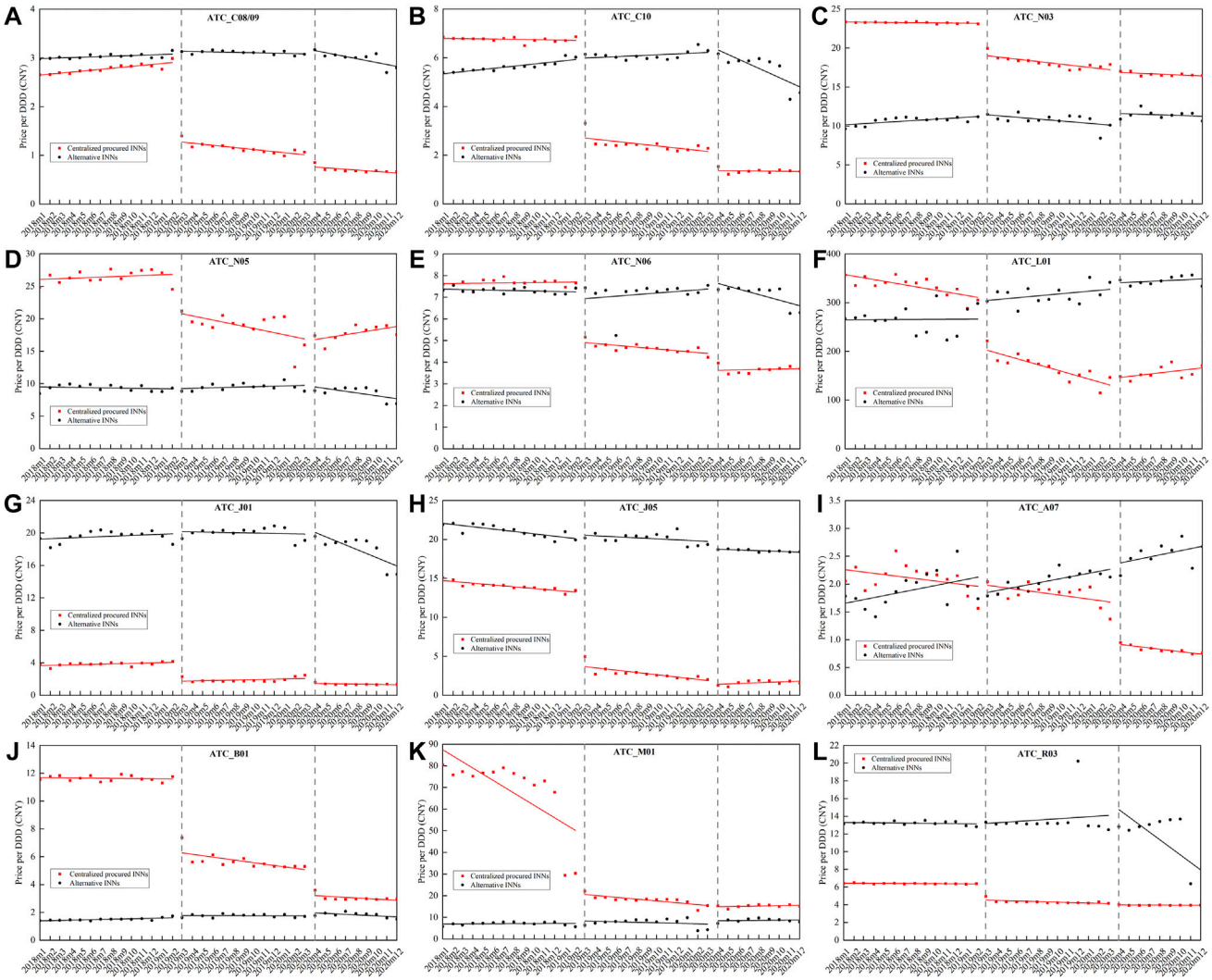

FIGURE 3 | Monthly trends in the price of centralized procured drugs and alternative drugs, stratified by therapeutic categories. **(A)** Hypotensive drugs (C08/09), **(B)** lipid-modifying agents (C10), **(C)** antiepileptics (N03), **(D)** psycholeptics (N05), **(E)** psychoanaleptics (N06), **(F)** antineoplastic agents (L01), **(G)** antibacterials for systemic use (J01), **(H)** antivirals for systemic use (J05), **(I)** antidiarrheals (A07), **(J)** antithrombotic agents (B01), **(K)** antiinflammatory and antirheumatic products (M01), **(L)** drugs for obstructive airway diseases (R03). *Note*: ATC, Anatomical Therapeutic and Chemical.

price distribution in alternative drugs were extremely high and exceeded 100%.

4.4 Change of Price Ratio

4.4.1 Overall Distribution

Figure 6 summarizes the distribution of PR among 25 centralized procured INNs in three observation periods. The medians of PR between generic drugs and original drugs were 0.58, 0.35, and 0.30 in the pre-intervention period, first procurement period, and second procurement period respectively (**Figure 6A**). The medians of PR between certificated generic drugs and original drugs were 0.55, 0.34, and 0.34 in three periods (**Figure 6B**). The medians of PR between uncertificated and certificated generic drugs were 0.93, 1.42, and 1.42 in three periods. The range (2.44, 9.88, and 25.61) and CV (55.01, 90.84, and 163.46%) of PR between uncertificated and certificated generic drugs showed a prominent upward trend in three periods.

4.4.2 Price Ratio by INN Categories

According to the bid-winning results (including original drug or not) in two centralized biddings, the 25 centralized procured INNs were divided into three groups: 1) INNs that original drug won the bid in two centralized biddings, coded as 1→1; 2) INNs that original drug only won the bid in the second bidding, coded as 0→1; and 3) INNs that original drug did not win the bid in two biddings, coded as 0→0. **Figure 7** graphs the monthly change of PR in three INN categories from January 2018 to December 2020. The corresponding ITS results are summarized in **Table 3**.

As for the PR between certificated generic drugs and original drugs, the 1→1 category showed an immediate increase ($\beta = 0.85$,

TABLE 2 | Multi-intervention ITS quantifying the impact of centralized procurement policy on prices of centralized procured INNs and alternative INNs, stratified by therapeutic categories.

Therapeutic Categories[a]	Centralized procured drugs										Alternative drugs									
	Number of INNs	Level_1		Trend_1		Level_2		Trend_2			Number of INNs	Level_1		Trend_1		Level_2		Trend_2		
		β_1	p	β_2	p	β_3	p	β_4	p			β_1	p	β_2	p	β_3	p	β_4	p	
Overall[b]	25	−0.59	**0.000**	−0.01	0.182	−0.21	**0.001**	0.02	0.186		96	0.02	0.243	−0.002	0.418	0.07	**0.036**	−0.02	**0.018**	
C08/09	7	−0.81	**0.000**	−0.03	**0.000**	−0.27	**0.000**	−0.003	0.790		25	0.02	0.064	−0.004	**0.004**	0.04	**0.010**	−0.01	**0.002**	
C10	2	−0.89	**0.000**	−0.02	**0.039**	−0.46	**0.000**	0.02	0.243		8	0.01	0.670	−0.01	**0.035**	0.06	0.131	−0.04	**0.000**	
N03	1	−0.19	**0.000**	−0.01	**0.001**	−0.02	0.276	0.01	0.058		7	0.03	0.370	−0.02	**0.003**	0.14	**0.027**	0.01	0.452	
N05	3	−0.23	**0.000**	−0.02	**0.043**	−0.02	0.828	0.03	**0.008**		16	0.001	0.983	0.01	0.257	0.01	0.838	−0.03	**0.016**	
N06	2	−0.44	**0.000**	−0.01	**0.002**	−0.20	**0.000**	0.01	0.122		10	−0.05	0.397	0.01	0.223	0.06	0.058	−0.02	**0.004**	
L01	3	−0.38	**0.000**	−0.03	**0.002**	0.08	0.234	0.05	**0.000**		6	0.13	0.052	0.01	0.416	0.04	0.247	−0.003	0.545	
J01	1	−0.85	**0.000**	0.01	0.709	−0.33	**0.001**	−0.03	0.079		6	0.01	0.603	−0.004	0.340	0.05	0.255	−0.03	**0.001**	
J05	2	−1.22	**0.000**	−0.04	**0.001**	−0.40	**0.003**	0.09	**0.000**		3	0.02	0.163	0.004	0.144	−0.05	**0.010**	0.001	0.729	
A07	1	0.03	0.688	−0.003	0.820	−0.58	**0.000**	−0.01	0.205		4	−0.16	0.075	−0.003	0.809	0.03	0.646	−0.002	0.863	
B01	1	−0.60	**0.000**	−0.02	**0.012**	−0.45	**0.000**	0.004	0.754		4	0.09	0.060	−0.01	**0.044**	0.14	**0.041**	−0.02	0.088	
M01	1	−0.85	**0.000**	0.02	0.263	−0.05	0.407	0.03	**0.000**		4	0.18	0.275	−0.02	0.458	0.21	0.349	0.02	0.418	
R03	1	−0.33	**0.000**	−0.01	0.062	−0.04	**0.034**	0.01	0.076		3	−0.002	0.939	0.01	0.477	0.23	0.323	−0.10	0.063	

[a]*Therapeutic category was classified based on the ATC, 2-level code, including hypotensive drugs (C08/09), lipid-modifying agents (C10), antiepileptics (N03), psycholeptics (N05), psychoanaleptics (N06), antineoplastic agents (L01), antibacterials for systemic use (J01), antivirals for systemic use (J05), antidiarrheals (A07), antithrombotic agents (B01), antiinflammatory and antirheumatic products (M01), drugs for obstructive airway diseases (R03).*

[b]*The regression model for overall price change applied fixed effect of therapeutic category.*

INNs, International Nonproprietary Names. Bold values indicate regression coefficients with statistical significance ($p < 0.05$*).*

$p < 0.001$) in the first procurement period, and an immediate decline (β = -0.24, $p < 0.001$) in the second procurement period. The 0→1 category showed an immediate decrease (β = -0.74, $p < 0.001$) in the first procurement period, and an immediate increase (β = 0.48, $p < 0.001$) in the second procurement period. The 0→0 category was observed with a significant PR decline in both the first (β = -0.89, $p < 0.001$) and second (β = -0.48, $p < 0.001$) procurement period. During the second procurement period, the PR of 1→1 and 0→1 category was about 0.8, and that of 0→0 was about 0.15 (**Figure 7B**).

In regards to the PR between uncertificated and certificated generic drugs, the 0→1 category was observed with immediate PR increment at the start of the first (β = 0.49, p = 0.001) and second (β = 0.24, p = 0.009) procurement period. A prominent increment was found in the PR of 0→0 category INNs at the start of the first procurement period (β = 1.30, $p < 0.001$), while the change trends significantly declined (β = -0.06, $p < 0.001$). During the second procurement period, the PR of 0→1 and 0→0 categories were about 1.0–1.5 (**Figure 7C**).

In each drug category, the monthly trend of PR between generics and original drugs is quite similar to PR between certificated generics and original drugs (**Figures 7A,B**), which related to the increased use of certificated generics (especially after policy intervention) and thus resulting in the domination of certificated generics in the price level of overall generic drugs.

5 DISCUSSION

As the current world's largest group purchasing organization, the centralized drug procurement organized by the Chinese government aims to gradually establish a market-driven drug price formation mechanism by adapting regular, institutional, state-level centralized procurement activities. We conducted a multi-intervention ITS to systematically explore the impacts of centralized procurement on drug price and price relations, by using drug procurement data of all public medical institutions in the 11 pilot cities (2018–2020). The study findings first revealed the difference between short-term (within 1-year procurement period) and mid- or long-term (1 year later) impacts of the policy on drug price, as well as the difference between policy impacts on centralized procured drugs (direct effect) and alternative drugs (indirect effect). In addition, the significant impact of the changes in drug price relation upon the policy implementation also provides strong empirical evidence for future policymaking.

5.1 Significant Price Decline of the Bid-Winning Drugs After Centralized Biddings

This study first observed significant price reductions of the bid-winning products by each bidding period, generally reflecting the direct price-cutting effect associated with the centralized procurement, which echoes other recent research (Wang et al., 2021). Similar findings were reported by Sigulem and Zucchi (2009) in the evaluation of joint procurement of seven university-

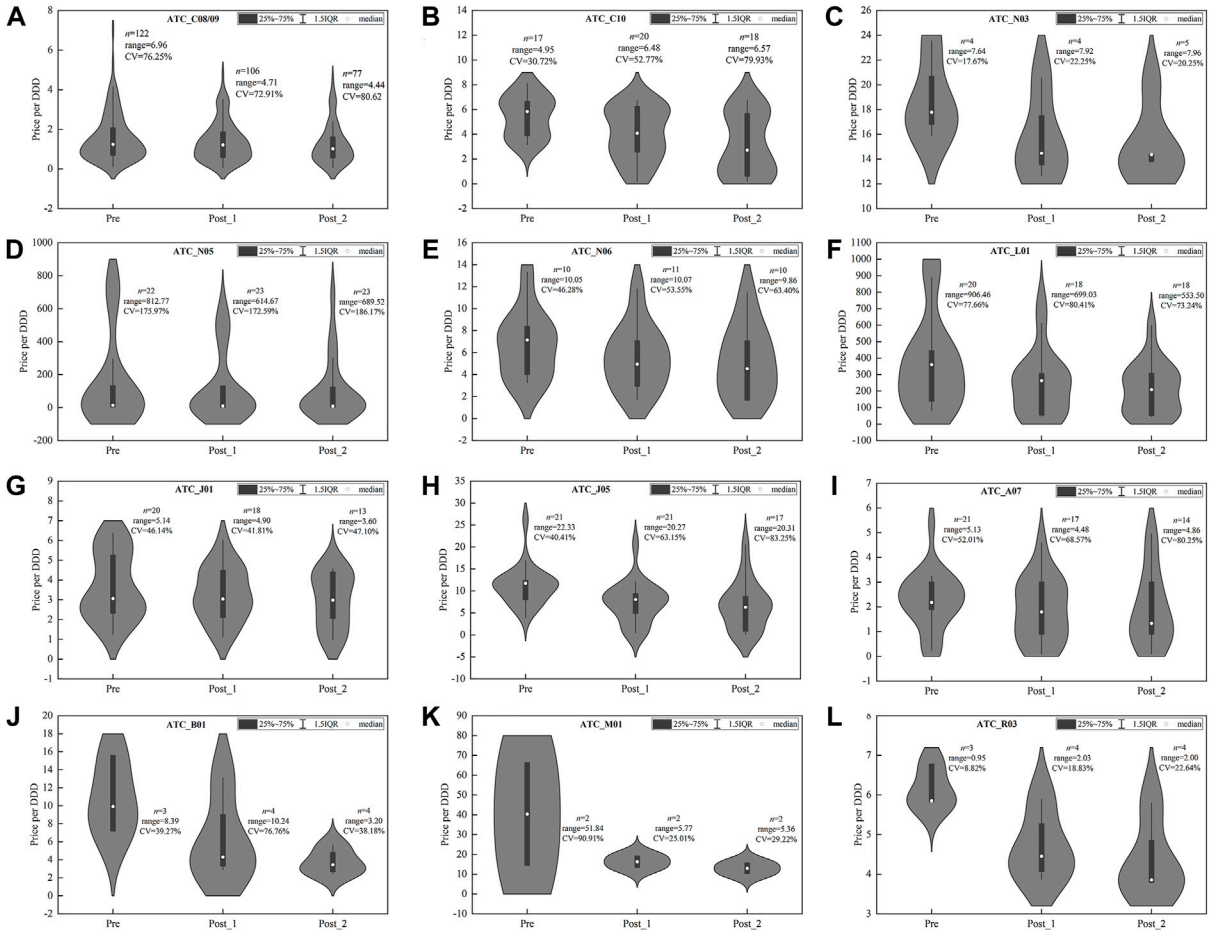

FIGURE 4 | Price distribution of drug products in centralized procured INNs among three observation periods. **(A)** Hypotensive drugs (C08/09), **(B)** lipid-modifying agents (C10), **(C)** antiepileptics (N03), **(D)** psycholeptics (N05), **(E)** psychoanaleptics (N06), **(F)** antineoplastic agents (L01), **(G)** antibacterials for systemic use (J01), **(H)** antivirals for systemic use (J05), **(I)** antidiarrheals (A07), **(J)** antithrombotic agents (B01), **(K)** antiinflammatory and antirheumatic products (M01), **(L)** drugs for obstructive airway diseases (R03). *Note*: DDD, defined daily dose; CV, coefficient of variation.

affiliated hospitals in Brazil, which observed prominent price changes of the same product in different centrally purchased batches (mainly with price drops). Specifically, this study observed that the price reduction in the second bidding period was significantly smaller and more stable compared with that in the first bidding period, which was generally consistent with market nature and the policy aim of "stabilizing drug price" (NHSA, 2021; Sun et al., 2021). In addition, in the second centralized bidding, the prices of a few INNs did undergo a rise trend. Also, significant differences were observed in the decrease of bid-winning prices among different INNs. Several factors might influence bidding price, findings derived from cross-country studies reported that more potential competitors, decentralized market, and older generation drugs were generally associated with lower centralized bidding prices (Dubois et al., 2021; Wang and Zahur, 2022). Evidence from China indicated that originators are likely to gain lower prices than generics in centralized bidding (Li et al., 2021; Sun et al., 2022). These to some extent explained the difference in price changes among centralized procured INNs in this study. We believe it is necessary for future centralized drug procurement practice to further differentiate and standardize pricing strategies for reshaped groups of varieties and pharmaceutical companies with different features, dynamically improving the sustainability and equity of the policy implementation.

5.2 Marked Differences Between Short- and Long-Term Effects in the Price Changes of Non-winning Products

When focusing on non-winning drugs, the study observed that the short-term effect of the price change was stronger than the mid- or long-term effect. In the first bidding period, we observed a drastic decline not only in the price level of bid-winning drugs but also of several non-winning drugs (N→Y products), indicating an emergence of the "spillover effect" brought by the policy implementation. This phenomenon was also reported by other scholars recently (Chen et al., 2020). Wang et al. (2022) and Xie et al. (2021) revealed that the price cut of overall non-winning drugs was mainly attributed to the proactive price reduction of certain

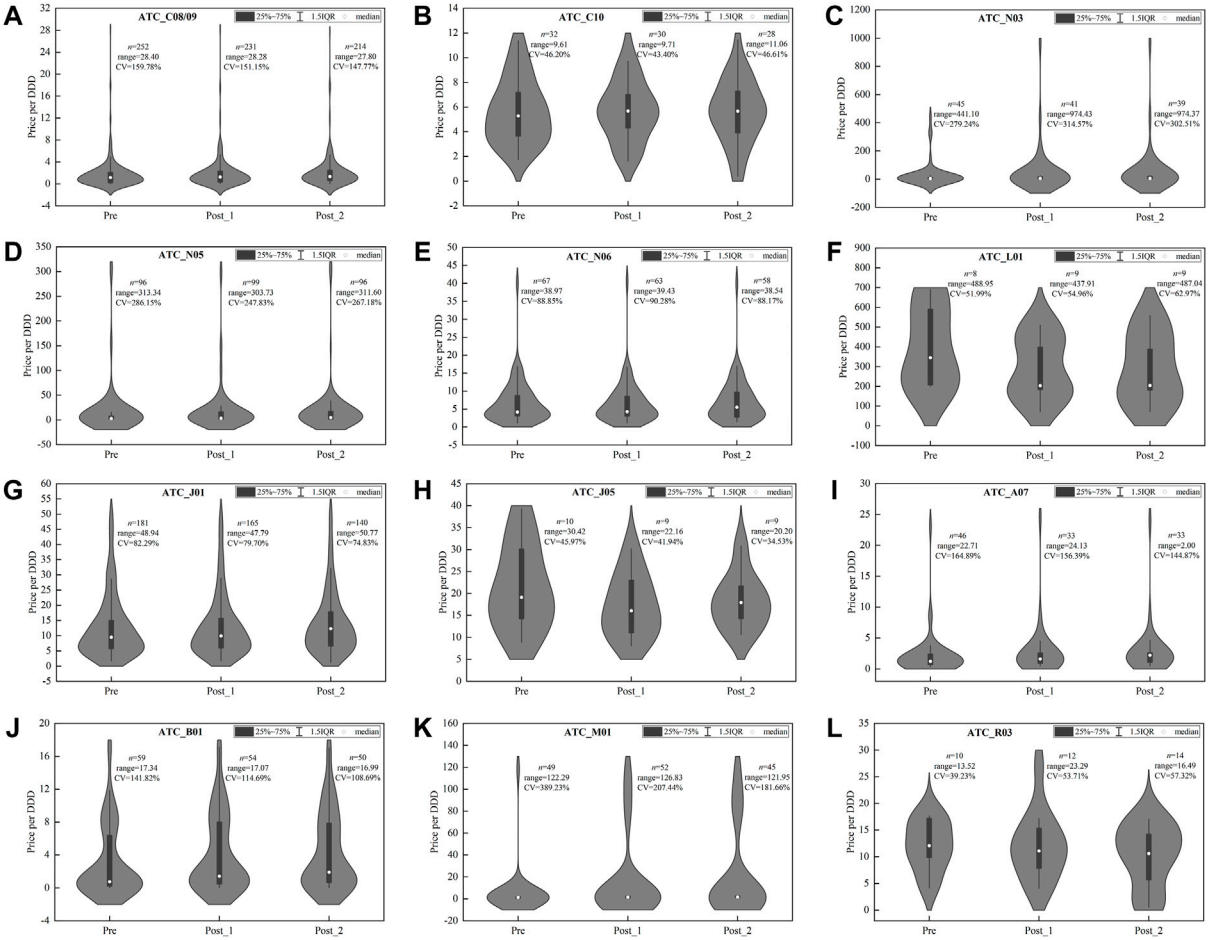

FIGURE 5 | Price distribution of drug products in alternative INNs among three observation periods. **(A)** Hypotensive drugs (C08/09), **(B)** lipid-modifying agents (C10), **(C)** antiepileptics (N03), **(D)** psycholeptics (N05), **(E)** psychoanaleptics (N06), **(F)** antineoplastic agents (L01), **(G)** antibacterials for systemic use (J01), **(H)** antivirals for systemic use (J05), **(I)** antidiarrheals (A07), **(J)** antithrombotic agents (B01), **(K)** antiinflammatory and antirheumatic products (M01), **(L)** drugs for obstructive airway diseases (R03). *Note*: DDD, defined daily dose; CV, coefficient of variation.

original enterprises. However, we found the price of those drugs that failed to win both tenders (we marked N→N category) did not significantly change. Luo et al. (2022) in their latest research also suggested that in the 18-months centralized procurement execution period, the level of price-cut among non-winning medicines (1.54%) was far lower than that of bid-winning counterparts (73.82%). Such evidence indicates that the policy effect on drug price reduction has not achieved universal coverage for all the participating products in the market, in that not all non-winning enterprises showed a willingness to actively lower their product prices.

In the second bidding period observation, the policy effect on the price level and slope of the non-winning products manifested as positive, yet no statistical difference was detected. The price of a subgroup of non-winning products which once won the bid in previous bidding periods (marked as Y→N) showed a significantly increasing trend (14.80%), indicating that these companies might have raised the prices after their products failed to win the bid. Similar changes were mentioned by Pérez et al. (2019) in the evaluation of Colombia's centralized procurement policy that enterprises intended to rapidly raise their product prices 1 or 2 years after initial price reduction, suggesting a need to assess the long-term effects of such policies on drug prices. In the evaluation of group purchasing on drug prices in French hospitals, Toulemon (2018) observed a slight rise in the price of oligopoly medicines a few months after policy implementation. Therefore, the long-term price-raising inkling observed in this study should be cautiously considered by policymakers. While price fluctuations are common in a market, frequent drug price adjustments, especially those with upward tendencies, are not likely to be the facilitators for achieving stable rational drug use and universal access to healthcare.

5.3 Increasingly Scattered Drug Price Distribution and Imbalanced Price Ratio

First, this study found that those drugs which lost the bid throughout the entire course maintained a relatively high price

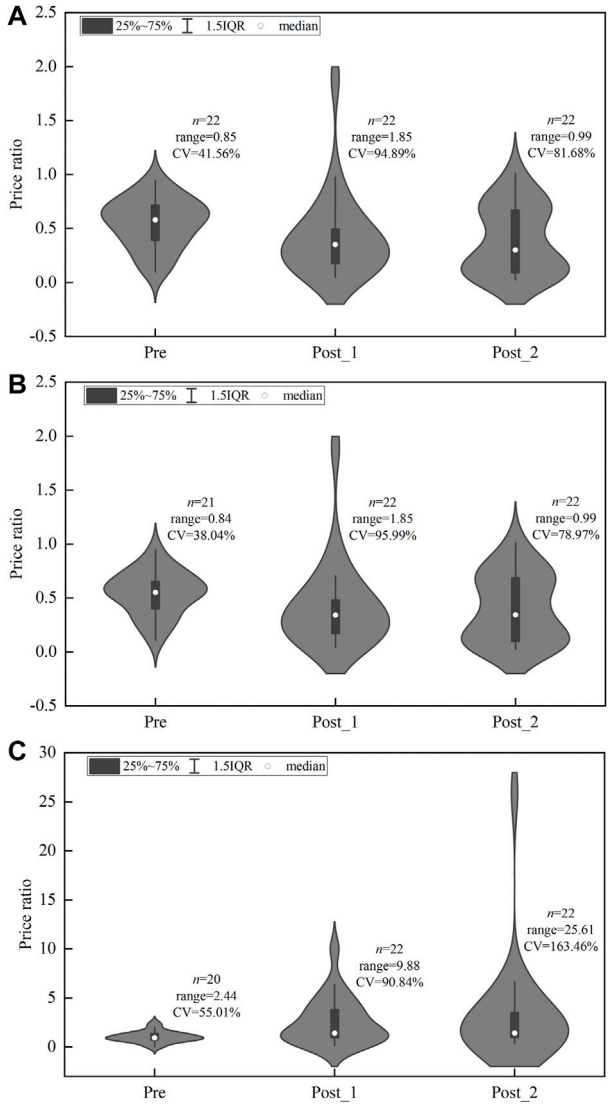

FIGURE 6 | Price ratio distribution of centralized procured INNs among three observation periods. **(A)** PR between generic drugs and original drugs, **(B)** PR between certificated generic drugs and original drugs, **(C)** PR between uncertificated and certificated generic drugs. *Note*: CV, coefficient of variation.

level, with no significant change in their price level and trends. This may indicate that China has not achieved the NHSA's goal of "uniform between medical insurance payment standards and procurement prices" (NHSA, 2019b) in "4 + 7" pilot cities. These continuous non-winning drugs may mainly come from enterprises with a small market share or with limited competitiveness or capability (e.g., uncertificated generic drugs). Moreover, our analysis of price ratios also found a significantly high price ratio between uncertificated and certificated generics, accompanied by a surge peaking at 2.0–3.0 after the policy execution. Luo et al. (2022) observed a similar rapid increase in the uncertificated generic drug prices (83.18%) in the 18th month of the policy initiation. Such continuously inflated drug prices and deviated price ratios may not only break the rational market equilibrium and affect competition fairness but also stand against the development process of value-based healthcare. These findings indicate that in the context of market-driven centralized procurement, it is of high necessity for proactive policy intervention or engagement in drug-price governance. Efforts should be specifically made on formulating standardized regulation for uncertificated generics' prices, so as to facilitate the process toward dynamically coordinated drug-pricing practice.

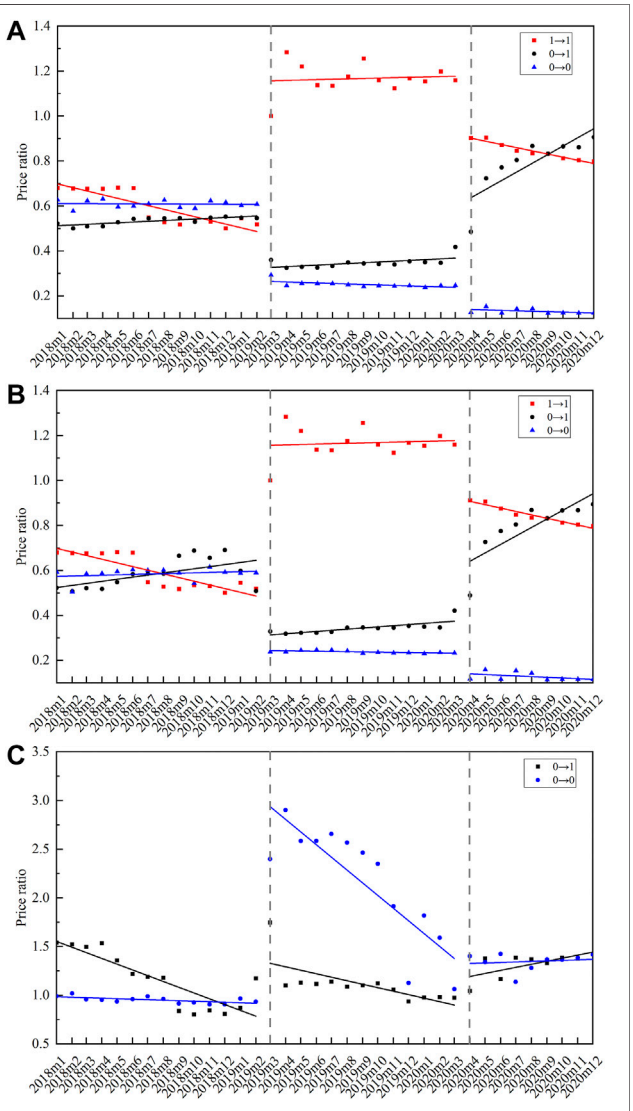

FIGURE 7 | Monthly trends of price ratio among centralized procured INNs with different bid-winning types. **(A)** Price ratio between generic drugs and original drugs, **(B)** price ratio between certificated generic drugs and original drugs, **(C)** price ratio between uncertificated and certificated generic drugs. *Note*: 1→1 represents INNs that the original drug won the bid in two centralized biddings (n = 3), 0→1 represents INNs that the original drug only won the bid in the second bidding (n = 3), 0→0 represents INNs that original drug did not win the bid in two biddings (n = 19).

TABLE 3 | Multi-intervention ITS quantifying the impact of centralized procurement policy on price ratio of centralized procured INNs with different bid-winning types.

Categories[a]	Level_1		Trend_1		Level_2		Trend_2	
	β_1	*p*	β_2	*p*	β_3	*p*	β_4	*p*
PR between generics and original drugs								
1→1	0.85	**0.000**	0.03	**0.000**	−0.25	**0.000**	−0.02	**0.002**
0→1	−0.54	**0.000**	0.003	0.564	0.50	**0.000**	0.04	**0.031**
0→0	−0.82	**0.000**	−0.01	0.072	−0.52	**0.000**	−0.01	0.555
Overall	−0.50	**0.000**	0.001	0.799	−0.19	**0.000**	0.003	0.483
PR between certificated generics and original drugs								
1→1	0.85	**0.000**	0.03	**0.000**	−0.24	**0.000**	−0.02	**0.001**
0→1	−0.74	**0.000**	−0.002	0.811	0.48	**0.000**	0.04	0.062
0→0	−−0.89	**0.000**	−0.01	**0.049**	−0.48	**0.000**	−0.02	0.183
Overall	−0.60	**0.000**	0.01	**0.002**	−0.06	0.247	−0.03	**0.000**
PR between uncertificated and certificated generics								
1→1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
0→1	0.49	**0.001**	0.02	0.284	0.24	**0.009**	0.06	**0.001**
0→0	1.30	**0.000**	−0.06	**0.000**	−0.06	0.641	0.07	**0.000**
Overall	0.96	**0.000**	−0.06	**0.000**	0.18	**0.025**	0.08	**0.000**

*[a]1→1 represents INNs that original drug won the bid in two centralized biddings (*n *= 3), 0→1 represents INNs that original drug only won the bid in the second bidding (*n *= 3), 0→0 represents INNs that original drug did not win the bid in two biddings (*n *= 19).*

*PR, price ratio. Bold values indicate regression coefficients with statistical significance (*p *< 0.05).*

Second, this study observed a further deviated difference between the generic and original drugs in the majority of centralized procured INNs. Before the policy implementation, the price ratio of certificated generics to their original counterparts was around 0.6, slightly higher than the figure in the 2014 Shanghai survey (0.54) (Zhang et al., 2016). While after the policy implementation, the changing level in the price ratio was strongly associated with whether the original product won the bid. The price ratio of INNs with the originator winning the bid was as high as 0.8 after policy intervention. The price of generics reached 70–90% of corresponding originators in the United States, Canada, Japan, and South Korea (Zhang et al., 2016). Whereas in the Netherlands, through insurance companies' bidding and enhancing prescribing competition, the price of omeprazole and simvastatin generics even down to 2% of pre-patent loss prices (Woerkom et al., 2012). We also found that the price ratio of INNs without an originator winning bid has witnessed a drastic drop to value at 0.2. This widening price difference could be associated with the fact that certain varieties failed to effectively participate in market competition to facilitate a fully competitive market between the originals and generics. Future efforts could be made on increasing the level of diversity and competitiveness in seller market by further incentivizing original enterprises to facilitate their participation in the centralized procurement activities.

Third, the downwardly distributed price intervals of the centrally procured varieties and diminished median prices among most selected pharmaceutical categories in this study could mainly the result of the price cuts of the bid-winning products. However, the variation coefficients of price distribution among most pharmaceutical categories did not significantly decrease, with even remark rising trends in certain therapeutic categories. This may indicate a great potential for future drug price governance to further narrow the price differences among different INNs which share similar clinical categories.

5.4 "Spillover Effects" on the Price of Alternative Drugs Upon Policy Implementation

This study has sub-grouped the included drugs by therapeutic categories to explore the policy effect on alternative drugs' price, while inconsistent patterns were observed in the change of alternative drug price distributions upon policy implementation.

On one hand, from a perspective of short-term policy effect, this study found that the price-cutting effect brought by the centralized procurement policy might at least partially "spillover" to the price change patterns of their alternative counterparts, given the significant decline in the slope of several alternative drugs' price in the first procurement period. The figure is generally in accordance with the findings reported by Wang et al. (2021) and Hao et al. (2020).

On the other hand, from a dynamic mid-to long-term policy effect perspective, a statistically significant increase (7.04%) in the alternative drug prices was observed since the second bidding period, despite that only a limited number of therapeutic categories experienced such price inclination. It can be explained by the typical "gourd effect" (Yu, 2017) in the course of drug pricing reform, meaning that the magnitude of the price-cutting effect could be neutralized by the increase of unaffected drug prices or other costs. Yu (2020) and Yang et al. (2021) have raised similar concerns about the factual effects on drug prices associated with the centralized procurement policy implementation. Therefore, it would be necessary for more stringent monitoring and regulating measures during the implementation of the centralized procurement policy in a long run; meanwhile, we call for further expanding the drug scope covered by the centralized procurement policy while integrating the categories sharing similar clinical use or functions.

Overall, the inconsistent changing pattern in the price distribution of alternative drugs upon the implementation of

the centralized procurement policy in China indicates a limited policy effect on the prices of unaffected INNs. This in turn also presents a deviated trend in the price difference between the bid-winning products and their alternative counterparts. In this situation, to avoid potential risks of market instability and irrational drug use, multiple and coordinated approaches, such as the practice in Scotland (Macbride-Stewart et al., 2021), might be considered pragmatic and effective. Also, in addition to further accelerating the scope of medicines covered by the centralized procurement, measures should be taken to enhance competition at the therapeutic class level rather than simply the INN level.

Several potential limitations should be mentioned regarding the present study. First, this study selected the first batch of "4 + 7" pilot cities for investigating the variations in drug prices over the two-year-long implementation period. Although this facilitated tracking the policy efficacy, the procurement regulations in the "4 + 7" pilot were not sufficiently mature compared to the subsequent batches of centralized procurement. Given the particularities of the "4 + 7" centralized procurement pilot, therefore, extrapolating results of this study to other policy batches should be cautiously performed. Second, since the "4 + 7" pilot was mainly carried out in public medical institutions, this study obtained data for price analysis from the CDSIP database, which extensively covers drug procurement data from public medical institutions. It should be noted that the drug procurement information of private departments (private hospitals, retail pharmacies, etc.), which accounted for about 20% of the total drug consumption, is not covered in the CDSIP database. Therefore, the findings derived from this study mainly present changes in drug prices in public healthcare institutions in China, which may not be fully extended to private departments until further research is conducted.

6 CONCLUSION

The centralized drug procurement policy in China has effectively reduced the price of bid-winning products. In the short term, partial enterprises (mainly originators' enterprises) that have failed to win the bids have proactively reduced drug prices, accompanied by subsequently dropped prices of alternative drugs under certain therapeutic categories, yielding a coordinated and integrated interaction in the pricing between different categories. Nonetheless, in the long run, the price-cutting effect was likely to be progressively diminished or even largely reversed. Overall, there are several prominent phenomena following the centralized procurement, including but not limited to imbalanced drug price ratio, deviated drug price distribution, abnormally low level of difference between the price of generic and original drugs, and the large price difference between the uncertificated and certificated generics.

Possible policy improvements in the future include: 1) Consistent monitoring and evaluation should be conducted against abnormal price rebounds. 2) Coverage of the centralized procurement list should be expanded based on the therapeutic categories of the medicine. 3) Initiative should be taken to stimulate the original drug enterprises to proactively participate in centralized procurement activities, and to enhance supply-side market competitiveness. 4) Efforts should be made to implement the standard drug medical insurance payment policy promptly.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Institutional Review Board of Wuhan University. In this research, we only included the medication procurement information and all the information was anonymous. Neither patients nor the public was involved in this research. Thus, according to the Institutional Review Board of Wuhan University, the requirement for patient consent was waived.

AUTHOR CONTRIBUTIONS

Conception and design: HL, YY, and ZHM; collection and assembly of data: HL, YY, XG, and ZFM; statistical analysis: HL and YY; interpretation: HL, YY, and XG; manuscript preparation: HL, YY, and XG; manuscript review: YY, ZFM, and ZHM.

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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.2022.944540/full#supplementary-material

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Cost-Effectiveness Analysis of Capecitabine Plus Oxaliplatin Versus Gemcitabine Plus Oxaliplatin as First-Line Therapy for Advanced Biliary Tract Cancers

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Background: In the first-line treatment of biliary tract cancers (BTCs), XELOX (capecitabine plus oxaliplatin) showed comparable clinical efficacy and safety to gemcitabine and oxaliplatin (GEMOX), with fewer visits and better treatment management. Our study aims to investigate the cost-effectiveness of XELOX and GEMOX as the first-line therapy for BTCs from the perspective of the Chinese healthcare systems and to provide valuable suggestions for clinical decision-making.

Methods: A Markov model was developed using the phase 3 randomized clinical trial (ClinicalTrials.gov number, NCT01470443) to evaluate the cost-effectiveness of XELOX and GEMOX. Quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) were used as the primary outcomes of the model. Uncertainty was assessed using univariate and probabilistic sensitivity analysis.

Results: The QALYs for the XELOX and GEMOX groups were 0.66 and 0.54, respectively. In China, the total cost of XELOX treatment is US $12,275.51, which is lower than that of the GEMOX regimen. In addition, XELOX is more effective than GEMOX, making it the preferred regimen. A sensitivity analysis determined that XELOX therapy has a stable economic advantage in China.

Conclusion: Compared to GEMOX, XELOX is a more cost-effective treatment as a first-line treatment for advanced BTC from the perspective of the Chinese health service system.

Keywords: cost-effectiveness, advanced biliary tract cancers, XELOX, GEMOX, first-line treatment

Abbreviations: (AE), adverse event; (ALT), alanine transaminase; (AST), aspartate transaminase; (BSA), body surface area; (BSC), best supportive care; (BTC), biliary tract cancer; (CDDP-GEM), gemcitabine plus cisplatin; (CNY), Chinese yuan; (CT), computerized tomography; (XELOX), capecitabine plus oxaliplatin; (GEMOX), gemcitabine plus oxaliplatin; (ICER), incremental cost-effectiveness ratio; (LMICs), Low- and middle-income countries; (OS), overall survival; (ORR), objective response rate; (PFS), progression-free survival; (PS), progression survival; (PSA), probabilistic sensitivity analysis; (QALY), Quality-adjusted life-year; and (SAE), serious adverse event.

INTRODUCTION

Biliary tract cancers (BTCs), including cholangiocarcinoma (both intrahepatic and extrahepatic) and gallbladder cancer, are low-incidence cancers carrying a poor prognosis (Bergquist and von Seth, 2015; Gamboa and Maithel, 2020; Valle et al., 2021). BTCs account for approximately 3% of all gastrointestinal tumors and are predominantly adenocarcinomas (Doherty et al., 2017). Surgery is the main treatment for localized disease (Bridgewater et al., 2016), and most patients (>65%) are diagnosed with the unresectable disease. There is a high recurrence rate in the minority of patients who undergo potentially curative surgery (Valle et al., 2017). The 5-year survival rate for BTCs is approximately 5–13% (Siegel et al., 2015).

For advanced BTCs, chemotherapy is the main systemic therapy. Early studies found fluoropyrimidine, platinum, and gemcitabine to be effective drugs for the treatment of advanced BTCs. Subsequently, based on the ABC-02 clinical trial, the combination of gemcitabine plus cisplatin (CDDP-GEM) became the recognized reference regimen for first-line treatment of patients with advanced BTCs (Valle et al., 2010). Numerous studies have been conducted over the last 10 years, and this combination remains the standard of care worldwide (Banales et al., 2020; Rizzo and Brandi, 2021a; Rizzo et al., 2021). Although cisplatin appears to be more effective, it is more toxic (Fiteni et al., 2014), and the gemcitabine and oxaliplatin (GEMOX) regimen has been widely used as first-line treatment for patients unsuitable for cisplatin.

In recent times, an open-label, randomized, phase 3, non-inferiority trial investigated the clinical effectiveness and safety of XELOX (capecitabine plus oxaliplatin) versus GEMOX therapy as first-line therapy for advanced BTCs (Kim et al., 2019). The results indicated that the median overall survival (OS) time was 10.6 months (95% confidence interval [CI], 7.3–15.5) in the XELOX group and 10.4 months (95% CI, 8.0–12.6) in the GEMOX group, with no statistically significant difference in OS curves between the two groups (p = 0.131). Meanwhile, the frequency of hospitalization was significantly lower in the XELOX group than in the GEMOX group (p < 0.001). Based on these results, XELOX therapy was approved for the first-line treatment of BTC.

Despite the survival benefits of available treatments for BTCs, the financial impact remains considerable. At present, the cost-effectiveness of XELOX versus GEMOX as first-line solutions for BTC has not been evaluated. To improve the effective use of limited healthcare resources and to help evidence-based healthcare decisions, we conducted a health economics evaluation of disease-related therapies.

Significant geographic differences in the incidence of BTCs have been reported, with higher prevalence in Thailand, Japan, China, and South Korea compared to Western countries (Rizzo and Brandi, 2021b). It is evident that financial expenditures for disease treatment will increase the burden on the medical insurance system of various countries. Thus, using the results of Kim's trial (Kim et al., 2019), this study assessed the cost-effectiveness of XELOX therapy versus GEMOX therapy in the treatment of BTC from the perspective of Chinese healthcare payers.

METHODS

Model Building

A decision-analytic model was developed to compare the costs and effectiveness of XELOX with those of GEMOX for advanced BTCs. As reported in the trial by Kim et al. (2019), treatment was repeated every 3 weeks for both groups for a total of eight cycles and was discontinued in cases of disease progression. The following two first-line treatment options were evaluated using the model: 1) XELOX: 1,000 mg/m^2 capecitabine was administered orally twice daily (bid) on days 1–14, and 130 mg/m^2 oxaliplatin as a 120-min infusion on day 1; and 2) GEMOX: 1,000 mg/m^2 gemcitabine was administered as a 100-min infusion on days 1 and 8, and 100 mg/m^2 oxaliplatin as a 120-min infusion on day 1. The analysis was conducted from the perspective of the Chinese healthcare system, with a lifetime horizon. We considered only direct medical costs. Each model cycle represented 21 days. The costs and effectiveness outcomes were discounted at 5% annually. A three-health-state Markov model was developed as follows: progression-free survival (PFS) with responsive/stable disease, progression survival (PS), and death (**Figure 1**) (Tsukiyama et al., 2017). Patients were in PFS at the initial stage of the model, and each cycle was left in PFS or converted to PS according to the transfer probability. Entering PS can only be in PS or into a state of death. After progress, the patients entered the best support treatment. Parametric survival curve fitting was performed in R (version 4.1.1) software, and the Markov model was developed and run in TreeAge Pro 2020.

Effectiveness Parameters and Utility Estimates

The three health states of the transfer probabilities of BTCs were estimated based on the OS and PFS Kaplan–Meier (KM) curves of Kim's trial (Kim et al., 2019). The GetData Graph Digitizer software package was used to reconstruct the individual data,

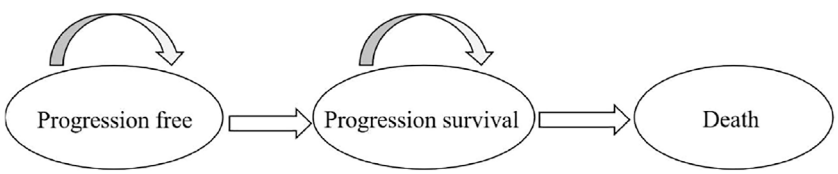

FIGURE 1 | The Markov state transition model. At the beginning of each Markov cycle, all patients entered the model in the progression-free survival (PFS) with a stable disease state and immediately commenced treatment. From this state, patients could either remain in a PFS state or experience progression and enter progression survival (PS). Patients in the PS could either remain in a PS state or transition to death. PS indicates the progression of the disease.

TABLE 1 | Key model parameters.

	Shape	Scale	Distribution	Source
PFS				
XELOX	0.201	0.690	Weibull	9
GEMOX	0.199	0.739	Weibull	9
OS				
XELOX	0.068	0.958	Weibull	9
GEMOX	0.038	1.260	Weibull	9

Abbreviations: PFS, progression-free survival; OS, overall survival

and the RStudio software was used to perform statistical analyses. The Weibull distribution was chosen to extrapolate PFS and OS. The survival functions were used to calculate the transfer probabilities among the states. These parameters were substituted into the equation $P(t) = 1 - \exp[\lambda(t-1)^{\gamma} - \lambda t^{\gamma}]$ to calculate the transition probability. Weibull distribution scale parameter λ and shape parameter γ are shown in **Table 1**.

Quality-adjusted life-year (QALY) was identified as the primary health outcome. It is often referred to as utility (the health-state utility ranges from 0 [death] to 1 [complete health]) (Li et al., 2021). Since BTC is a relatively rare cancer, no independent health status utility values have been published in this area. We obtained the values of the health utility values from the previously published literature (Roth and Carlson, 2012; Tsukiyama et al., 2017) (**Table 2**). A discount rate of 5% was applied to the QALY calculations.

Cost Estimates

The costs involved in this study mainly included direct medical expenses, such as drug expenses, follow-up testing, management of treatment-related serious adverse events (SAEs), best supportive care (BSC), and terminal care (**Table 3**). The Chinese yuan (CNY) was converted to the US dollar using an average exchange rate in 2020 of 6.8976 CNY = 1.00 US dollar (National Bureau of Statistics of China, 2021).

We used a mean body surface area (BSA) of 1.72 m^2 (Liubao et al., 2009) to calculate the doses of gemcitabine (1,000 mg/m^2 BSA), oxaliplatin (100 mg/m^2 BSA or 130 mg/m^2 BSA), and capecitabine (1,000 mg/m^2), which was based on the trial by Kim et al. (2019). The prices of drugs in China were obtained from the Yaozhi network (Yaozh, 2021). Routine disease management costs, including biochemical tests, blood routine examinations, and computerized tomography (CT), are calculated according to the actual charging standards of local medical institutions. This study considered the cost of follow-up testing for the PFS state and calculated it throughout the treatment process. The costs involved in this study use US dollars as the unit.

Adverse event (AE) costs were taken from the previously published studies. Grade 3/4 AEs were defined as SAEs. Only SAEs were considered in our study (Kim et al., 2019), which included nausea, vomiting, diarrhea, stomatitis, hand–foot syndrome, neutropenia, neutropenic fever, thrombocytopenia, elevated aspartate transaminase (AST)/ alanine transaminase (ALT), asthenia, and anorexia. These AE costs were calculated by multiplying the estimated incidence rate of each AE by the corresponding unit treatment cost (Wu et al., 2014; Qin et al., 2018; Zheng et al., 2018). All AEs were assumed to occur in the first cycle of treatment. The incidence rates of each AE are listed in **Table 2**, and all unit AE costs used in the base analysis are listed in **Table 3**.

Because of the lack of recommended second-line treatment options, the costs of treatment after the disease progresses consist of BSC and terminal care. We assume that terminal care costs were considered as a one-time cost in the final state. All costs were inflation-adjusted to 2020 US dollars depending on the Chinese Consumer Price Index healthcare services group.

Sensitivity Analysis

The uncertainty of the model was tested using univariate sensitivity analysis and probabilistic sensitivity analysis (PSA). Univariate sensitivity analysis was carried out to evaluate the influence of each applicable parameter on the model. The parameter was adjusted successively to its respective low and high values, which were obtained

TABLE 2 | Ranges and distribution of other parameters.

Variable		Baseline value	Range	Dis	References
Utilities	PFS	0.69	0.455–0.925	Beta	10,12
	PS	0.71	0.455–0.965	Beta	10,12
SAEs rates					
XELOX therapy	Stomatitis	0.01	0.008–0.012	Beta	9
	Hand-foot syndrome	0.03	0.024–0.036	Beta	9
	Neutropenia	0.04	0.032–0.048	Beta	9
	Thrombocytopenia	0.09	0.072–0.108	Beta	9
	Asthenia	0.02	0.016–0.024	Beta	9
	Anorexia	0.02	0.016–0.024	Beta	9
GEMOX therapy	Nausea	0.01	0.008–0.0012	Beta	9
	Vomiting	0.01	0.008–0.0012	Beta	9
	Diarrhea	0.01	0.008–0.0012	Beta	9
	Stomatitis	0.01	0.008–0.0012	Beta	9
	Neutropenia	0.14	0.112–0.0168	Beta	9
	Neutropenic fever	0.01	0.008–0.0012	Beta	9
	Thrombocytopenia	0.11	0.088–0.0132	Beta	9
	Elevated AST/ALT	0.02	0.016–0.0024	Beta	9

Abbreviations: PFS, progression-free survival; PS, progression survival; SAEs, serious adverse events, Dis, Distribution; AST, aspartate transaminase; ALT, alanine transaminase.

TABLE 3 | Cost parameters.

Input Parameter		Value ($)	Range ($)	Dis	Source [ref.]
Drug cost of XELOX	Capecitabine ($/500 mg)	3.19	2.55–3.83	Gamma	20
	Oxaliplatin ($/50 mg)	304.45	243.56–365.34	Gamma	20
Drug cost of GEMOX	Gemcitabine ($/1.0g)	229.94	183.95–275.93	Gamma	20
	Oxaliplatin ($/50 mg)	304.45	243.56–365.34	Gamma	20
Drug administration	XELOX	5.8	4.64–6.96	Gamma	#
	GEMOX				
SAEs costs/unit	Nausea	66.34	53.07–79.61	Gamma	21
	Vomiting	66.34	53.07–79.61	Gamma	21
	Diarrhea	13.27	10.61–15.92	Gamma	21
	Stomatitis	-	-	Gamma	-
	Hand-foot syndrome	4.08	3.27–4.9	Gamma	21
	Neutropenia	3974.49	3179.59–4769.39	Gamma	22
	Neutropenic fever	2231.69	1785.35–2678.03	Gamma	22
	Thrombocytopenia	6526.06	5220.85–7831.27	Gamma	22
	Elevated AST/ALT	60.22	48.17–72.26	Gamma	21
	Asthenia	3.06	2.45–3.67	Gamma	21
	Anorexia	26.54	21.23–31.84	Gamma	21
Follow-up tests costs/cycle	Hospitalization cost	14.5	11.6–17.4	Gamma	#
	Laboratory tests	30.45	24.36–36.53	Gamma	#
	CT scan	65.24	52.19–78.29	Gamma	#
BSC cost		123.69	98.95–148.42	Gamma	23
Terminal care cost		1,567.89	1,254.31–1881.47	Gamma	23

Abbreviations: XELOX, capecitabine plus oxaliplatin; GEMOX, gemcitabine plus oxaliplatin; SAEs, serious adverse events, Dis, Distribution; AST, aspartate transaminase; ALT, alanine transaminase; CT, computerized tomography; BSC, best supportive care. #: Hospital charges

from the CIs or 20% variance of the hypothetical baseline case value. We used a 1,000-time Monte Carlo simulation to perform PSA, with variables simultaneously varied, with a specific pattern of distribution. The ranges and distribution of the parameters used in the sensitivity analyses are shown in **Tables 2** and **3**, respectively.

Owing to the lack of an acceptable threshold for the Chinese population, according to the World Health Organization's recommendations for cost-effectiveness analysis, this study will take 3 × China's gross domestic product (GDP) per capita in 2020, which is US $31,315.24, as the threshold value.

RESULTS

Base Case Results

The results of the basic analysis in **Table 4** show that the QALYs for the XELOX and GEMOX groups were 0.66 and 0.54, respectively. The total cost of XELOX treatment was US $12,275.51 in China, which was lower and more effective than the GEMOX regimen, thereby making it the preferred regimen.

Sensitivity Analyses

Tornado plots are used to show the results of univariate sensitivity analyses to determine the parameters of the model, which have the greatest impact on incremental QALY and cost. The cost of gemcitabine has the greatest impact on the incremental cost-effectiveness ratio (ICER) results, and the remaining sensitive parameters are, in order, the cost of oxaliplatin, the cost of capecitabine, and the utility values of patients in PFS versus PS status, with the other parameters having little impact, as shown in **Figure 2**. In short, changing the parameter values within a certain range has a limited effect on the outcome.

TABLE 4 | Base case results in China.

Result	XELOX	GEMOX	Incremental
QALY	0.66	0.54	0.12
The total cost of the regimen $	12275.51	13649.62	−1,374.11
ICER, US$/QALY	−12070.42		

Abbreviations: XELOX, capecitabine plus oxaliplatin; GEMOX, gemcitabine plus oxaliplatin; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratios.

Using PSA, the effect of all model input parameters on the results of the study was observed, which were constantly changing and met different distributions. According to the PSA results, XELOX treatment is extremely cost effective compared with GEMOX treatment in the first line of treatment. **Figure 3** shows scatterplots with a sloping line as the willingness-to-pay (WTP) threshold line. The 95% CI for ICER is represented by an ellipse. In China, when the WTP threshold is adjusted to 1–3 × GDP per QALY, the probability of the cost-effectiveness of XELOX treatment is 92.1, 96.2, and 99.8%, respectively. Based on the cost-effectiveness acceptable curve, XELOX treatment is a superior choice in China (**Figure 4**).

DISCUSSION

Advanced BTC is a rare disease characterized by a high rate of recurrence and distant metastasis. At present, there are few cost-

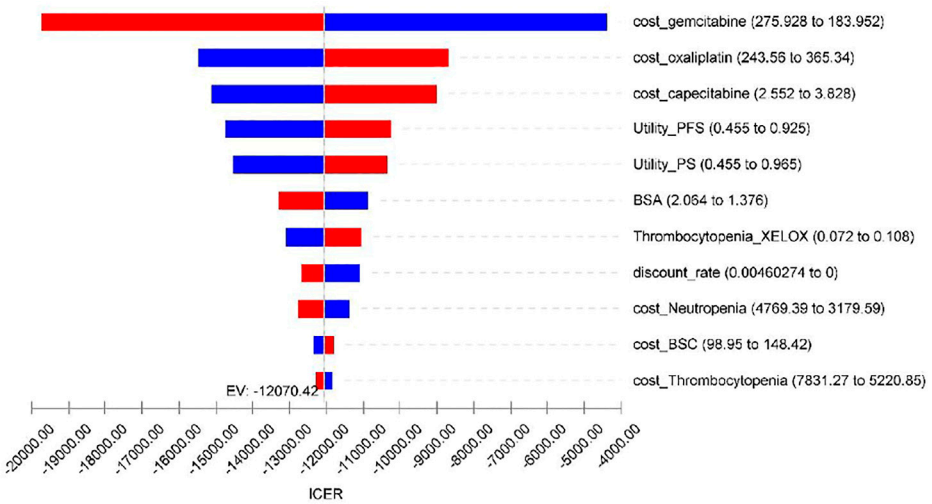

FIGURE 2 | Univariate sensitivity analysis. The tornado plots show the ICER of the XELOX therapy versus the GEMOX therapy for different input parameters in the model. The horizontal axis of the figure represents the range of influence of each element on the results, and the vertical axis shows the name of each uncertainty factor. The horizontal bars indicate the value of the effect of each element on the result and the value of the effect of each element itself. The effects of the factors on the ICER are listed in descending order of significance. Abbreviations: EV, expected value; BSA, body surface area; BSC, best supportive care; PFS, progression-free survival; and PS, progression survival.

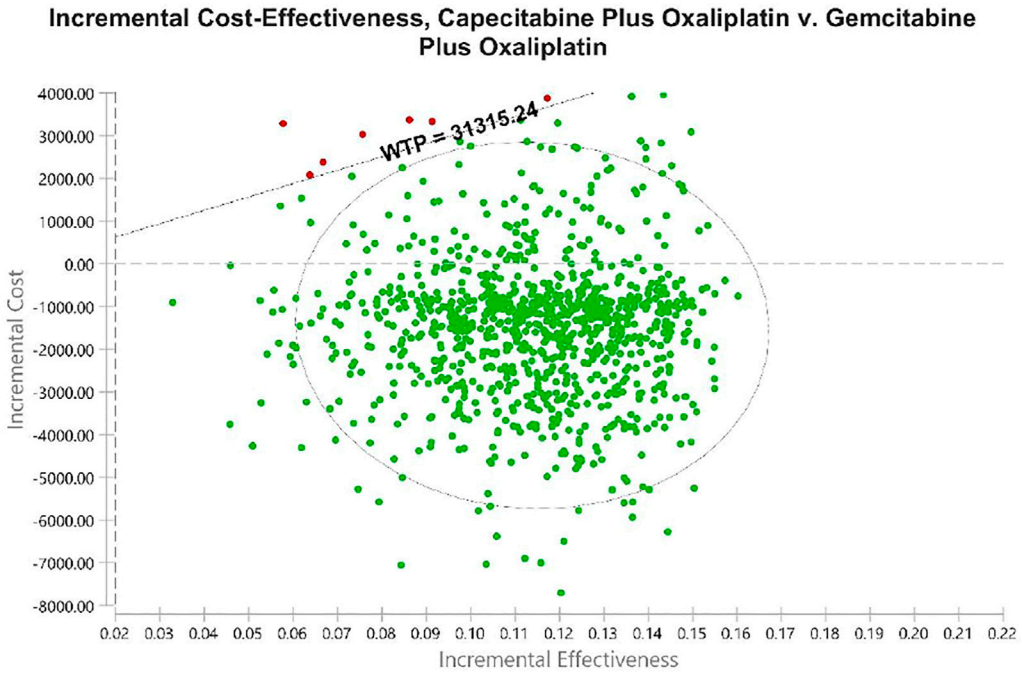

FIGURE 3 | Probabilistic sensitivity analyses. Dots indicate the results of Monte Carlo simulations, and ellipses indicate 95% confidence intervals. The diagonal line shows WTP. Dots located below the diagonal line indicate cost-effectiveness for the experimental group compared to the corresponding control group. Abbreviations: WTP, willingness to pay. All costs are in United States dollars.

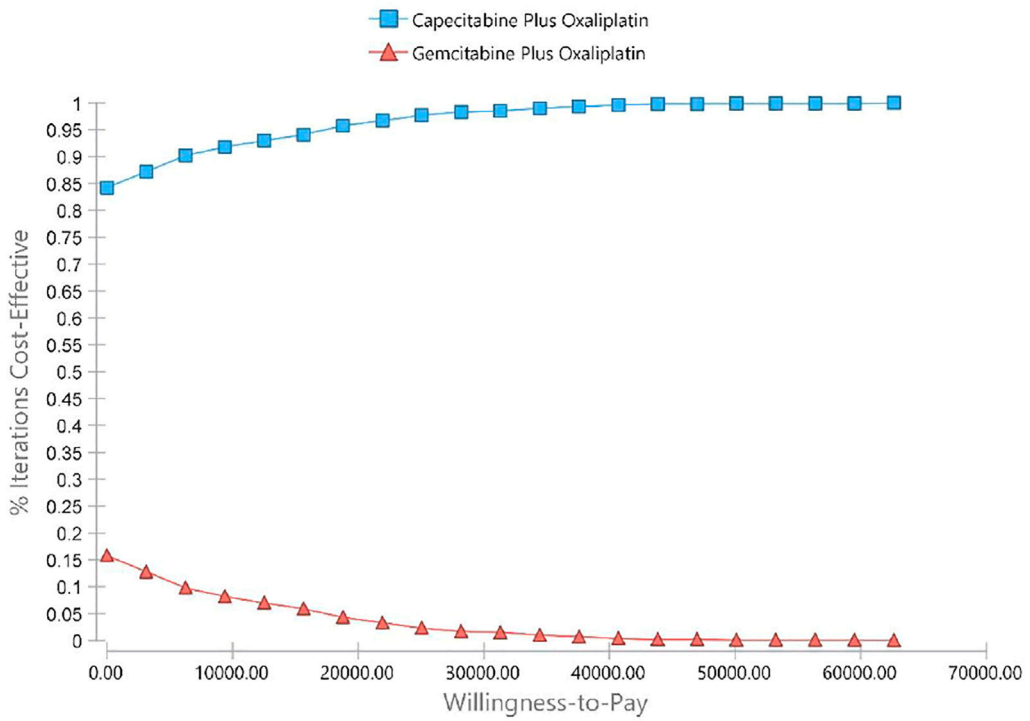

FIGURE 4 | Cost-effectiveness acceptability curves (CEACs). The CEAC represents the economic probability of a drug. The curve shows the percentage of cost-effectiveness simulated using different treatment solutions.

effectiveness evaluations of first-line treatment options for advanced BTCs. The high prices of anti-cancer drugs have led to a sharp increase in the consumption of medical resources, which has troubled clinicians and medical managers. Healthcare spending in high-income countries, such as the United States and Europe, has been increasing year by year (Laviana et al., 2020; Godman et al., 2021). They have explored potential approaches to pricing cancer therapeutics in the hope of maintaining a sustainable impact on the healthcare system (Godman et al., 2021). Low- and middle-income countries (LMICs) are also actively addressing the rising costs of cancer treatment. In particular, as cancer treatments diversify, the selection of novel antineoplastic drugs, such as trastuzumab, may not be cost effective in LMICs (Gershon et al., 2019; Al-Ziftawi et al., 2021). Therefore, it is very important to evaluate treatment options economically and to use limited medical resources rationally and effectively.

To date, the CDDP-GEM regimen remains the standard of care for the first-line treatment of advanced BTC worldwide. In actual clinical practice, the more common hematologic and renal toxicity of cisplatin leads to treatment discontinuation (Yamada et al., 2015; Markussen et al., 2020), so clinicians tend to choose oxaliplatin for frail patients. According to Fiteni's (Fiteni et al., 2014) study, oxaliplatin-based regimens are relatively uniform (oxaliplatin doses range from 80 to 100 mg/m^2), while CDDP-GEM regimens have significant heterogeneity, with cisplatin doses ranging from low (25–35 mg/m^2) to high (60–80 mg/m^2). Multiple doses of cisplatin would interfere with our study. Compared to the CDDP-GEM regimen, which has comparable efficacy but an increased incidence of adverse effects, an oxaliplatin-based combination regimen is a better choice.

Our results showed that XELOX treatment is a better option in China because it is less costly and more effective. One-way sensitivity analysis showed that drug price was the parameter that caused the greatest change in ICER values. The costs of capecitabine and gemcitabine were the main influencing factors. This was consistent with the findings of several published studies. For instance, in the study by Atieno et al. the drug was the main factor contributing to the cost of cancer treatment (Atieno et al., 2018). However, in our study, the relationship between ICER and WTP thresholds remained unchanged by varying the values of key parameters within reasonable limits. As far as we know, medical insurance in China has covered as many people as possible. However, there were great differences in reimbursement rates between different regions and different types of medical insurance. Choosing a treatment option with better results and lower costs is conducive to the rational use of health insurance. Therefore, we suggest that health insurance authorities should appropriately increase the reimbursement rate of the XELOX regimen for BTC patients, which will help save health insurance costs and benefit more BTC patients.

To date, two cost-effectiveness analyses of BTC have been published, but they provided comparisons with the CDDP-GEM

regimen and gemcitabine monotherapy strategy. Roth's study (Roth and Carlson, 2012) evaluated the cost-effectiveness of adding cisplatin to standard gemcitabine therapy from the US societal perspective and revealed that, relative to gemcitabine monotherapy, the ICER for the combination was US $59,480 per QALY, which is cost effective. However, combination therapy is less costly than monotherapy for advanced BTC in Japan (Tsukiyama et al., 2017). The reason may be that the cost of long-term palliative care in Japan is higher than that in the United States. In contrast to these two studies, our study compared the economics of XELOX and GEMOX in BTC treatment. Overall, from the perspective of the Chinese payers, XELOX therapy was a cost-effective strategy for the first-line systemic treatment for BTC.

Our study has some limitations. First, clinical data were obtained from a phase 3 trial conducted in Korea (Kim et al., 2019), which was limited to Asian patients. In previous studies (Valle et al., 2010; Lee et al., 2012), the combination of gemcitabine and platinum analogs showed antitumor activity in both Asian and non-Asian populations. These factors may have had a slight influence on our results. Second, our literature search did not identify any studies reporting the practical value of health status in patients with advanced BTC. Therefore, we used data from Roth's study (Roth and Carlson, 2012) on hepatocellular carcinoma, and the authors suggest that similar health-state utility values exist for patients with advanced BTC. We referred to previous literature (Roth and Carlson, 2012; Tsukiyama et al., 2017) to vary health utility values over a considerable range (±0.34) to account for the uncertainty of this factor. One-way sensitivity analysis showed that changes in health utility values had only a slightly significant effect on the model. Third, our study may not be timely enough. The results of the TOPAZ-1 (NCT03875235) trial have just been published, with an objective response rate (ORR) of 73.4% in the duvalizumab plus chemotherapy (D + CDDP-GEM) arm and a median OS of 18.1 months (Oh et al., 2022), which is significantly better than the historical data for the CDDP-GEM regimen (11.7 months). However, the final analysis has not yet been published, which hindered our study. We will follow up further in the future to ensure the timeliness of the study. Fourth, to reduce the impact of parameter uncertainty, we simplified the model and made several assumptions. There may be different treatment options after disease progression, but currently, there is no uniform recommended treatment option after first-line treatment for advanced BTC. Many studies are exploring the feasibility of alternative endpoints with survival (Prasad et al., 2015; Wild et al., 2016; Paoletti et al., 2020); however, the results are unfortunate, and there is limited evidence for using surrogate endpoints (e.g., PFS) as a proxy for overall tumor survival. Therefore, we did not consider drug options after disease progression. Our study also did not discuss the decrease in utility values caused by adverse effects. However, sensitivity analyses showed that changes in utility values did not qualitatively alter outcomes. Therefore, the state from PFS to death was not considered in the model. Fifth, indirect costs, such as loss of income from discontinuation and premature death, were not considered in our analysis because the high variability of the condition makes it difficult to calculate accurately. Drug prices and treatment costs were obtained from the previously published literature or local data, which may not apply to all regions. To avoid the impact of these costs on the model, we varied treatment costs over a considerable range (±20%) in the one-way sensitivity analysis. The variation was mediated by these factors and was limited. Sixth, modeling long-term OS in patients with advanced BTC using the Weibull distribution is an unavoidable limitation of our study. In the future, with a more appropriate approach, we could better fit the long-term survival data of patients.

Although there were some limitations to our research, the variables in the model did not affect the final result. Sensitivity analysis showed that the probabilities, utilities, and costs in the model had a limited impact on the final results, which illustrates the robustness of the model.

CONCLUSION

The XELOX regimen is more cost effective as a first-line treatment for advanced BTC than the GEMOX regimen from the perspective of the Chinese health service systems. However, for specific patients, clinical decision-makers need to consider all effective treatment options for advanced BTC.

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

RC, YH, and NL designed the study. YZ and KL did the statistical analysis. DH, MY, YL, and JW participated in the design and coordination of the study. RC, YZ, and YH drafted the article with inputs and feedback from all the other authors. All authors read and approved the final manuscript. RC and YZ contributed equally to this work. NL and YH were the corresponding authors of this paper.

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The impacts of the "4+7" pilot policy on the volume, expenditures, and daily cost of Serotonin-Specific Reuptake Inhibitors (SSRIs) antidepressants: A quasi-experimental study

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Objectives: The purpose of this study was to quantitatively evaluate the impacts of the"4 + 7" pilot policy on purchase volume, purchase expenditures, and daily cost and to find the changes in the use of SSRIs.

Methods: Data was collected covering 31 months, before, during, and after the "4 + 7" pilot policy was implemented in Shenzhen. Interrupted time-series (ITS) analysis was used to examine whether there had been a significant effect with the onset of the "4 + 7" pilot policy in March 2019.

Findings: The daily cost of policy-related drugs had a substantial drop of 2.93 yuan under the "4 + 7" pilot policy. The result has shown a 76.70% increase in volume and a 3.39% decrease in the expenditure on policy-related drugs. This study found that the "4 + 7" pilot policy increased the proportion of purchasing winning drugs, with an increment of 85.60 percent. After the implementation of the "4 + 7" pilot policy, policy-related drugs decreased by 443.55thousand Chinese yuan. The study indicated that volume of winning products significantly increased as shown in the regression with a level coefficient (β_2) of -224.17 ($p < 0.001$) and trend coefficient (β_3) of 15.74 ($p < 0.001$). The result revealed that both volume and expenditures on branded products showed a significant decrease in the regression in the post-intervention period (level coefficient of volume: β_2 = -57.65, $p < 0.01$, trend coefficient of volume: β_3 = -3.44, $p < 0.01$; level coefficient of expenditure: β_2 = -712.98, $p < 0.01$, trend coefficient of expenditure: β_3 = -40.10, $p < 0.01$).

Abbreviations: CNY, Chinese yuan renminbi; OECD, Organization for Economic Co-operation and Development; DDD, Defined Daily Dose DDDc, Defined Daily Dose cost; ITS, Interrupted time-series.

Conclusion: The volume-based procurement has successfully led to price reductions and improved the affordability of medicines, especially for those with chronic diseases. The volume-based procurement has demonstrated initial success in reshaping the composition of the Chinese pharmaceutical market in favor of generics with high quality and low prices.

KEYWORDS

the "4+7" pilot policy, volume-based procurement, price, expenditures, serotonin-specific reuptake inhibitors (SSRIs), antidepressants, interrupted time-series analysis (ITSA), quasi-experimental design and analysis

Introduction

Global drug costs are growing rapidly and are set to exceed $1.5 trillion by 2023 (Science HD, 2019). Growing pharmaceutical spending remains a persistent challenge in many countries all over the world. Large sections of the global population can't afford pharmaceutical spending (Cameron et al., 2009; Babar et al., 2019; Rodwin, 2021; San-Juan-Rodriguez et al., 2021). Notably, the problem is more severe in low-middle-income countries. Pharmaceutical expenditure in lower-middle-income countries can be up to 70% of total health expenditure, compared with 17% in higher-income countries (Papanicolas et al., 2018; Parente, 2018). China's economic burden on pharmaceuticals has increased steadily over the last decade. Pharmaceutical spending doubled from 2009 to 2017, reaching up to 34% of total health care expenditure in 2017 (China National Health Development Research Center, 2018). The percentage of pharmaceutical expenses in total health care expenditure in China was much higher than in some developed countries such as the United States (12.6%) and Australia (13.8%), as well as most Asian countries such as Japan (17.8%) and South Korea (19.3%) (OECD, 2021). China's relatively high proportion of drug costs has induced an increasing financial burden on patients. Thus, the Chinese government is currently exploring strategies to contain rapidly growing pharmaceutical spending.

Pharmaceutical expenditures depend on drug prices and drug volume, which were corresponding to the supply and demand sides of drugs respectively (Han et al., 2015). Price reduction strategies were direct measures to reduce pharmaceutical expenditures, which were associated with the supply side of drugs (Hakonsen et al., 2009; Lee et al., 2015; Rodwin, 2020; Yousefi et al., 2020). In China, to lower the prices of procured drugs, the Volume-Based Drug Centralized Procurement National Pilot Policy was officially launched in March 2019, aiming to reduce intermediates and marketing costs, promote marketing mode adjustment, and purify industry ecology. Four municipalities (Beijing, Tianjin, Shanghai, and Chongqing) and seven sub-provincial cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, and Xi'an) were chosen as pilot cities. Therefore, the Volume-Based Drug Centralized Procurement Pilot Policy is also called the "4 + 7" pilot policy.

In the "4 + 7" pilot policy, the purchase volume was predefined by centralizing the purchase volume from the public medical institutions in 11 selected cities. The Volume-Based Drug Centralized Procurement aimed to achieve lower prices through large-volume procurement, to implement the so-called "volume for price" strategy. It also can be seen as group purchasing which had bargaining power in the drug purchasing process (Noto et al., 2017). The drug supply enterprises reduced drug prices to obtain a larger market. Only one company would win the bidding for each policy-related drug, and the purchasing cycle was 12 months. The drug will be purchased with a bidding price until the purchase cycle expired. The policy-related drugs include branded drugs, generic drugs, and corresponding reference preparations. The quality of policy-related drugs was ensured by Generic Quality Consistency Evaluation (GQCE) approval. The prices of policy-related drugs were chopped, and price cuts ranged from 25 to 96% (Yuan et al., 2021). The massive price cuts dramatically impacted overall drug expenditures.

Depression is characterized by marked and lasting depressed mood and sadness, slow thinking, loss of interest or pleasure, decreased willpower, low self-worth, feelings of tiredness, and poor concentration (Guajardo et al., 2013; Lim et al., 2018). Depression is the leading cause of suicide in China (Phillips et al., 2002; Cheng et al., 2020). In the most severe form of depression, it can lead to suicide and increased risk of mortality (Yang et al., 2013). Furthermore, patients experiencing depression may endure periodic irritation, anxiety, emotional disorders, and/or other mental agonies (Jantaratnotai et al., 2017); therefore, taking the antidepressant for the patients is a relatively long even lasting process. As one of the most common mental disorders, depression is characterized by a significant and continuous low mood state and seriously affects the patients' learning ability as well as life and social functions (WHO, 2017).

In China, with the rapid economic development, the accelerated pace of modern life, and the increasingly fierce social competition, life pressure is also increasing, and depression has become a common public health problem. With 50 million depression patients in China, the DALYs have increased by 36.5% in the past 30 years (Ren et al.,

2020). If appropriate treatment is not applied, patients may develop a disability, premature death, and severe aftermath to their families from depression. However, in a national cross-sectional epidemiological survey from 157 representative points in 31 provinces across China, only 0.5% of participants with depressive disorders were treated adequately (Yu et al., 2021), indicating that only a few people have received adequate treatments. If the treatments of depression are not effective and standardized, it will result in a huge social and economic burden. A previous survey estimated the economic consequences of depressive disorders in China, conducted in five cities (Beijing, Changsha, Chengdu, Shanghai, and Suzhou) which represented the four broad geographic areas in China (North, Central, Southwest, and East Coast regions). As per the result of this survey, the proportion of medication costs in outpatients was 74.01% (Hu et al., 2007). To a certain extent, reducing the burden of drug costs can improve the compliance of depressive disorder patients. In China, national programs are needed to remove barriers to accessibility, availability, and affordability of medication treatment for depression (Yu et al., 2021).

After the "4 + 7" pilot policy, more patients could receive drug treatments. Considering the incidence of depression in the Chinese population and the economic burden of the disease, this study limits the research scenario to Serotonin-Specific Reuptake Inhibitors (SSRIs) drugs, which are the most recommended treatments for depression according to the second version of the Chinese Guideline for Prevention and Treatment of Depression (Ya-June 2018).

The purpose of this study was to quantitatively evaluate the impacts of the "4 + 7" pilot policy on purchase volume, purchase expenditures, and daily cost and to find the changes in the use of SSRIs. Firstly, this study aimed to verify whether the "4 + 7" pilot policy would lead to a decrease in the overall expenditure of SSRIs. Second, the research team tried to conduct a subgroup analysis for policy-related drugs and alternative drugs, winning drugs and non-winning drugs, generic drugs, and branded drugs. Last but not least, our team members examined the trend of the volumes of and the expenditures on SSRIs and their subgroups.

Materials and methods

Data sources

Data on products purchased between June 2017 and December 2019 were extracted from the Drug Trading Platform of Shenzhen—Shenzhen Group Purchasing Organization (Shenzhen GPO). The team was able to compare the changes in volume, expenditure, and daily costs of drugs for depression treatment after a national-level interference. The project collected monthly drug purchase orders from June 2017 to December 2019 in each medical institution. Each drug purchase order included the code of drug, generic name, dosage form, strengths, procurement unit, price per unit, net quantity of contents, pharmaceutical manufacturer, medical institution, purchase date, purchase volume, purchase expenditures, etc.

Study setting

As the first of China's Special Economic Zones, Shenzhen has undergone unprecedented economic development and social change, which has also led to tremendous changes in disease epidemiology (Gong et al., 2012). Consequently, the prevalence of depressive disorders in Shenzhen was the highest in China (Searle et al., 2019). Shenzhen started to investigate group purchasing strategies for certain types of drugs such as before and became one of 11 pilot cities to carry out drug volume-based purchasing. In this study, the team analyzed the SSRIs class which included Escitalopram, Paroxetine, Citalopram, Fluvoxamine, Fluoxetine, and Sherqulin. Escitalopram and Paroxetine were policy-related drugs. Citalopram, Fluvoxamine, Fluoxetine, and Sherqulin were alternative drugs. Then the research team divided policy-related drugs (including Escitalopram and Paroxetine) into two groups (winning products and non-winning products) based on whether the drugs won the bid in the "4 + 7" pilot policy. Only one company would win the bidding for each policy-related drug. Policy-related drugs were also divided into two subgroups based on whether the drugs were branded drugs or generic drugs. In this article, "product" hereafter designates a distinctive strength of a drug produced by a particular pharmaceutical manufacturer under the same generic name or the same strengths produced by different pharmaceutical manufacturers under the same generic name.

Variables and measurements

The primary measure is aimed at purchase volume, purchase expenditures, and daily costs of drugs. The defined daily dose (DDD) is the average daily dose of a particular drug set for use in adults for the treatment of a primary indication. The DDD of Escitalopram, Paroxetine, Citalopram, Fluvoxamine, Fluoxetine, and Sherqulin were 10, 20, 20, 100, 20, and 50 mg respectively. DDDs were standard measurements to calculate and compare drug purchase volume. According to the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2021), DDDs were calculated by the formula:

$$\mathrm{DDD_s} = \sum_{i=1}^{n}\left(\frac{\text{net quantity of contents} \times \text{strengths}}{DDD} \times N\right)$$

In this formula, the net quantity of contents expresses the numerical count of one specific drug in a marketed inner retail container (usually interchangeably immediate container in

China). The net quantity of contents is the number of units of preparation contained in the smallest sales packaging unit. The strength is the amount of drug in the dosage form or a unit of the dosage form (e.g. 10 mg capsule, 20 mg/5 ml suspension). Thus, this formula can conduct calculations (in this case, additions or subtractions) between different products with different net quantities of contents and/or different strengths of drugs with a standardized and unified measurement that multiplied "net quantity of contents" and "strengths", divided by "Defined Daily Doses," and finally timed by the total purchased quantity. Each drug purchase order can be measured by DDDs. Then we convert the purchase volume of drugs to DDDs which was a standardized and unified consumption unit for this situation (Wessling and Boethius, 1990; Rodriguez and Vega, 2010). DDDs used as the drug utilization index comparable across regions, countries, and stages, allowing for long-term monitoring and continuous evaluation of drug utilization (Natsch et al., 1998).

The purchase expenditures were calculated by the amount of drug purchase orders in Chinese yuan (CNY). The daily costs of drugs were measured by Defined Daily Dose cost (DDD), a standard measure of the procurement cost of each product (Guan et al., 2018). In this study, DDDc was calculated by the ratio of expenditures and DDDs.

Statistical analysis

Two types of analysis were applied in this study: descriptive analysis and interrupted time-series analysis (ITSA). Descriptive analysis was used to present differences in DDDs, expenditures, and DDDc of SSRIs between before and after implementation of the "4 + 7" pilot, as the policy was effective in March 2019.

The effect of the "4 + 7" pilot policy was evaluated by interrupted time-series (ITSA) with segmented regressions. ITS was the best and most commonly used approach for evaluating the longitudinal effects on interventions occurring at a fixed point of time, e.g. the date on which the policy was implemented (Xiao et al., 2021). Many researchers considered ITS analysis as the most practical quasi-experimental design to evaluate the effects of interventions (Zhao et al., 2021). The model this study uses a linear trend in the outcome within each segment. The specification of the linear regression model to be analyzed is as the following equation:

$$\begin{aligned} Y_{it} = {} & \beta_0 + \beta_1 * \text{Time}_t + \beta_2 * \text{Intervention}_t \\ & + \beta_3 * \text{Time\_after\_Intervention} + \beta_4 * \sin(2\pi m_i) \\ & + \beta_5 * \cos(2\pi m_i) + \varepsilon_{it} \end{aligned}$$

In this model, Y_{it} is the independent outcome variable (DDDs, expenditures, or DDDc). β_0 reflects the baseline level of the outcome, which is a constant. β_1 represents the change in the baseline trend that is independent of the intervention, which is the structural trend. β_2 captures the change in the level of the outcome, representing SSRIs use after the intervention; and β_3 estimates the change in trend in SSRIs use after the intervention. Some previous studies revealed a seasonal trend of depression (Yang et al., 2010; Ayers et al., 2013; Soreni et al., 2019). In this study, the seasonality effect was considered by β_4 and β_5. m_i is equal 1/12 for January, 2/12 for February, and so on with 12/12 for December (Hunsberger et al., 2002). ε_{it} is an estimate of the random error at Time_t (Lagarde, 2012). In this research, ITS was utilized to evaluate the impact on DDDs, expenditures, and DDDc after the implementation of the policy. The time of implementation of the "4 + 7" pilot policy in March 2019 was regarded as the intervention time point for ITS analysis. Intervention—binary indicator denoting 0 during the pre-intervention period and one during the postintervention period. Time since intervention (in months)—ordinal indicator denoting months since time interruption (i.e., implementation of intervention). Therefore, two segments with one interruptive point were constructed, where one is the pre-intervention period (from June 2017 to February 2019), and the other one is the post-intervention period (from March 2019 to December 2019).

Pre-requisite tests were conducted, for example, unit roots, white noise test, and autocorrelation (Phillips and Perron, 1988; Goodhart et al., 1993). Autocorrelation may lead to underestimated standard errors and overestimated significance of the effects of an intervention. Durbin–Watson statistic was performed to ensure that models adequately corrected for first-order autocorrelation. Values of the Durbin–Watson statistic close to 2.0 indicated the absence of serial autocorrelation (Bohnert et al., 2018). The specific estimation method in the ITS analysis was Newey-West standard errors for coefficients estimated. If autocorrelation is detected, a generalized least squares estimator, such as the Prais–Winsten method, was used to estimate the regression (Wagner et al., 2002; Lagarde, 2012). Data management and analysis were performed using Stata 16.0 (Stata Corporation, College Station, TX, United States). Statistical significance was noted when p-values were less than 0.05.

Results

Descriptive analysis of changes in volume, expenditures, and DDDc

Six SSRIs (Escitalopram, Paroxetine, Citalopram, Fluvoxamine, Fluoxetine, Sherqulin) were included in this study where Escitalopram and Paroxetine were "4 + 7" policy-related drugs and their alternatives were Citalopram, Fluvoxamine, Fluoxetine and Sherqulin (Table 1). The applied method of analysis was descriptive statistics, which was designed to compare the measures from two periods, which were 10 same selected months (March to December) from 2018 to 2019, since

TABLE 1 The information of all the SSRI medicines.

Category	Winning/Non-winning	Branded/Generic	DDD (mg)	Number of products	Number of pharmaceutical manufacturers
Policy-related drugs					
Escitalopram	Winning products	Generic drugs	10	1	1
Escitalopram	Non-winning products	Branded drugs	10	2	2
Escitalopram	Non-winning products	Generic drugs	10	2	2
Paroxetine	Winning products	Generic drugs	20	1	1
Paroxetine	Non-winning products	Branded drugs	20	1	1
Paroxetine	Non-winning products	Generic drugs	20	1	1
Alternative drugs					
Citalopram	-	-	20	0	0
Fluvoxamine	-	-	100	0	0
Fluoxetine	-	-	20	2	2
Sherqulin	-	-	50	2	2

TABLE 2 Descriptive analysis of SSRIs in Shenzhen.

Categories	DDDs (thousand)			Expenditures (thousand CNY)			DDDc (CNY)		
	Mar.-December 2018	Mar.-December 2019	Growth rate (%)	Mar.-December 2018	Mar.-December 2019	Growth rate (%)	Mar.-December 2018	Mar.-December 2019	Growth rate (%)
Policy-related drugs	1,924.99	3,401.49	76.70	13,100.32	12,656.86	-3.39	6.81	3.72	-45.32
Escitalopram	1,045.15	1,691.52	61.85	9,152.14	9,283.74	1.44	8.76	5.49	-37.32
Paroxetine	879.84	1,709.97	94.35	3,948.18	3,373.12	-14.57	4.49	1.97	-56.04
Alternative drugs	2,233.48	2,830.06	26.71	12,366.51	15,662.93	26.66	5.54	5.53	-0.04
Fluoxetine	467.49	623.28	33.33	3,589.83	4,710.64	31.22	7.68	7.56	-1.58
Sherqulin	1,765.99	2,206.78	24.96	8,776.68	10,952.30	24.79	4.97	4.96	-0.14
SSRI	4,158.46	6,231.55	49.85	25,466.83	28,319.79	11.20	6.12	4.54	-25.79

the intervention of the policy was launched in March 2019, and this study sought to conduct an unbiased comparison between pre-and post-intervention of the policy. Descriptive statistics also calculated the growth rate between the two periods. In Table 2, the DDDs indicated that the purchase volume of Escitalopram and Paroxetine increased by 76.70% after the intervention of the "4 + 7" policy; meanwhile, the expenditures and DDDc of Escitalopram and Paroxetine drugs decreased by 3.39%, 45.32% respectively. The DDDs and expenditures on alternative drugs increased by 26.71%, and 26.66% respectively. The DDDs and expenditures of SSRIs increased by 49.85%, and 11.20% respectively. The DDDc of SSRIs decreased by 25.79%. As shown in Supplementary Figures S1, 2 , the DDDs and expenditures of SSRIs increased after the policy inter*vention. At the same time, the DDDc of SSRIs and policy-related drugs both were decreased* (SupplementaryFigure S3).

The DDDs and expenditures of Escitalopram increased by 61.85%, and 1.44%, respectively; the DDDc of Escitalopram decreased by 37.32%. The DDDs of Paroxetine increased by 94.35%; the expenditures and DDDc of Paroxetine decreased by 14.57%, and 56.04%, respectively. The DDDs of Fluoxetine and Sherqulin increased by 33.33%, and 24.96% respectively.

The constituent ratio (CR) of DDDs and expenditures of SSRIs between pre-and post-intervention periods are listed in Table 3. Before implementation of the policy, 25.13% of Escitalopram and 21.16% of Paroxetine comprised SSRIs measured in DDDs, while DDDs of both Escitalopram and Paroxetine increased after the policy was implemented. Especially, DDDs of Paroxetine increased by 6.28 percent. DDDs of policy-related drugs increased by 8.29 percent in the post-intervention period, and expenditures on policy-related drugs dropped by 6.75 percent. Moreover, the DDDs of

TABLE 3 Descriptive analysis of SSRIs CR in Shenzhen.

Categories	The CR of DDDs (%)			The CR of expenditures (%)		
	Mar.-December 2018	Mar.-December 2019	Variation	Mar.-December 2018	Mar.-December 2019	Variation
Policy-related drugs	46.29	54.58	8.29	51.44	44.69	-6.75
Escitalopram	25.13	27.14	2.01	35.94	32.78	-3.16
Paroxetine	21.16	27.44	6.28	15.50	11.91	-3.59
Alternative drugs	53.71	45.42	-8.29	48.56	55.31	6.75
Fluoxetine	11.24	10.00	-1.24	14.10	16.63	2.54
Sherqulin	42.47	35.41	-7.05	34.46	38.67	4.21
SSRI	100.00	100.00	0.00	100.00	100.00	0.00

TABLE 4 Descriptive analysis of SSRI policy-related drugs in Shenzhen.

Categories	DDDs (thousand)			Expenditures (thousand CNY)			DDDc (CNY)		
	Mar.-December 2018	Mar.-December 2019	Growth rate (%)	Mar.-December 2018	Mar.-December 2019	Growth rate (%)	Mar.-December 2018	Mar.-December 2019	Growth rate (%)
Policy-related drugs	1,924.99	3,401.49	76.70	13,100.32	12,656.86	-3.39	6.81	3.72	-45.32
Winning products	0.00	2,911.55	-	0.00	8,467.86	-	-	2.91	-
Non-winning products	1,924.99	489.94	-74.55	13,100.32	4,189.00	-68.02	6.81	8.55	25.64
Escitalopram	1,045.15	1,691.52	61.85	9,152.14	9,283.74	1.44	8.76	5.49	-37.33
Winning products	0.00	1,311.11	-	0.00	5,795.12	-	-	4.42	-
Non-winning products	1,045.15	380.41	-63.60	9,152.14	3,488.62	-61.88	8.76	9.17	4.73
Paroxetine	879.84	1,709.97	94.35	3,948.18	3,373.12	-14.57	4.49	1.97	-56.04
Winning products	0.00	1,600.44	-	0.00	2,672.74	-	-	1.67	-
Non-winning products	879.84	109.53	-87.55	3,948.18	700.38	-82.26	4.49	6.39	42.50
Policy-related drugs	1,924.99	3,401.49	76.70	13,100.32	12,656.86	-3.39	6.81	3.72	-45.32
Branded drugs	801.24	342.59	-57.24	9,113.00	3,595.24	-60.55	11.37	10.49	-7.73
Generic drugs	1,123.75	3,058.90	172.21	3,987.32	9,061.61	127.26	3.55	2.96	-16.51
Escitalopram	1,045.15	1,691.52	61.85	9,152.14	9,283.74	1.44	8.76	5.49	-37.32
Branded drugs	549.74	252.66	-54.04	7,080.63	2,954.62	-58.27	12.88	11.69	-9.21
Generic drugs	495.41	1,438.86	190.44	2,071.52	6,329.12	205.53	4.18	4.40	5.20
Paroxetine	879.84	1,709.97	94.35	3,948.18	3,373.12	-14.57	4.49	1.97	-56.04
Branded drugs	251.50	89.93	-64.24	2,032.37	640.62	-68.48	8.08	7.12	-11.85
Generic drugs	628.34	1,620.04	157.83	1,915.81	2,732.50	42.63	3.05	1.69	-44.68

Sherqulin decreased by 7.05 percentage points, while expenditures raised by 4.21 percentage points with the interference of the "4 + 7" policy.

As displayed in Table 4, the DDDs and expenditures of all products in the non-winning group decreased by 74.55%, and 68.02%, respectively. The DDDc of policy-related products in

TABLE 5 Descriptive analysis of SSRIs policy-related CR drugs in Shenzhen.

Categories	The CR of DDDs (%)[a]			The CR of expenditures (%)[a]		
	Mar.-December 2018	Mar.-December 2019	Variation	Mar.-December 2018	Mar.-December 2019	Variation
Policy-related drugs	100.00	100.00	0.00	100.00	100.00	0.00
Winning products	0.00	85.60	85.60	0.00	66.90	66.90
Non-winning products	100.00	14.40	-85.60	100.00	33.10	-66.90
Escitalopram	54.29	49.73	-4.56	69.86	73.35	3.49
Winning products	0.00	38.55	38.55	0.00	45.79	45.79
Non-winning products	54.29	11.18	-43.11	69.86	27.56	-42.30
Paroxetine	45.71	50.27	4.56	30.14	26.65	-3.49
Winning products	0.00	47.05	47.05	0.00	21.12	21.12
Non-winning products	45.71	3.22	-42.49	30.14	5.53	-24.60
Policy-related drugs	100.00	100.00	0.00	100.00	100.00	0.00
Branded drugs	41.62	10.07	-31.55	69.56	28.41	-41.16
Generic drugs	58.38	89.93	31.55	30.44	71.59	41.16
Escitalopram	54.29	49.73	-4.56	69.86	73.35	3.49
Branded drugs	28.56	7.43	-21.13	54.05	23.34	-30.71
Generic drugs	25.74	42.30	16.57	15.81	50.01	34.19
Paroxetine	45.71	50.27	4.56	30.14	26.65	-3.49
Branded drugs	13.07	2.64	-10.43	15.51	5.06	-10.45
Generic drugs	32.64	47.63	14.99	14.62	21.59	6.96

[a]The CR, presented in Table 5 shows only the proportion of all policy-related drugs.

the non-winning group increased by 25.64%. Table 4 proved that the DDDs of Escitalopram in the winning group increased from 0 to 1311.11 thousand. The DDDc of Entecavir, as a winning product, was 4.42 CNY. The DDDs of Paroxetine, another winning product, increased from 0 to 1600.44 thousand, and the DDDc of it was 1.67 CNY. Supplementary Figures S4, 5 revealed that the DDDs and expenditures of winning products were increased which both were 0 before the implementation of the "4 + 7" policy. Supplementary Figure S6 revealed that the DDDc of policy-related drugs decreased.

<On the other hand, for those policy-related generic products, Table 4 indicated that the DDDs and the expenditures of them increased by 172.21%, and 127.26%, respectively, while the DDDc of all policy-related generic products decreased by 16.51%. Moreover, DDDs of generics of Escitalopram increased by 190.44%; meanwhile, expenditures and DDDc of those generics of Escitalopram also increased by 205.53 and 5.20%, respectively.

Supplementary Figures S7, 8 revealed that the DDDs and expenditures of branded drugs were obviously decreased after the implementation of the "4 + 7" policy. Supplementary Figure S9 revealed that the DDDc of policy-related drugs decreased.

Table 5 demonstrated the CR changes of DDDs, expenditures, and DDDc of winning and non-winning products, branded and generic products between pre-and post-intervention periods. Before the implementation of the "4 + 7" pilot policy, in public hospitals, the market share was 0 for some specific products of Escitalopram and Paroxetine in the winning group but after the implementation of the policy, these products of Escitalopram and Paroxetine achieved significant growth with market shares of 38.55 and 47.05%, respectively. The market share of policy-related generic products was 58.38% before intervention. Finally, the market share of Escitalopram and Paroxetine generic products in SSRIs measured by DDDs increased by 16.57 and 14.99%, respectively.

ITS analysis of changes in DDDs, expenditures, and DDDc

Table 6 represented the results of the segmented linear analysis with ITS. The DDDc of SSRIs dropped by 1.56 yuan ($p < 0.001$) with the "4 + 7" pilot policy.

The DDDs of policy-related drugs has a baseline trend increased before the "4 + 7" pilot policy by 5.41 thousand

TABLE 6 The result of the ITS analysis of SSRIs in Shenzhen.

Categories	DDDs (thousands)	Expenditures (thousands of CNY)	DDDc (CNY)
	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)
Policy-related drugs			
Baseline trend β_1	5.41 (0.83,9.98)*	36.81 (8.59,65.02)*	-0.01 (-0.07,0.05)
Change in level β_2	67.34 (-1.41,136.09)	-443.55 (-865.17,-21.93)*	-2.93 (-3.68,-2.19)***
Change in trend β_3	4.93 (-6.73,16.58)	-3.64 (-40.25,32.97)	-0.02 (-0.16,0.11)
Seasonal effects sin β_4	-1.01 (-37.21,35.20)	36.68 (-190.33,263.70)	0.10 (-0.27,0.47)
Seasonal effects cos β_5	-10.20 (-41.68,21.27)	-65.62 (-219.55,88.30)	-0.27 (-0.60,0.06)
Constant β_0	114.14 (74.72,153.56)***	797.39 (575.43,1019.35)	7.15 (6.42,7.88)***
Escitalopram			
Baseline trend β_1	2.88 (0.31,5.45)*	27.70 (8.22,47.17)**	0.04 (-0.06,0.14)
Change in level β_2	5.50 (-28.60,39.60)	-350.09 (-653.31,-46.86)*	-3.17 (-4.33,-2.01)***
Change in trend β_3	6.06 (0.89,11.22)*	9.50 (-13.56,32.56)	-0.16 (-0.39,0.07)
Seasonal effects sin β_4	4.15 (-17.12,25.42)	44.22 (-126.40,214.84)	-0.07 (-0.64,0.50)
Seasonal effects cos β_5	-8.97 (-25.10,7.17)	-70.32 (-185.50,44.86)	-0.16 (-0.54,0.23)
Constant β_0	64.28 (44.09,84.47)*	540.59 (402.26,678.93)***	8.50 (7.46,9.55)***
Paroxetine			
Baseline trend β_1	2.52 (0.30,4.75)*	9.11 (-1.48,19.69)	-0.05 (-0.08,-0.03)***
Change in level β_2	61.84 (21.00,102.68)**	-93.46 (-237.24,50.31)	-1.90 (-2.41,-1.38)***
Change in trend β_3	-1.13 (-8.17,5.91)	-13.14 (-29.56,3.28)	0.01 (-0.04,0.06)
Seasonal effects sin β_4	-5.16 (-22.97,12.65)	-7.54 (-81.48,66.41)	0.13 (-0.06,0.32)
Seasonal effects cos β_5	-1.24 (-18.14,15.67)	4.70 (-48.14,57.53)	-0.16 (-0.34,0.03)
Constant β_0	49.86 (26.91,72.81)***	256.79 (144.42,369.17)***	5.21 (4.90,5.53)***
Alternative drugs			
Baseline trend β_1	4.86 (0.42,9.31)*	28.90 (3.24,54.55)*	0.02 (0.00,0.04)
Change in level β_2	-36.17 (-106.65,34.31)	-211.47 (-606.34,183.40)	-0.09 (-0.38,0.20)
Change in trend β_3	7.85 (-2.85,18.55)	41.45 (-17.99,100.88)	-0.02 (-0.06,0.02)
Seasonal effects sin β_4	-1.94 (-34.66,30.79)	1.19 (-190.62,193.00)	0.02 (-0.13,0.16)
Seasonal effects cos β_5	-5.64 (-30.32,19.04)	-50.78 (-198.45,96.90)	-0.10 (-0.29,0.08)
Constant β_0	160.54 (120.04,201.05)***	861.41 (612.60,1110.23)***	5.29 (5.03,5.56)***
Fluoxetine			
Baseline trend β_1	1.76 (0.39,3.13)*	13.87 (3.35,24.39)*	0.01 (0.00,0.02)*
Change in level β_2	-8.62 (-30.09,12.84)	-79.84 (-242.61,82.93)	-0.24 (-0.40,-0.09)**
Change in trend β_3	0.76 (-2.28,3.80)	6.08 (-17.02,29.18)	0.00 (-0.02,0.02)
Seasonal effects sin β_4	2.30 (-9.99,14.59)	19.21 (-76.02,114.44)	-0.01 (-0.09,0.07)
Seasonal effects cos β_5	-2.53 (-12.31,7.26)	-17.69 (-93.15,57.78)	0.05 (-0.03,0.13)
Constant β_0	23.03 (8.53,37.52)**	172.97 (63.25,282.69)**	7.52 (7.38,7.66)***
Sherqulin			
Baseline trend β_1	3.10 (-0.43,6.63)	15.02 (-3.14,33.19)	0.00 (-0.01,0.02)
Change in level β_2	-27.54 (-85.17,30.09)	-131.64 (-418.25,154.97)	0.00 (-0.17,0.18)
Change in trend β_3	7.09 (-1.49,15.67)	35.37 (-6.83,77.57)	0.00 (-0.03,0.02)
Seasonal effects sin β_4	-4.24 (-30.46,21.98)	-18.02 (-156.67,120.63)	0.03 (-0.11,0.16)
Seasonal effects cos β_5	-3.11 (-24.82,18.59)	-33.09 (-149.40,83.22)	-0.11 (-0.24,0.03)
Constant β_0	137.52 (105.35,169.69)***	688.44 (505.60,871.29)***	4.92 (4.68,5.15)***
SSRIs			
Baseline trend β_1	10.27 (1.70,18.84)*	65.70 (13.93,117.47)*	0.01 (-0.01,0.02)
Change in level β_2	31.17 (-97.66,160.00)	-655.02 (-1384.02,73.97)	-1.56 (-1.95,-1.18)***
Change in trend β_3	12.77 (-8.97,34.52)	37.81 (-53.05,128.66)	-0.02 (-0.08,0.04)

(Continued on following page)

TABLE 6 (*Continued*) The result of the ITS analysis of SSRIs in Shenzhen.

Categories	DDDs (thousands)	Expenditures (thousands of CNY)	DDDc (CNY)
	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)
Seasonal effects sin β_4	-2.94 (-66.56,60.68)	37.88 (-348.48,424.23)	0.06 (-0.14,0.26)
Seasonal effects cos β_5	-15.84 (-59.41,27.72)	-116.40 (-355.01,122.21)	-0.15 (-0.31,0.01)
Constant β_0	274.68 (200.27,349.09)***	1658.80 (1215.55,2102.05)***	6.05 (5.86,6.24)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

($p < 0.05$). The expenditures on policy-related drugs ($\beta_1 = 36.81$, $p < 0.05$) represented an increasing baseline trend. And the expenditures on policy-related drugs showed decreasing in level with statistical significance ($\beta_3 = -443.55$, $p < 0.05$). Moreover, the DDDc of those drugs had a substantial drop of 2.93 CNY ($p < 0.001$) after implementing the policy, but the change in trend after the intervention had only decreased by 0.02 CNY with no statistical significance.

The trend coefficient indicated that DDDs of Escitalopram increased after the implementation of the policy ($\beta_3 = 6.06$, $p < 0.05$). The expenditures of Escitalopram with level coefficient: $\beta_2 = -350.09$ ($p<0.05$), on the other hand, decreased. DDDc of Escitalopram showed a positive relation to expenditure, which also dropped by 3.22 CNY($p < 0.001$). Similarly, DDDs of Paroxetine increased by the influence of the policy with a level coefficient: $\beta_2 = 61.84$ and $p < 0.01$. DDDc of Paroxetine dropped by 1.90 CNY ($p < 0.001$) after the policy was launched.

The model for alternative drugs suggested that over the period studied, the baseline trend was a 4.86 thousand increase in the DDDs per month ($p < 0.05$). The analysis showed a change in the baseline trend of expenditures of a 28.90 thousand CNY increase. And Fluoxetine had a similar change in the baseline trend.

Overall, for SSRIs, the post-intervention period presented an increase in DDDs, which level coefficient (β_2) equaled 31.17, and trend coefficient (β_3) equaled 12.77, but the p-value both were more than 0.05. The expenditures demonstrated a decreasing trend with no statistical significance (level coefficient: $\beta_2 = -655.02$, $p > 0.05$). After the intervention, there was a significant decline in DDDc since the level coefficient was equaled to -1.56 ($p < 0.001$).

Table 7 indicated that DDDs of non-winning products significantly decreased as shown in the regression with a level coefficient (β_2) of -156.83 ($p < 0.001$) and trend coefficient (β_3) of -10.81 ($p < 0.001$). As well as the expenditures on non-winning products they also had a significant decrease with a level coefficient (β_2) of -1028.73 ($p < 0.001$) and trend coefficient (β_3) of -64.38 ($p < 0.001$). Furthermore, DDDc had an increase of 0.31 CNY ($p < 0.01$) after the implementation of the policy. Table 7 also indicated that DDDs of non-winning products in Escitalopram and Paroxetine significantly decreased as shown in the regression with level coefficient and trend coefficient ($p < 0.01$).

Table 7 indicated that DDDs of winning products significantly increased as shown in the regression with a level coefficient (β_2) of -224.17 ($p < 0.001$) and trend coefficient (β_3) of 15.74 ($p < 0.001$). As well to the expenditures of winning products they also had a significant increase with a level coefficient (β_2) of 585.18 ($p < 0.001$) and trend coefficient (β_3) of 60.74 ($p < 0.001$). The winning products in Escitalopram and Paroxetine The winning products in Escitalopram showed similar changes. The winning products in Paroxetine only showed an increase in level.

Table 8 demonstrated that both DDDs and expenditures on branded products showed a significant decrease in the regression in the post-intervention period (level coefficient of DDDs: $\beta_2 = -57.65$, $p < 0.01$, trend coefficient of DDDs: $\beta_3 = -3.44$, $p < 0.01$; level coefficient of expenditure: $\beta_2 = -712.98$, $p < 0.01$, trend coefficient of expenditure: $\beta_3 = -40.10$, $p < 0.01$). The DDD of branded products shrunk as shown in Table 8 (level coefficient: $\beta_2 = -1.47$, $p < 0.001$). The branded drugs in Escitalopram and Paroxetine have similar changes.

Table 8 demonstrated that both DDDs and expenditures of generic products showed a significant increase in the regression in the post-intervention period (level coefficient of DDDs: $\beta_2 = 124.99$, $p < 0.001$; level coefficient of expenditure: $\beta_2 = 269.43$, $p < 0.01$, trend coefficient of expenditure: $\beta_3 = -40.10$, $p < 0.01$). But the DDDc of generic products increased as shown in Table 8 (trend coefficient: $\beta_3 = 0.11$, $p < 0.01$). The generic drugs in Escitalopram have similar changes.

Discussion

The "4 + 7" pilot policy has shown the initial success of lowering prices by government-oriented group purchases. Thus, this study analyzed the effect of the "4 + 7" pilot policy on the daily cost of SSRIs in Shenzhen. For example, the DDD of SSRIs decreased with the "4 + 7" pilot policy by 1.56 yuan ($p < 0.001$). The DDD of policy-related drugs had an immediate drop of

TABLE 7 The result of ITS analysis of SSRIs policy-related drugs in Shenzhen.

Categories	DDDs (thousands)	Expenditures (thousands of CNY)	DDDc (CNY)
	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)
Escitalopram			
Non-winning products			
Baseline trend β_1	2.94 (0.40,5.48)*	27.94 (8.64,47.24)**	0.04 (-0.06,0.14)
Change in level β_2	-71.16 (-116.78,-25.54)**	-688.92 (-1064.63,-313.21)**	-1.03 (-3.09,1.03)
Change in trend β_3	-6.48 (-9.86,-3.09)**	-45.89 (-71.07,-20.70)**	0.27 (-0.06,0.59)
Seasonal effects sin β_4	6.48 (-13.80,26.76)	54.52 (-116.80,225.83)	-0.04 (-0.71,0.64)
Seasonal effects cos β_5	-1.79 (-12.47,8.90)	-38.58 (-135.54,58.38)	-0.23 (-0.66,0.20)
Constant β_0	63.93 (43.82,84.04)***	539.04 (401.61,676.47)***	8.51 (7.46,9.56)***
Winning products			
Baseline trend β_1	-0.05 (-0.24,0.13)	-0.24 (-1.07,0.59)	-
Change in level β_2	76.66 (48.13,105.19)***	338.83 (212.72,464.95)***	-
Change in trend β_3	12.53 (7.17,17.90)***	55.39 (31.68,79.10)***	-
Seasonal effects sin β_4	-2.33 (-10.47,5.81)	-10.30 (-46.28,25.68)	-
Seasonal effects cos β_5	-7.18 (-17.51,3.15)	-31.74 (-77.38,13.91)	-
Constant β_0	0.35 (-1.73,2.43)	1.55 (-7.63,10.74)	-
Paroxetine			
Non-winning products			
Baseline trend β_1	2.58 (0.40,4.75)*	9.19 (-1.33,19.71)	-0.05 (-0.08,-0.03)***
Change in level β_2	-85.68 (-117.68,-53.68)***	-339.81 (-494.66,-184.96)***	2.12 (1.40,2.84)***
Change in trend β_3	-4.33 (-6.77,-1.90)**	-18.49 (-30.28,-6.71)**	0.17 (0.04,0.30)*
Seasonal effects sin β_4	-0.68 (-14.87,13.51)	-0.06 (-71.22,71.10)	0.12 (-0.07,0.30)
Seasonal effects cos β_5	6.04 (-5.20,17.28)	16.85 (-30.40,64.09)	-0.20 (-0.40,0.00)
Constant β_0	49.61 (26.82,72.39)***	256.37 (144.09,368.65)***	5.22 (4.90,5.53)***
Winning products			
Baseline trend β_1	-0.05 (-0.26,0.16)	-0.09 (-0.44,0.26)	-
Change in level β_2	147.51 (108.10,186.93)***	246.35 (180.52,312.18)***	-
Change in trend β_3	3.20 (-3.24,9.65)	5.35 (-5.41,16.11)	-
Seasonal effects sin β_4	-4.48 (-14.48,5.53)	-7.48 (-24.19,9.23)	-
Seasonal effects cos β_5	-7.28 (-18.53,3.98)	-12.15 (-30.94,6.64)	-
Constant β_0	0.25 (-1.84,2.35)	0.42 (-3.07,3.92)	-
Policy-related drugs			
Non-winning products			
Baseline trend β_1	5.51 (1.02,10.00)*	37.13 (9.17,65.10)*	-0.01 (-0.07,0.05)
Change in level β_2	-156.83 (-231.64,-82.03)***	-1028.73 (-1540.24,-517.23)***	0.67 (-0.49,1.84)
Change in trend β_3	-10.81 (-16.13,-5.49)***	-64.38 (-97.73,-31.03)**	0.31 (0.12,0.49)**
Seasonal effects sin β_4	5.80 (-26.60,38.20)	54.46 (-171.12,280.04)	0.24 (-0.22,0.69)
Seasonal effects cos β_5	4.25 (-15.84,24.35)	-21.73 (-150.34,106.87)	-0.39 (-0.74,-0.04)*
Constant β_0	113.53 (74.44,152.63)***	795.41 (574.52,1016.30)***	7.16 (6.44,7.89)***
Winning products			
Baseline trend β_1	-0.11 (-0.49,0.28)	-0.33 (-1.48,0.83)	-
Change in level β_2	224.17 (165.38,282.96)***	585.18 (417.04,753.33)***	-
Change in trend β_3	15.74 (5.20,26.27)**	60.74 (29.47,92.01)***	-
Seasonal effects sin β_4	-6.81 (-22.65,9.04)	-17.77 (-64.67,29.12)	-
Seasonal effects cos β_5	-14.46 (-35.27,6.36)	-43.89 (-106.44,18.66)	-
Constant β_0	0.60 (-3.47,4.68)	1.98 (-10.48,14.43)	-

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 8 The result of ITS analysis of SSRIs policy-related drugs in Shenzhen.

Categories	DDDs (thousands)	Expenditures (thousands of CNY)	DDDc (CNY)
	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)	Coef. (95%*C.I.*)
Escitalopram			
Branded drugs			
Baseline trend β_1	2.11 (1.03,3.19)***	27.27 (13.31,41.23)***	0.00 (0.00,0.00)
Change in level β_2	-43.99 (-66.42,-21.56)***	-592.76 (-882.19,-303.33)***	-1.07 (-1.39,-0.74)***
Change in trend β_3	-2.35 (-4.03,-0.68)**	-31.50 (-52.48,-10.53)**	-0.04 (-0.09,0.02)
Seasonal effects sin β_4	3.63 (-6.99,14.25)	42.58 (-92.58,177.73)	0.02 (-0.02,0.06)
Seasonal effects cos β_5	-4.69 (-11.64,2.26)	-55.53 (-140.85,29.80)	0.03 (-0.03,0.08)
Constant β_0	26.73 (18.38,35.07)***	343.70 (236.26,451.14)***	12.88 (12.87,12.89)***
Generic drugs			
Baseline trend β_1	0.77 (-0.85,2.38)	0.43 (-6.11,6.96)	-0.09 (-0.18,-0.01)*
Change in level β_2	49.49 (22.91,76.07)***	242.67 (122.95,362.39)***	0.77 (0.05,1.49)*
Change in trend β_3	8.41 (2.61,14.21)**	41.01 (15.74,66.27)**	0.10 (0.02,0.19)*
Seasonal effects sin β_4	0.52 (-13.63,14.68)	1.65 (-58.31,61.60)	0.01 (-0.14,0.15)
Seasonal effects cos β_5	-4.27 (-16.59,8.04)	-14.79 (-69.58,39.99)	0.11 (-0.13,0.34)
Constant β_0	37.55 (24.34,50.77)***	196.89 (147.76,246.02)***	5.49 (4.28,6.70)***
Paroxetine			
Branded drugs			
Baseline trend β_1	0.26 (-0.54,1.07)	2.14 (-4.38,8.67)	0.00 (0.00,0.00)
Change in level β_2	-13.66 (-24.97,-2.34)*	-120.22 (-213.48,-26.96)*	-0.79 (-1.24,-0.34)***
Change in trend β_3	-1.09 (-2.07,-0.11)*	-8.60 (-16.17,-1.03)*	-0.05 (-0.12,0.02)
Seasonal effects sin β_4	0.28 (-5.42,5.98)	2.88 (-42.99,48.75)	0.03 (-0.03,0.08)
Seasonal effects cos β_5	-0.56 (-3.68,2.57)	-3.26 (-28.28,21.76)	0.04 (-0.04,0.12)
Constant β_0	20.90 (11.82,29.98)***	168.85 (95.50,242.20)***	8.08 (8.07,8.09)***
Generic drugs			
Baseline trend β_1	2.26 (0.75,3.77)**	6.96 (2.43,11.49)**	0.00 (0.00,0.00)
Change in level β_2	75.49 (37.88,113.11)***	26.76 (-47.82,101.33)	-1.31 (-1.40,-1.22)**
Change in trend β_3	-0.04 (-6.73,6.65)	-4.54 (-16.53,7.44)	-0.01 (-0.03,0.00)
Seasonal effects sin β_4	-5.44 (-19.03,8.15)	-10.41 (-42.63,21.80)	0.00 (-0.01,0.01)
Seasonal effects cos β_5	-0.68 (-15.88,14.52)	7.96 (-27.11,43.02)	0.01 (-0.01,0.02)
Constant β_0	28.96 (13.52,44.40)**	87.95 (41.34,134.55)**	3.05 (3.05,3.05)***
Policy-related drugs			
Branded drugs			
Baseline trend β_1	2.38 (0.64,4.11)**	29.42 (10.38,48.46)**	0.04 (0.00,0.07)*
Change in level β_2	-57.65 (-89.51,-25.79)**	-712.98 (-1079.18,-346.77)***	-1.47 (-2.02,-0.93)***
Change in trend β_3	-3.44 (-5.65,-1.24)**	-40.10 (-65.04,-15.16)**	-0.01 (-0.14,0.12)
Seasonal effects sin β_4	3.91 (-10.74,18.56)	45.45 (-120.88,211.79)	0.14 (-0.23,0.51)
Seasonal effects cos β_5	-5.25 (-13.88,3.38)	-58.79 (-156.41,38.84)	-0.07 (-0.30,0.17)
Constant β_0	47.63 (32.04,63.21)***	512.55 (350.19,674.91)***	10.89 (10.51,11.26)***
Generic drugs			
Baseline trend β_1	3.03 (0.10,5.96)*	7.39 (-2.64,17.42)	-0.07 (-0.12,-0.01)*
Change in level β_2	124.99 (66.06,183.92)***	269.43 (98.45,440.41)**	-0.29 (-0.76,0.18)
Change in trend β_3	8.37 (-3.54,20.27)	36.46 (1.19,71.74)*	0.11 (0.04,0.17)**
Seasonal effects sin β_4	-4.92 (-31.06,21.22)	-8.77 (-96.51,78.98)	0.08 (-0.05,0.22)
Seasonal effects cos β_5	-4.95 (-31.30,21.39)	-6.83 (-89.97,76.30)	-0.01 (-0.22,0.21)
Constant β_0	66.51 (41.14,91.89)***	284.84 (208.37,361.31)***	4.48 (3.69,5.28)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

2.93 yuan (95%*CI* -3.68 to -2.19, $p < 0.001$) under the "4 + 7" pilot policy. The "4 + 7" pilot policy was designed to achieve lower prices through competitive bidding processes between accredited generic drug manufacturers.

The reduced price of drugs may improve the accessibility of drugs. A previous survey revealed that the proportion of medication costs in outpatient costs was 74.01%, conducted in five cities (Beijing, Changsha, Chengdu, Shanghai, and Suzhou) (Hu et al., 2007). The result revealed that the proportion of medication costs in outpatient costs was 86.14%, which surveyed 652 outpatients with depression in Shanghai (Zhou Xuedong et al., 2008). Reducing the burden of drug costs may improve the compliance of depressive disorder patients. Medicine's price control measures were used to increase medicine's affordability (Rawson, 2020). This study revealed that the "4 + 7" pilot policy led to an increase in the total volume of SSRIs, as well as each of the four study medications. The DDDs of SSRIs increased by 49.85%. The result has shown a 76.70% increase in the purchased volume of policy-related drugs and a 3.39% decrease in the expenditure on policy-related drugs. Over the first 9 months of implementation, this study found that the "4 + 7" pilot policy increased the proportion of purchasing policy-related drugs. It was consistent with the result of the study conducted in one of 11 pilot cities Dalian (Sheng Liang-Liang and Hu, 2019).

New Zealand controlled pharmaceutical expenditures by a combination of strong negotiation, bundling agreements, tendering sole supply, and contracts. Then it resulted in immediate savings on pharmaceutical expenditures with up to 90 percent on some drugs, despite a 50% increase in volumes (Lybecker, 2013). After the implementation of the "4 + 7" pilot policy, policy-related drugs decreased by 443.55 thousand CNY. The "4 + 7" pilot policy led to significant savings and improvement in the efficient resource allocation of the healthcare system, which was consistent with previous studies (Qi et al., 2020; Yang et al., 2021).

But the policy effects were smaller observed in SSRIs, including price reductions, cost-saving, unleashing medication demand, and improving accessibility. A previous study revealed that the largest reduction in spending occurred on drugs for the treatment of cardiovascular diseases in the "4 + 7" pilot policy (Chen et al., 2021). Another study in Shenzhen revealed that the post-intervention period witnessed a significant increase in the regression level for nucleos(t)ide analogs DDDs (level coefficient: $\beta_2 = 631.87$, $p < 0.05$). The expenditures (trend coefficient: $\beta_3 = 392.24$, $p < 0.05$) and DDDc (level coefficient: $\beta_2 = -6.17$, $p < 0.001$; trend coefficient: $\beta_3 = -0.21$, $p < 0.05$) of NAs showed decreasing trend in the post-intervention period (Wen et al., 2021). It may be due to SSRIs having less market competition because of fewer generic drug manufacturers, as well as less willingness for healthcare providers to clinical conversion in patients taking antidepressant medication for a long time (Yang et al., 2021). The volume and expenditures of alternative drugs increased after the "4 + 7" pilot policy. It was a side effect of pharmaceutical policies (Kwon et al., 2013; Kwon et al., 2019; Chen et al., 2020; Yang et al., 2021). In this study, the volume and expenditures of alternative drugs didn't show statistic significant changes in the interrupted time-series analysis. Most of depression patients got prescription based on a doctor's diagnosis. We need monitor the using of SSRIs for a long term to ensure rational use of drugs.

The volume-based procurement policy is aimed at reducing pharmaceutical expenditures by creating economies of scale and improving purchasing power (Seidman and Atun, 2017). On the one hand, pharmaceutical companies offered lower prices in exchange for a larger volume of purchases, given the result of winning drugs replacing the non-winning drugs. Winning products were given priority to use, which resulted in putting winning products in the place of non-winning products (Jialing et al., 2021). This study found that the "4 + 7" pilot policy increased the proportion of purchasing winning drugs, with an increment of 85.60 percent. The volume of non-winning products had a significant decrease ($\beta_2 = -156.83$, $p < 0.001$; $\beta_3 = -10.81$, $p < 0.001$). The volume of non-winning products experienced attenuation following the entry of winning products, and both Escitalopram and Paroxetine decreased. Because all public medical institutions (including public hospitals and government-run primary healthcare centers) in the "4 + 7″ pilot cities need to give priority to using drugs which won the bidding.

Volume-based procurement policy potentially reshaped the market share of pharmaceuticals by substituting branded with generic drugs (World Health Organization, 2007; Waning et al., 2009; Lybecker, 2013). The proportion of branded drugs decreased by 31.55 percent. Only one company would win the bidding for each policy-related drug in the "4 + 7" pilot policy. And the company won the bidding in the "4 + 7" pilot policy for Escitalopram and Paroxetine both were generic products. All public hospitals and primary healthcare centers in the "4 + 7″ pilot cities gave priority to using drugs that won the bidding. In this way, the decrease mainly occurred in branded drugs. The promotion of generic drugs using was a commonly used strategy, which could improve medicine's affordability and accessibility. Most of the Association of Southeast Asian Nations (ASEAN) countries also applied generic medicine promotion, which can enhance the use of much cheaper generic medicines (You et al., 2019). The result revealed that the volume of branded drugs both showed a significant decrease in the regression level and trend in the post-intervention period ($\beta_2 = -57.65$, $p < 0.01$; $\beta_3 = -3.44$, $p < 0.01$). The volume-based procurement policy accredited generics in place of off-patent branded drugs, which also resulted in lower SSRIs total drug purchasing costs. It was consistent with previous studies (Dylst et al., 2015; Wouters et al., 2017). The volume-based procurement policy relieves the overall drug burden on patients (Son, 2021). It also

accomplished the goal of controlling drug costs (Nunes et al., 2020). For example, generic substitution was compulsory in Greece (Wouters et al., 2017). Policymakers usually require generic prescribing and substitution to achieve significant savings in the United States. They also streamline the generic drug approval process for this purpose.

The implementation of the "4 + 7" pilot policy, improves the quality of medicines because the generic drugs winning the bid got generic quality consistency evaluation approval (Lijun, 2019). Generic drugs which did not get generic quality consistency evaluation approval would be out of the market very soon. Some small pharmaceutical companies could not take part in the bidding or lost the bid. Then they may stop manufacturing and exit the market (Hu et al., 2015). The volume-based procurement policy drove small drug manufacturers with inferior research and production capacity out of business.

However, it is unclear whether the lowest price for a drug will always be the best value, and it is an issue that many purchasers must consider (van Valen et al., 2018). In the "4 + 7" pilot policy, sole supply may cause drug shortages (Zhang, 2019). The researchers also found that later rounds of volume-based procurement have to change the number of pharmaceuticals in the bidding rules. Considering all other factors will lead to the timely, reliable delivery of safe, high-quality products, and ultimately result in lower prices from increased competition. Big data analytics might help set reasonable cap prices and monitor the real-world data and evidence to support price negotiations for procurement. To deliver safe and cost-effective medicines, it was necessary to systematically evaluate the effectiveness, safety and economics are necessary (Li et al., 2018). With the moving toward value-based medical, health decision-making pays more attention to Health Technology Assessment. In volume-based procurement. Health Technology Assessment could serve as an effective tool based on real-world data.

More rounds of volume-based procurement have been rapidly carried out in the country, and assessing long-term trends in volume and expenditure is significant. Evaluation of the effect of policy could guide policymakers, healthcare providers, and patients to better understand the reform and adapt accordingly. And it is still important to evaluate the policy effects on special disease categories by assessing further data from more rounds of volume-based procurements.

The main strength of this study was using ITS quantitative analysis of the impact of the "4 + 7″ pilot policy. It may be a valuable reference for policy effect evaluation. It offered suggestions for policy promotion.

Limitations

The present study had some limitations that should be borne in mind when interpreting the results. First, one of the limitations was the lack of inclusion of drugstores, as one of the main stakeholders of the pharmaceutical industry in the study. The reason was only public medical institutions were included in the purchasing alliance in the "4 + 7″ pilot policy. Second, this study only used 9 months of time series data post-intervention. In exploring the long-term trend of the "4 + 7″ pilot policy, it would be better if this study could get access to all pilot cities as research objects and full purchasing cycle as research time points. The purchasing cycle was 12 months. The drug will be purchased with a bidding price until the purchase cycle expired. We didn't get purchasing records for the other 3 months during purchasing cycle at present. But the trend would same as the result of this study.

Conclusion

The volume-based procurement has successfully led to price reductions and improved the affordability of medicines, especially for those with chronic diseases. The volume-based procurement has demonstrated initial success in reshaping the composition of the Chinese pharmaceutical market in favor of generics with high quality and low prices. Future studies are needed to investigate the long-term impact of the volume-based procurement policy on various outcomes, such as patient outcomes, drug utilization, and changes in the pharmaceutical industry.

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

Author Contributions: Conceptualization, ZM, DC, and XW; Formal analysis, XW; Funding acquisition, ZM and DC; Investigation, XW, ZW, LX, JL, XG, XC, and YY; Methodology, XW and YY; Project administration, ZM, DC, and XW; Supervision, ZM and DC; Writing—original draft, XW and ZW; Writing—review and editing, XW, ZW, LX, JL, XG, XC, and YY; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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Supplementary Material

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Atezolizumab plus platinum-based chemotherapy as first-line therapy for metastatic urothelial cancer: A cost-effectiveness analysis

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Purpose: According to the IMvigor130 trial, adding atezolizumab to platinum-based chemotherapy was effective in the treatment of metastatic urothelial cancer (mUC). Based on the perspective of the United States and China, the current study evaluated cost-effectiveness of atezolizumab plus chemotherapy for mUC patients in the first-line setting.

Methods: A partitioned survival model was adopted for mUC patients. The survival data were derived from the IMvigor130 trial. Direct cost values were collected from the Centers for Medicare and Medicaid Services (CMS), Chinese Drug Bidding Database, and published literatures. The utility and toxicity data were gathered from related research studies and IMvigor130 trial. The incremental cost–utility ratios (ICURs) and incremental cost-effectiveness ratios (ICERs) were calculated and analyzed. Scenario analyses and sensitivity analyses were performed to observe the outputs and uncertainties.

Results: The base-case analysis showed that the ICUR of atezolizumab plus chemotherapy versus chemotherapy in American and Chinese settings is $ 737,371 /QALY and $ 385,384 /QALY, respectively. One-way sensitivity analyses showed that the ICUR ranged from $ 555,372/QALY to $ 828,205/QALY for the United States. Also, the range was from $ 303,099/QALY to $ 433,849/QALY in the Chinese setting. A probabilistic sensitivity analysis showed the likelihood that atezolizumab plus chemotherapy becoming the preferred strategy was a little low even if the price reduction strategy was applied.

Conclusion: Adding atezolizumab to chemotherapy improved survival time, but it is not a cost-saving option compared to chemotherapy for metastatic urothelial cancer patients in the American and Chinese settings.

KEYWORDS

atezolizumab, cost-effectiveness, partitioned survival model, metastatic urothelial cancer, the perspective of the United States and China

Introduction

Globally, bladder cancer is the 10th most common cancer, with 573,000 new cases and 213,000 deaths estimated in 2020 (Sung et al., 2021). Urothelial cancer is the most common type of bladder cancer, accounting for 90%–95% of all cases (Chen et al., 2020; Ren et al., 2020). Early-stage urothelial cancer is curable, but invasive urothelial cancer with progressive or recurrent disease usually has a poor prognosis (Lopez-Beltran et al., 2021). Patients with metastatic urothelial carcinoma (mUC), a chemotherapy-sensitive condition, typically receive platinum-based chemotherapy as their first course of treatment. A high proportion of patients who undergo such a treatment eventually develop platinum resistance and progressive diseases, even though the response rate is >50% (Holmsten et al., 2016). Nevertheless, many new regimens are currently being investigated because cytotoxic chemotherapy did not produce long-lasting results. A variety of cancers have responded to cancer immunotherapy in recent years. The mechanisms of action of all immunotherapies are the same: the agents engage the own immune system of the body to inhibit and kill cancer cells (Yang, 2015). In other words, immunotherapy is defined as a type of biotherapy that works by sensitizing the patient's immune system to cancer, increasing selectivity to prevent immune escape (Akkın et al., 2021). The program death protein 1 (PD-1)/program death ligand 1 (PD-L1) axis is one key pathway that cancer cells use to avoid the body's immune response. Many PD-1/PD-L1 blockers were produced to inhibit immune escape. Several clinical trials were conducted for mUC patients receiving PD-1/PD-L1 blockers. The KEYNOTE-045 trial showed that the median overall survival was 10.3 months with the pembrolizumab (A PD-1 inhibitor) group and 7.4 months with the chemotherapy group in the mUC patient (Bellmunt et al., 2017). The JAVELIN Bladder 100 trial indicated that adding avelumab (a PD-L1 inhibitor) to best supportive care prolonged the overall survival significantly in the mUC patients. The OS (overall survival) at 1 year was 79.1% and 60.4% in the avelumab group and control group, respectively (Powles et al., 2020). The IMvigor130 trial found that the addition of atezolizumab to chemotherapy prolonged PFS (progression-free survival) time (8.2 months vs. 6.3 months) and also improved the OS time (16 months vs. 13.4 months) compared with the chemotherapy group (Galsky et al., 2020). The results of these trials revealed that PFS/OS of mUC patients showed significant clinical improvement following treatment with PD-1/PD-L1 inhibitors. Based on these surprising results, some PD-1/PD-L1 inhibitors, such as atezolizumab, have been approved by the US Food and Drug Administration for urothelial cancer (US Food and Drug Administration, 2021). Several anti-neoplastic agents were concerned after approving, which might typically include concerns with increased prices and limited health gain (Cohen, 2017). Many health economic researchers have been thinking about why cancer occupies such a dominant position within healthcare systems across the world (Haycox, 2016). As a result, continual increases in expenditure on cancer medicines is continuing, which causes problems to healthcare systems across countries (Godman et al., 2021). To the best of our knowledge, there were few research studies that revealed the potential economic burden of mUC patients receiving atezolizumab. More evidence of economic studies and analyses to explore the economic burden of new anti-neoplastic drugs to decision makers or patients are very urgently needed. Although the IMvigor130 trial revealed a statistically significant PFS benefit in mUC patients receiving atezolizumab, the OS results did not cross the pre-specified threshold for significance. Whether the survival benefit reaches the expected value that matches the pricing needs to be further explored. Our study conducted the cost-effectiveness analysis of atezolizumab plus chemotherapy versus placebo plus chemotherapy to explore whether the current price is acceptable for mUC patients. Then, we conducted a comparative analysis from the perspectives of the United States and China because there is a large gap in threshold and affordability between middle-income and high-income countries, especially some drugs that have proved to be cost-effective in developed countries are not so cost-effective in developing countries (Al-Ziftawi et al., 2021). Also, investigating the differences of cost-effectiveness in atezolizumab plus chemotherapy for mUC between the US and China from the economic context is needed.

Materials and methods

Model structure

An analysis of the cost-effectiveness was conducted using a partitioned survival model (PSM) to simulate the disease survival states of mUC patients beyond the follow-up period of the clinical trial. The characteristics of included patients of the study were consistent with those of the IMvigor130 trial (Galsky et al., 2020), who were aged 18 years or older with locally advanced or metastatic urothelial carcinoma and had not received previous systemic therapy in the metastatic setting. One of two interventions is offered to patients in this study until disease progression occurs: (i) platinum-based chemotherapy (34% of patients received cisplatin with gemcitabine and 66% of patients received carboplatin with gemcitabine); (ii) atezolizumab plus platinum-based chemotherapy (30% of patients received cisplatin with atezolizumab and gemcitabine and 70% of patients received carboplatin with atezolizumab and gemcitabine). In case of disease progression, it is assumed that the current treatment regimen became invalid, and the initial regimen would be replaced by subsequent best supportive therapies for the patients with the progressed disease.

Three mutually exclusive disease health states were set in the partitioned survival model, including progression-free (PF)

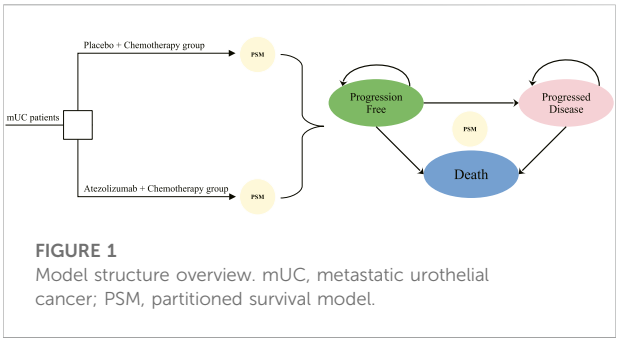

FIGURE 1
Model structure overview. mUC, metastatic urothelial cancer; PSM, partitioned survival model.

survival, progressed disease (PD), and death. The decision tree diagram and bubble diagram of the model are shown in Figure 1. The initial health state that mUC patients entered the model is the PF state, which is able to move to the PD or death state based on survival data. Patients were assumed to be unable to return to previous health states. In accordance with the IMvigor130 protocol, the period for the model cycle was 21 days. In order to fully understand the outcome of the disease, one needs to extrapolate limited survival data to predict long-term outcomes. The ten-year timeframe was therefore set to ensure that mUC patients fully transited to the terminal state.

Clinical data

The available observational time of the IMvigor130 trial was around 30 months for OS and PFS. Also, extrapolating over follow-up time was needed in order to predict survival over a ten-year period. We used algorithms proposed by Guyot to get the simulated individual patient-level data (Guyot et al., 2012). Engauge Digitizer, a tool for digitizing pictures, is used to digitize the OS and PFS Kaplan–Meier curves for each treatment regimen. The generated individual patient-level data (IPD) were applied to fit a range of parametric distributions, including Weibull, exponential, Gompertz, log-logistic, and log-normal. In general, the most appropriate distribution is determined by the Akaike information criterion (AIC) (Kuk and Varadhan, 2013). The key clinical data are shown in Table 1.

Costs and utilities

This analysis adopted the perspective of the health sector with different settings of the United States and China. The direct medical costs that were considered are as follows: agent acquisition costs, administration costs for intravenous injection, management of adverse events (AEs), and palliative care. The doses of agents are kept with those of the IMvigor130 trial. In the platinum-based chemotherapy regimen, gemcitabine was used at a dose of 1,000 mg/m^2 body surface area (BSA) administered intravenously on days 1 and 8 of each model cycle. Carboplatin (area under the curve of 4.5 mg/ml per min administered intravenously) or cisplatin (70 mg/m^2 BSA administered intravenously) was administered on day 1 of each cycle. In the atezolizumab plus chemotherapy regimen, the doses

TABLE 1 Projected survival data and safety data summary.

Parameter	Expected value	Range	Distribution	Reference
PFS: atezolizumab + chemotherapy	Shape = 1.7445; scale = 10.9865	1.5951–1.9078 9.9954–12.076	Log-logistic	Galsky et al. (2020)
PFS: placebo + chemotherapy	Shape = 2.0017; scale = 9.6519	1.8263–2.1939 8.8593–10.5154	Log-logistic	Galsky et al. (2020)
OS: atezolizumab + chemotherapy	Shape = 1.5267; scale = 23.5327	1.3676–1.7044 20.9135–26.48	Log-logistic	Galsky et al. (2020)
OS: placebo + chemotherapy	Shape = 1.6106; scale = 20.2234	1.4404–1.801 18.0261–22.6886	Log-logistic	Galsky et al. (2020)
Probability of main grade 3 or 4 adverse events in the atezolizumab + chemotherapy arm				
Neutrophil count decreased	5.3%	4.0%–6.6%	Beta	Galsky et al. (2020)
Anemia	8.2%	6.1%–10.3%	Beta	Galsky et al. (2020)
Neutropenia	8.4%	6.3%–10.5%	Beta	Galsky et al. (2020)
Thrombocytopenia	4.0%	3.0%–5.0%	Beta	Galsky et al. (2020)
Probability of main grade 3 or 4 adverse events in the placebo + chemotherapy arm				
Neutrophil count decreased	6.4%	4.8%–8.0%	Beta	Galsky et al. (2020)
Anemia	7.4%	5.6%–9.3%	Beta	Galsky et al. (2020)
Neutropenia	4.4%	3.3%–5.5%	Beta	Galsky et al. (2020)
Thrombocytopenia	3.6%	2.7%–4.5%	Beta	Galsky et al. (2020)

PFS, progression-free survival; OS, overall survival; AIC, Akaike information criterion.

TABLE 2 Model costs, utility estimates, and other parameters.

Parameter	Distribution	US		China	
Treatment cost		**Value (range), USD**	**Reference**	**Value (range), USD**	**Reference**
Atezolizumab (per 1,200 mg)	Gamma	9,569.88 (7,177–9,569.88)	Centers for Medicare&Medicaid Services, (2022)	5,073.55 (3,805.16–5,073.55)	Yaozh, (2022)
Gemcitabine (per 200 mg)	Gamma	70.98 (53.24–88.73)	Centers for Medicare&Medicaid Services, (2022)	7.17 (5.38–8.96)	Yaozh, (2022)
Cisplatin (per 10 mg)	Gamma	1.77 (1.33–2.21)	Centers for Medicare&Medicaid Services, (2022)	1.17 (0.88–1.46)	Yaozh, (2022)
Carboplatin (per 50 mg)	Gamma	2.643 (1.98–3.30)	Centers for Medicare&Medicaid Services, (2022)	12.22 (9.17–15.28)	Yaozh, (2022)
Administration (per cycle)	Gamma	399.88 (299.91–499.85)	Centers for Medicare and Medicaid Services, (2022)	61.72 (46.29–77.15)	Liu et al. (2021)
Best supportive care (per cycle)	Gamma	6,199.62 (4,649.72–7,749.53)	Aly et al. (2019)	1,415.02 (1,061.27–1,768.78)	Liu et al. (2021)
Terminal care	Gamma	11,820 (8,865–14,775)	Wu et al. (2018)	2,099.15 (1,574.36–2,623.94)	Liu et al. (2021)
AE unit costs		**Value (range), USD [in 2015, USD]**	**Reference**	**Value (range), USD**	**Reference**
Neutrophil count decreased	Gamma	51,308 (38,481–64,135) [43,707]	Agency for Healthcare Research and Quality, (2022)	104.95 (78.71–131.19)	Liu et al. (2021)
Neutropenia	Gamma	51,337 (38,503–64,171) [43,732]	Agency for Healthcare Research and Quality, (2022)	526.90 (395.18–658.63)	Liu et al. (2021)
Anemia	Gamma	36,264 (27,198–45,330) [30,892]	Agency for Healthcare Research and Quality, (2022)	607.06 (455.30–758.83)	Liu et al. (2021)
Thrombocytopenia	Gamma	45,332 (33,999–56,665) [38,617]	Agency for Healthcare Research and Quality, (2022)	4,082.99 (3,062.24–5,103.74)	Lang et al. (2020)
Utility estimate		**Value (range)**		**Reference**	
Progression-free disease	Beta	0.80 (0.77–0.82)		Hale et al. (2021)	
Progressive disease	Beta	0.75 (0.70–0.79)		Hale et al. (2021)	
Other parameter		**Value (range)**	**Reference**	**Value (range)**	**Reference**
Body surface area, m^2	Normal	1.85 (1.49–2.21)	Slater et al. (2020)	1.72 (1.50–1.90)	Lu et al. (2017)
Proportion of cisplatin in the initial treatment regimen		**Value (range)**		**Reference**	
AC group	Beta	30% (22.5%–37.5%)		Galsky et al. (2020)	
PC group	Beta	34% (25.5%–42.5%)		Galsky et al. (2020)	
Proportion of carboplatin in the initial treatment regimen		**Value (range)**		**Reference**	
AC group	Beta	70% (62.5%–77.5%)		Galsky et al. (2020)	
PC group	Beta	66% (57.5%–74.5%)		Galsky et al. (2020)	
Proportion of patients receiving subsequent therapy		**Value (range)**		**Reference**	
AC group	Beta	26% (19.5%–32.5%)		Galsky et al. (2020)	
PC group	Beta	41% (30.8%–51.3%)		Galsky et al. (2020)	

The costs of AEs presented in this table were paid on a per-event basis. All costs reported for years prior to 2021 are updated to December 2021 USD using the American and Chinese CPI. All costs sourced from China in this study were converted into US dollars ($1 = RMB 6.4649, average exchange rate from January to October 2021).
AC, atezolizumab plus chemotherapy; PC, placebo plus chemotherapy; AEs, adverse events; CPI, Consumer Price Index; USD, US dollars; CMS, Centers for Medicare and Medicaid Services.

of chemotherapy agents are adopted in keeping with the aforementioned chemotherapy regimen, and atezolizumab was administered at a dose of 1,200 mg on day 1 of each cycle. In this analysis, the mean BSA of 1.85 m^2 is adopted for American patients (Slater et al., 2020), and that of Chinese patients is 1.72 m^2 (Lu et al., 2017). The prices of gemcitabine, carboplatin, cisplatin, and atezolizumab in the US were sourced from the Centers for Medicare and Medicaid Services (CMS) (Centers for Medicare&Medicaid Services, 2022), and those of China were acquired from drug acquisition costs in a local charge database (Yaozh, 2022). Costs related to administration cost for intravenous injection, palliative care, and best supportive care (BSC) were derived from CMS or related articles for analysis in an American setting (Centers for Medicare and Medicaid Services, 2022; Wu et al., 2018; Aly et al.,2919), and the cost data for analysis in the Chinese setting were gathered from published literatures (Liu et al., 2021). The IMvigor130 trial shared data about incidences of adverse events. It was assumed that AEs of grades 1 and 2 could be well managed, and the costs of that were not included. So, only the management costs of grade 3 or 4 AEs were considered. The data about costs of managing AEs were sourced from open-accessed databases or published literatures (Liu et al., 2021; Agency for Healthcare Research and Quality, 2022; Lang et al., 2020). As the IMvigor130 trial reported, around 26% of patients in the atezolizumab plus chemotherapy group and 41% of those in the chemotherapy group receive subsequent therapies. The proportions corresponded to the baseline data and were only used for cost estimates. All costs reported for years prior to 2021 are updated to December 2021 in US dollars (USD) using

the Consumer Price Index (CPI). All costs sourced from China in this study were converted into US dollars based on the average exchange rate from January to October 2021. More details about costs are summarized in Table 2.

In this partitioned survival model, each health state was assigned a health utility value based on the disease progression context. Since the data from the EuroQol 5-Dimension (EQ-5D) in the IMvigor130 trial would not be reported in their clinical study report, the direct quality of life data could not be available. Highly relevant and robust data are extremely crucial. Since the quality of life is related to the progressive stage, the utility estimates for PF and PD states were assumed to be 0.80 and 0.75, respectively, based on similar UC studies (Hale et al., 2021).

Analyses

In the base-case analysis, we used incremental cost-effectiveness ratios (ICERs) to evaluate the incremental cost per additional life-year (LY) gained between atezolizumab plus chemotherapy and placebo plus chemotherapy regimens. Incremental cost–utility ratios (ICURs) were used to assess the incremental cost per additional quality-adjusted life-year (QALY). All QALYs and costs were discounted at an annual rate of 3% for the United States, and 5% was adopted for China. If the ICUR of atezolizumab plus chemotherapy compared with placebo plus chemotherapy is below the willingness-to-pay (WTP) threshold, the atezolizumab plus chemotherapy regimen is regarded as a cost-effective option. The threshold for WTP in the United States is usually in the range of approximately $ 100,000–150,000/QALY (Verma et al., 2018). In this analysis, we adopted $ 100,000/QALY as the WTP threshold for the cost-effectiveness analysis in the setting of the United States. In China, the WTP threshold was set at thrice the per capita gross domestic product (GDP, calculated to be $31,316 in 2020) (Hutubessy et al., 2003).

We conducted one-way and probabilistic sensitivity analyses (PSA) for model input parameters in order to assess the robustness of our results and to identify the variables that had a considerable impact on them. In one-way sensitivity analyses, the range of the discount rate is from 0 to 8 %, and other inputs were assumed a variation by ± 25% of the base-case value. In addition, Monte Carlo simulation of 1,000 iterations was used to run the PSA. According to specific probability distributions, all input parameters were sampled simultaneously. Health utilities and incidence of adverse events or proportions were sampled from beta distribution and gamma distribution for costs (Briggs et al., 2012). A cost-effectiveness acceptability curve (CEAC) was generated to clearly present the likelihood that atezolizumab plus chemotherapy was cost-effective at a range of WTP threshold. The partitioned survival model and cost-effectiveness analysis model were created and programmed in R (version 4.1.2, http://www.r-project.org).

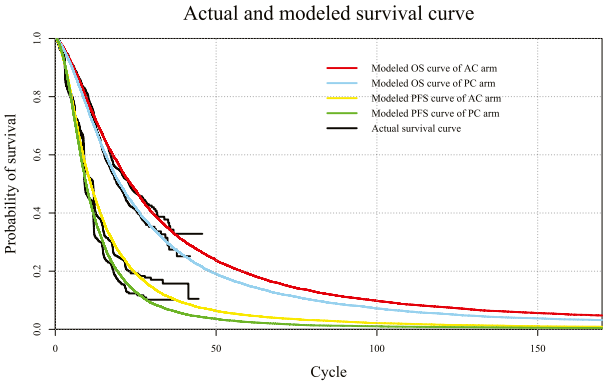

FIGURE 2
Diagram of modeled PFS and OS fit curves in different regimens. The colored lines represent the modeled survival curves, and the black lines represent the actual survival curves. Each cycle of the x-axis is 3 weeks. PFS, progression-free survival; OS, overall survival; AC, atezolizumab plus chemotherapy; PC, placebo plus chemotherapy.

Results

Validity of the fitted parametric survival function

Log-logistic-predicted PFS and OS models of atezolizumab plus chemotherapy and placebo plus chemotherapy regimens and actual survival curves are shown in Figure 2. The selected distribution of the projected curve is shown in Table 1. All detailed values of the parametric distributions for each arm are listed in Supplementary Table S1.

Base-case analysis

In the US context, patients with mUC receiving the atezolizumab plus chemotherapy regimen gained 2.290 LYG, 1.651 QALYs, and expended $ 233,492, and patients receiving the placebo plus chemotherapy regimen resulted in 1.957 LY, 1.419 QALYs gained, and $ 62,422 expended. Compared with the placebo plus chemotherapy regimen, the atezolizumab plus chemotherapy regimen increased the overall cost by $ 171,070. For effectiveness, the atezolizumab plus chemotherapy regimen showed an increase of 0.333 LYG and 0.232 QALYs compared with the placebo plus chemotherapy regimen. The results of the average cost-effectiveness ratios of atezolizumab plus chemotherapy are $ 101,962 /LY and $ 141,425 /QALY, and those of the placebo plus chemotherapy regimen are $ 27,259 /LY and $ 37,809 /QALY, respectively. The ICER and ICUR of atezolizumab plus chemotherapy compared with placebo plus chemotherapy are $ 513,724 /LY and $ 737,371 /QALY, respectively.

TABLE 3 Results of the base-case analysis and subgroup analysis.

Country	Regimen	LY	QALY	Cost, US$	ICER ($/LY)	ICUR ($/QALY)
US	Placebo plus chemotherapy	1.957	1.419	62,422	-	-
	Atezolizumab plus chemotherapy	2.290	1.651	233,492	513,724	737,371
China	Placebo plus chemotherapy	1.957	1.365	9,912	-	-
	Atezolizumab plus chemotherapy	2.290	1.580	96,946	261,363	404,809

LY, life-year; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost–utility ratio.

In the context of China, patients with mUC receiving the atezolizumab plus chemotherapy regimen gained 2.290 LYG, 1.580 QALYs, and expended $ 96,946, and patients receiving the placebo plus chemotherapy regimen resulted in 1.957 LY, 1.365 QALYs gained, and $ 9,912 expended. Compared with the placebo plus chemotherapy regimen, the atezolizumab plus chemotherapy regimen increased the overall cost by $ 87,034. For effectiveness, the atezolizumab plus chemotherapy regimen showed an increase of 0.333 LYG and 0.215 QALYs compared with the placebo plus chemotherapy regimen. The results of the average cost-effectiveness ratios of atezolizumab plus chemotherapy are $ 42,334 /LY and $ 61,358 /QALY, and those of the placebo plus chemotherapy regimen are $ 5,065 / LY and $ 7,262 /QALY, respectively. The ICER and ICUR of atezolizumab plus chemotherapy compared with placebo plus chemotherapy are $ 261,363 /LY and $ 404,809 /QALY, respectively. All results of the base-case analysis for the United States and China are summarized in Table 3.

One-way sensitivity analysis

The one-way sensitivity analyses were conducted to test the modeling assumptions. The results are shown in the form of tornado diagrams (Figure 3). In the setting of the United States, the tornado diagram showed that the price of atezolizumab and the discount rate were the top two variables that have a significant impact on ICUR. Also, the proportion of receiving subsequent therapy for the placebo plus chemotherapy group ranked third in the tornado diagram. In addition, the higher this proportion is, the lower the value of ICUR is. The utility of PFS, utility of PD, and the proportion of receiving subsequent therapy for the atezolizumab plus chemotherapy group also have a significant impact on ICUR. The result of the one-way sensitivity analysis ranged from $ 555,372/QALY to $ 828,205/QALY for the United States. The impact of the AE-related, BSC-related, or palliative-related expenditure on the outcome was minimal. Similar to the results of the American setting, the one-way sensitivity analysis for China revealed that the top-ranked variables are still the price of atezolizumab, discount rate, the utility of PFS, the utility of PD, and the proportion of receiving subsequent therapy. The range for the one-way sensitivity analysis was from $ 303,099/QALY to $ 433,849/ QALY in the Chinese setting. Either in the United States or China, reducing the price of atezolizumab contributes the most to the reduction of the ICUR value.

Probabilistic sensitivity analysis

A total of 1,000 iterations were conducted to sample all the model parameters from probability distributions simultaneously. To assess whether atezolizumab plus chemotherapy would be considered cost-effective at various levels of WTP in terms of health gains, we designed a CEAC (Figure 4). Either in the setting of the United States or China, the CEAC revealed a zero probability of adding atezolizumab to chemotherapy being cost-effective. As the tornado diagram indicated that the price of atezolizumab contributes the most to the reduction of the ICUR value, additional probabilistic sensitivity analyses of adjusting the price of atezolizumab to 75%, 50%, and 25% of its price were conducted. Also, two scenarios of the WTP threshold were analyzed for the United States ($ 100,000/QALY and $ 200,000/QALY) and China ($ 31,316/QALY and $ 60,000/QALY).

In the context of the United States, if the WTP threshold was $ 100,000/QALY, the likelihood of atezolizumab plus chemotherapy in the price reduction setting was 0%, 0%, and 3.2% of being cost-effective, respectively (settings of 25%, 50%, and 75% reduction in the price of atezolizumab). When the threshold of $ 200,000/QALY was adopted, the likelihood of atezolizumab plus chemotherapy was 0%, 2.1%, and 54.8%, respectively. Also, in the setting of China, if the WTP threshold was $ 31,316/QALY, the likelihood of atezolizumab plus chemotherapy was 0%, 0%, and 0.1%, respectively. When the threshold of $ 60,000/QALY was used, the likelihood of atezolizumab plus chemotherapy was 0%, 0%, and 5.3%, respectively. The CEAC of price reduction assumption is shown in Supplementary Figure S1. The probability of a regimen becoming the preferred strategy is summarized in Supplementary Table S2.

Discussion

The durable activity and good tolerability of atezolizumab for urothelial cancer were reported based on a clinical trial of phase

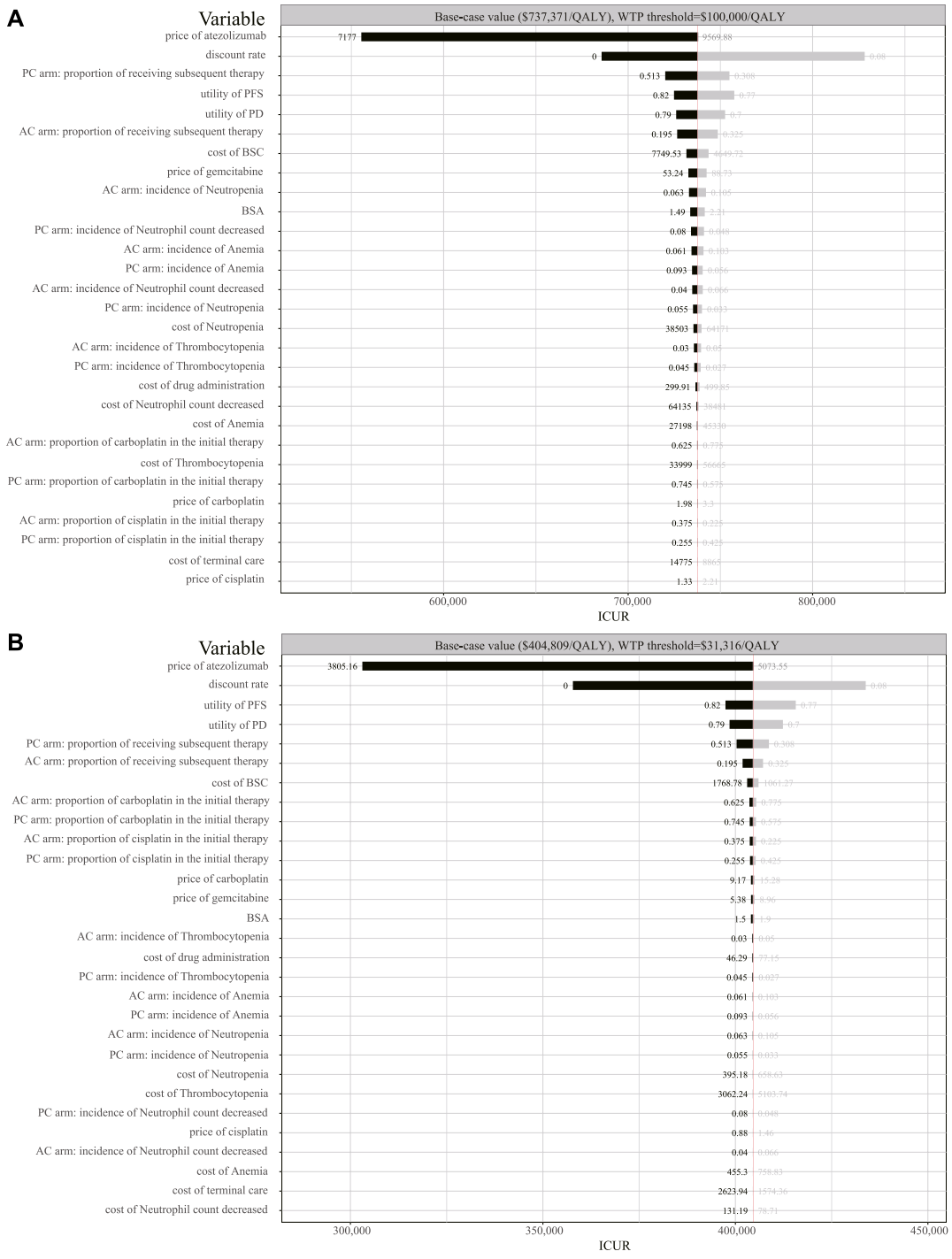

FIGURE 3
Tornado diagram of the one-way sensitivity analysis. **(A)** Output in the American setting. **(B)** Output in the Chinese setting. QALY, quality-adjusted life-year; BSC, best supportive care; BSA, body surface area; ICUR, incremental cost–utility ratio; AC, atezolizumab plus chemotherapy; PC, placebo plus chemotherapy.

II (Rosenberg et al., 2016). It provided a new therapy choice for mUC patients, and the FDA issued an accelerated approval for atezolizumab in the second-line treatment of urothelial cancer in 2016. A study revealed that the agent brought a significant economic burden (Savage, 2017). However, recent reports about the clinical benefits of atezolizumab plus chemotherapy

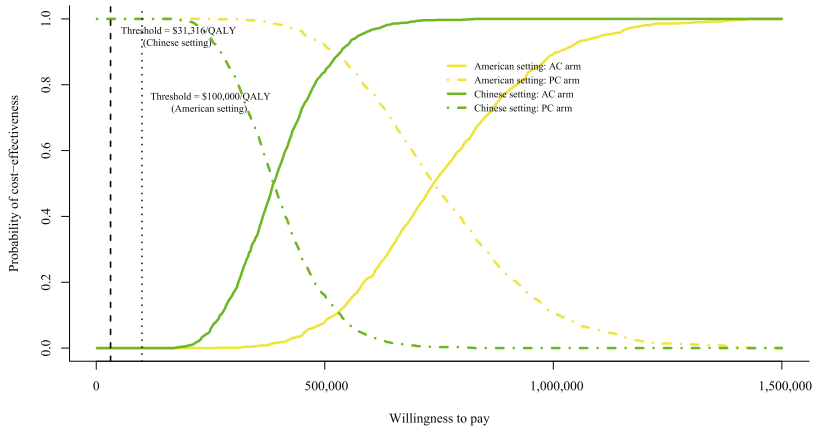

FIGURE 4
Cost-effectiveness acceptable curve. The y-axis indicates the probability that a regimen is cost-effective across the willingness-to-pay threshold (x-axis). QALY, quality-adjusted life-year; AC, atezolizumab plus chemotherapy; PC, placebo plus chemotherapy.

for mUC patients based on a clinical trial of phase III sparked great interest among both oncologists and patients (Galsky et al., 2020). This evaluation explored the cost-effectiveness of adding atezolizumab to platinum-based chemotherapy based on the latest survival data in the American and Chinese settings. The base-case analysis results showed that the ICUR of atezolizumab plus chemotherapy compared with chemotherapy alone is $ 737,371/QALY in the American setting and $ 404,809/QALY in the Chinese context. The ICUR values sharply exceed the average threshold of $ 100,000/QALY in the United States and $ 31,316/QALY in China. Our one-way sensitivity showed that the variable that made the greatest impact on ICUR was the price of atezolizumab. To further investigate whether the lower price of atezolizumab or in the setting of high-income regions or cities could make this regimen become cost-effective, we made following assumptions: (i) the price of atezolizumab was cut by 25%, 50%, and 75%; (ii) the WTP threshold was increased to $ 200,000/QALY in the American setting and $ 60,000/QALY in the Chinese setting. The additional CEAC showed that at the threshold of $ 100,000/QALY, even if the price of atezolizumab is reduced by 75%, it is only 3.2% of the likelihood to be cost-effective in the American context. Under the same premise, the probability of atezolizumab plus chemotherapy is around 54.8% at a $ 200,000/QALY threshold. In the context of China, even if the price of atezolizumab is cut by 75%, it is only 0.1% of probability of being cost-effective at the threshold of $ 31,316/QALY. Under the same assumption, the probability of atezolizumab plus chemotherapy is around 5.3 % at the $ 60,000/QALY threshold.

Our additional analysis revealed that although the price of atezolizumab plays a key role, lowering the price of atezolizumab does not improve the likelihood of becoming cost-effective significantly. Also, the QALY gained in the atezolizumab plus chemotherapy group just exceeded 0.23 QALY compared with the placebo plus chemotherapy group. Therefore, the atezolizumab regimen hardly became a cost-effective treatment choice for patients and oncologists. We noted that similar economic studies on pembrolizumab for urothelial cancer showed an improvement in survival benefit significantly. Hale et al. (2021) concluded that pembrolizumab was a cost-effective alternative to chemotherapy based on a US third-party healthcare payer's perspective, with a significant QALY benefit (2.91 QALYs in the pembrolizumab group vs. 0.90 QALYs in the chemotherapy group). Similarly, Patterson et al. (2019) concluded that pembrolizumab was a cost-effective choice compared to chemotherapy from a Swedish healthcare perspective. The QALY of Patterson's study was 2.93 QALYs and 0.82 QALYs in pembrolizumab and chemotherapy groups, respectively. We found that, also as immune checkpoint inhibitors, differences in survival time between PD-1 inhibitors and PD-L1 inhibitors were significant for urothelial cancer under a similar premise. Pembrolizumab, a PD-1 blocker, improved the OS time and QALYs significantly, and its price matched its survival improvement. But the OS improvement of adding atezolizumab to chemotherapy was not statistically significant, and the price of atezolizumab exceeded the value that matches its survival improvement. In other words, the significant improvement of OS is also important; only the significant improvement of PFS contributes little to the economic results of drugs. This might be a major reason why atezolizumab plus chemotherapy was not a cost-effective alternative.

Some weakness existed in our study. First, our survival data were derived from IMvigor130, in which around three-fourths of

the patients were white. Asian patients accounted for around one-fifth. However, our survival analysis was based on the overall patients whether in the American or Chinese setting. Inevitably, the accuracy of survival data was slightly shaken by race. Second, our study relied on modeling techniques. It was not an actual IPD in this model, but a projected IPD generated by a specific algorithm. Third, the analysis results using parametric models to extrapolate the survival outcomes beyond the time horizon may result in a slight hypothesis bias compared to the analysis results with sufficient survival data of the follow-up. Although it could undermine the robustness, the sensitivity analyses covered the substantial ranges of all variables in order not to ignore the uncertainties. By using modeling techniques, it is possible to predict certain changes in the results. Finally, the data about quality of life, sourced from the IMvigor130 trial, were not reported. Direct health-associated utility data were not available. Thus, we can only extract utility data from published literatures. However, our sensitivity analysis shows that the change in utility did not have a significant impact on ICUR. Furthermore, our analysis had one notable feature in addition to its limitations. As we selected models, we put in a great deal of effort. In this study, we considered the Markov model, partitioned survival model, and cure model. Considering the characteristics of the survival curve, the cure model was not adopted. Likewise, in order to reduce the deviation caused by the hypothesis, we ultimately chose the partitioned survival model over the Markov model. By using the partitioned survival model, it is possible to obtain the survival cohort proportion directly from the survival curve, thereby reducing the hypothesis bias in calculating the transition probability from PF or PD to death.

It is hoped that this analysis can provide help to clinicians, health decision-makers, and patients. More studies of this kind are also expected to be published as evidence is updated to continuously improve credibility of this economic evaluation.

Conclusion

Patients with metastatic urothelial cancer following treatment with atezolizumab plus chemotherapy showed more survival benefits than those with the placebo plus chemotherapy regimen. Although the economic gap between the United States and China is obvious, the conclusions of the cost-effectiveness analysis are consistent. Our economic evaluation concluded that the addition of atezolizumab to chemotherapy is not cost-effective compared with the chemotherapy regimen at a $ 100,000/QALY threshold in the United States. The conclusion is also applicable in the context of China. Adding atezolizumab to chemotherapy compared with chemotherapy alone is not cost-effective in the threshold of a $ 31,316/QALY setting.

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

YZ and XL were involved in the design of the study. YTL, QC, and XL collected the data, performed the economic analysis, and wrote the manuscript. YL and YHL collected data and reviewed the results. All authors approved the final version for publication.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.872196/full#supplementary-material

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The change of drug utilization in China's public healthcare institutions under the "4 + 7" centralized drug procurement policy: Evidence from a natural experiment in China

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Background: Improving drug accessibility and rational drug use are major challenges for China's healthcare reform. In 2018, the Chinese government introduced a novel nationwide policy of centralized drug procurement for off-patent drugs, focusing on improving drug utilization patterns of public medical institutions.

Objective: To estimate the impacts of the Chinese centralized drug procurement policy (the so-called "4 + 7" policy) on drug utilization in public medical institutions.

Methods: A retrospective natural experimental design and difference-in-difference method were applied using cross-region data extracted from the national procurement database. Eleven "4 + 7" pilot cities (intervention group) and eleven non-pilot provinces (control group) were matched. In addition, "4 + 7" policy-related drugs (n = 116) were selected as study samples, including 25 drugs in the 4 + 7" procurement List ("4 + 7" List drugs) and their alternative drugs (n = 91) that have not yet been covered by centralized procurement policy. Then, the "4 + 7" List drugs were divided into bid-winning and non-winning drugs according to the bidding results, and they were sorted into generic and original drugs. Defined daily dose (DDD) was used to standardize the quantity of drugs used.

Results: In the 1-year procurement period, the overall completion rate of agreed procurement volume reached 191.4% in pilot cities. Owing to policy impact, the consumption increased by 405.31% in bid-winning drugs (β = 1.62, $p < 0.001$) and decreased by 62.28% (β = −0.98, $p < 0.001$) in non-winning drugs. The overall use proportion of bid-winning drugs increased from 17.03% to 73.61% with statistical significance (β = 1.48, $p < 0.001$), and increments were also detected in all healthcare settings, regions, and anatomical therapeutic

chemical (ATC) categories (all p-values < 0.05). Generics and originators were detected with 67.53% increment (β = 0.52, p < 0.001) and 26.88% drop (β = −0.31, p = 0.006) in consume volume. The use proportion of generics increased from 59.23% to 78.44% with significance (β = 0.24, p < 0.001), as well as in tertiary hospitals (β = 0.31), secondary hospitals (β = 0.23), and primary healthcare centers (β = 0.11) (all p-values < 0.001). The use proportion of relatively quality-guaranteed drugs (i.e. bid-winning and original drugs) increased from 56.69% to 93.61% with significance (β = 0.61, p < 0.001), and similar increments were also detected in all healthcare settings, regions, and ATC categories (all p-values < 0.05).

Conclusion: Healthcare providers demonstrated good compliance with the "4 + 7" policy in completing contracted procurement volume. Centralized drug procurement policy promoted drug consumption gradually concentrated on bid-winning drugs, generic drugs, and more importantly, quality-guaranteed drugs.

KEYWORDS

drug utilization, drug use, centralized procurement, pooled procurement, China

Introduction

In China, obtaining access to appropriate medicines at affordable prices is still a pressing healthcare issue for 1.4 billion Chinese citizens (Fu, 2017; Shi, 2020). Medical institutions are the primary setting of patients' drug use in China, and more than 80% of consumed drugs reached patients through the medical institution channel (other than retail pharmacies). However, it is known that a general benefit connection existed between hospitals and pharmaceutical enterprises, which lead to induced demands and made physicians exhibit strong financial motivation to prescribe more expensive drugs (Yip et al., 2012; Zeng et al., 2014). Even after the abolition of hospital drug markups, the benefit connection has not been completely severed (Yi et al., 2015). In this context, drug spending in China constantly increased at a growth rate of about 15% (Zeng, 2013; Zeng et al., 2014), and from 2010 to 2018, it accounted for 30–40% of the total health expenditures (NHC, 2020). More worryingly, no effective incentive is found for rational drug production or drug prescribing under the policy context (Hu and Mossialos, 2016).

In 2018, the Chinese government introduced the implementation of national centralized drug procurement of off-patent drugs, to explore the market-oriented drug price formation mechanism. Except for the primary purpose of price reduction by improving competition, the centralized drug procurement policy bears the mission to cut off the space of drug rebates and lead the standardized clinical medication (General Office of the State Council, 2019a). Through the policy measures of "guarantee of use" (Yang et al., 2021a), physicians are encouraged to give priority to prescribing bid-winning ones among products that share an International Nonproprietary Name (INN). The first round pilot of the centralized procurement policy was implemented in four municipalities (Beijing, Tianjin, Shanghai, and Chongqing) and seven subprovincial cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, and Xi'an) in mainland China, thus known as the "4 + 7" pilot, with 25 drug INNs procured (Joint Procurement Office, 2018a).

Previous studies revealed fruitful evidence on drug utilization change after the implementation of "4 + 7" centralized drug procurement: for instance, the prominently increased use of bid-winning drugs after policy intervention (Yang et al., 2021a; Yang et al., 2021b; Chen et al., 2021; Wen et al., 2021; Wang et al., 2022). Besides, Wang et al. (2022), Yang et al. (2022a), and Xie et al. (2021) revealed the increase in substitution rate of generic drugs based on the descriptive comparison before and after "4 + 7" policy. Wang Y. et al. (2021) reported a reduction in the irrational utilization rate of antiplatelet drugs from 10.54 to 1.60% in one hospital. He et al. (2021) surveyed related physicians and patients, and they reported their generally good recognition and acceptance of bid-winning drugs.

However, the abovementioned research findings were mainly derived from descriptive analysis derived from limited sampled data, which might restrict causal inference and the extrapolation of research findings. In addition, in China, drug utilization condition varies between different healthcare settings, geographical regions, drug therapeutic categories, etc. (Chinese Pharmaceutical Association, 2020; Yang et al., 2022b). In light of this, a need exists for comprehensive empirical studies to systematically landscape the changing patterns in drug utilization under the "4 + 7" policy implementation in different regions, healthcare settings, and INN categories. In the present study, we conducted a natural experiment using the national centralized drug procurement data in China to estimate the changing pattern of drug utilization in the

context of the "4 + 7" centralized drug procurement pilot implementation.

Research framework

Intervention elements

As a pharmaceutical reform with multidimensional target attributes and multiple intervention measures, the policy practices of the national centralized procurement policy has been systematically introduced by previous scholars (Yang et al., 2021a; Chang, 2021; Hu, 2021; Yuan et al., 2021). In this study, we focus on the policy measures mostly directly related to medical institutions' drug utilization, which are systematically elaborated as follows:

1) *Drug selection and the determination of centralized procurement List*. Drug INNs with more historical clinical consumption as well as high historical procurement costs were selected as target procurement drugs to conduct centralized bidding (General Office of the State Council, 2019a).
2) *Eligibility criteria for bidding in terms of drug quality*. The Generic Consistency Evaluation (GCE), which was introduced by the National Medical Products Administration (NMPA) to ensure the quality of Chinese generic drugs, is equivalent to their counterpart originators and was set as the eligibility criteria for some particular drugs to be able to participate in bidding activities. In this regard, only the generic drugs passed the GCE, and original drugs were considered eligible to participate in the "4 + 7" centralized procurement (General Office of the State Council, 2019a).
3) *Ancillary supporting policy measures by healthcare commissions*. The National Health Commission (NHC) introduced the supporting policy to encourage the priority use of bid-winning drugs in public medical institutions. To ensure the completion of the contracted procurement volume, a standardized assessment mechanism has been established (NHC, 2019a; NHC, 2019b).
4) *Ancillary supporting policy measures by the healthcare insurance sector*. The National Healthcare Security Administration (NHSA) launched a supporting policy to reward behaviors to save medical insurance funds by using low-priced bid-winning drugs (NHSA, 2019a).

Analytical framework

Metrics for measuring pharmaceutical policy outcomes linked to core objectives can be classified as a framework consisted of input, process, and output parameters. In this study, the abovementioned policy measures related to drug utilization were considered as input parameters. The process parameter refers to the path that leads to changes in drug use after the implementation of policy measures, defined as "medical institutions purchase and use contacted procurement quantity of the bid-winning drugs in the contracted procurement period." Next, the output parameter refers to the outcomes emerged after the implementation of the policy over a specific period, which was defined as drug utilization changes. In this study, the drug utilization changes under policy implementation were measured from two dimensions: consumption volume dimension and drug use structure dimension, which were defined in detail below (the Methods section). Furthermore, we analyzed the change in drug use among different anatomical therapeutic chemical (ATC) classifications, different healthcare settings, and different geographical regions. Figure 1 outlined the framework of this study.

Methods

Study design

This study adopted a natural experimental study design with a standard difference-in-difference (DID) analysis method. One of the preconditions of constructing the standard DID model is that the target intervening measure only affects relevant factors in the treatment group and demonstrates no effect on the control group. Previous literature provided evidence that the influence of centralized procurement policy may involve different drug dimensions: drugs covered by the policy and those alternatives that were not, drugs that won the bid and those that did not, and generic and original drugs (Chen et al., 2020; Yang et al., 2021a; Wang et al., 2022). Therefore, in this study, the design of the DID model mainly discussed differences in regional and time dimensions. Further, we evaluated drug utilization changes in the treatment group (regions covered by the centralized procurement policy) vs. control group (regions where the policy did not cover) before and after policy implementation. The design of the empirical analysis strategy and the reporting of research results followed the reporting guideline for natural experiments issued by the Medical Research Council (Craig et al., 2012).

Intervention time point

In this study, the implementation of "4 + 7" bid-winning results was defined as the intervention measure. As the 11 "4 + 7" pilot cities start purchasing bid-winning drugs between 15 March 2019 and 1 April 2019, in this study, we determined March 2019 as the implementation ending time point of the "4 + 7" pilot.

Intervention group

In the present study, all eleven "4 + 7" pilot cities were assigned to the intervention group, namely Beijing, Shanghai,

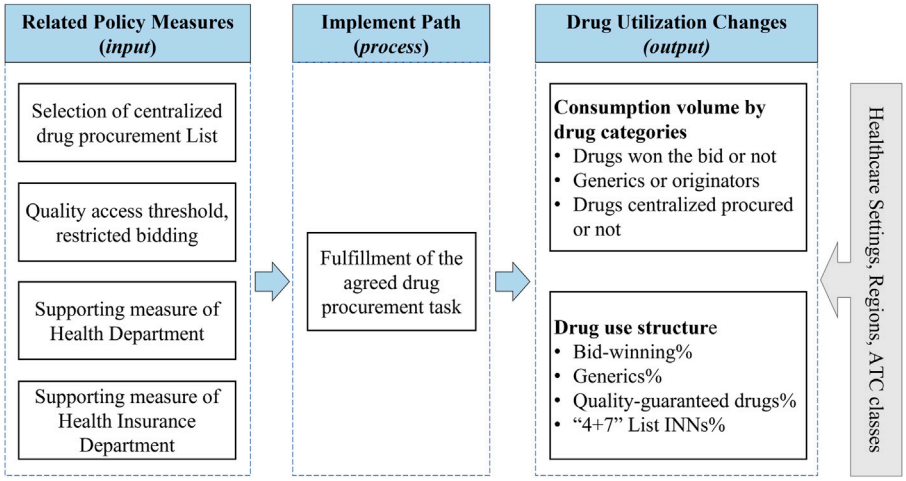

FIGURE 1
Research framework. Note: ATC, anatomical therapeutic chemical.

Tianjin, Chongqing, Guangzhou, Shenzhen, Xiamen, Shenyang, Dalian, Xi'an, and Chengdu. According to the geographical region of China, the 11 pilot cities are distributed in east China (Shanghai, Xiamen), North China (Beijing, Tianjin), Central China (Guangzhou, Shenzhen), Northeast China (Dalian, Shenyang), Southwest China (Chengdu, Chongqing), and Northwest China (Xi'an).

Control group

The determination of a comparable control group to the intervention group is the key step in natural experiment design. Considering China's regional variation in drug use habits, pharmaceutical industry distribution, economic level, and health resources (Li et al., 2013; Zhang and Zhang, 2015; Yan and Yan, 2019), we first stratify the observation area samples by geographical regions, and then, we determine comparable control area samples within each geographical region. According to Li et al. (2021) and Tang (2016)'s method, the unweighted TOPSIS (technique for order performance by similarity to ideal solution) method was adopted to identify control samples with the highest matching degree (the closest TOPSIS score) among the provinces that did not implement "4 + 7" pilot as the control group. Nine matching variables were considered, including per capita gross domestic product (GDP), population size, number of health institutions, number of hospital beds, number of skilled health workers, number of licensed (assistant) doctors, per capital health expenditure, annual average clinical visits, and annual hospitalization rate. Twenty-one provinces that did not implement the "4 + 7" policy were initially available for matching, and finally, eleven provinces with the closest TOPSIS score of the pilot cities were included as the control group. Details of the TOPSIS results are listed in Supplementary Table S1.

Data sources

The data used in this study came from the China Drug Supply Information Platform (CDSIP) (NHC, 2015), which covered the drug procurement order data of all provincial centralized procurement platforms across 31 provinces (autonomous regions and municipalities) in the mainland China. The data of CDSIP exhibit the features of great authenticity, integrality, and representativeness, and the details and sample coverage of the CDSIP database were introduced in the previous study by our team (Yang et al., 2022b).

The procurement data extracted from the CDSIP database include drug name, the name of medical institution, procurement date, dosage form, specification, packaging, manufacturer, unit price, procurement unit (by box, bottle, or branch), procurement quantity, procurement expenditures, etc. In the present study, we selected "4 + 7"-related drugs as study samples (Wang N. et al., 2021; Yang et al., 2022a; Wang et al., 2022), which were defined as drug INNs in the "4 + 7" procurement List ("4 + 7" List drugs) as well as their alternative drugs that have not yet been covered by the "4 + 7" procurement policy. Next, the identification of alternative drugs followed the definition of the NHSA in the Monitoring Plan for Centralized Drug Procurement and Use Pilot Work (NHSA, 2019b), which refers to the clinically substitutable drugs of the same kind with "4 + 7" List drugs. The list of included drugs is presented in Supplementary Table S2.

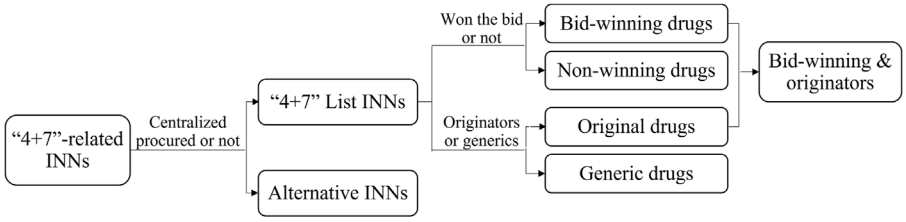

FIGURE 2
The classification of included drugs.

Then, the "4 + 7" List drugs were divided into bid-winning and non-winning drugs based on the "4 + 7" city procurement bid-winning results (Joint Procurement Office, 2018a), and they were sorted into off-patent original branded products and generic products according to the Catalogue of Marketed Drug in China (NMPA, 2017) (Figure 2). Since the Chinese government implemented the GCE work, generic drugs that pass the pharmacokinetics equivalence and bioequivalence trials are certified for quality and efficacy consistency to their corresponding originators. The assumption exists that certificated generics are of the same quality level as originators, and they demonstrate a higher quality level than uncertificated generics. Therefore, we defined bid-winning drugs and non-winning originators as relatively quality-guaranteed drugs, as only certificated generics and originators can participate and win the bid according to the policy requirements (General Office of the State Council, 2019a). In addition, included drug INNs were aggregated into 8 ATC groups: C-cardiovascular system (n = 8), N-nervous system (n = 7), L-antineoplastic and immunomodulating agents (n = 3), J-antiinfectives for systemic use (n = 3), A-alimentary tract and metabolism (n = 1), B-blood and blood forming organs (n = 1), M-musculoskeletal system (n = 1), and R-respiratory system (n = 1). Next, public medical institutions were divided into tertiary hospitals, secondary hospitals, and primary healthcare centers (PHCs). Then, finally, in this study, a total of 116 drug INNs (twenty-five "4 + 7" List drugs and 91 alternative drugs) were included.

Outcome measures

The standardization of drug use quantity is the primary work of drug utilization research (Hollingworth and Kairuz, 2021). In this study, following the recommendation of the World Health Organization (WHO), we applied defined daily dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2020) as the measurement unit to standardize the quantity of drugs used, to ensure the comparability of drugs in quantity with different generic names, dosage forms, and specifications. The DDD of several drugs, which could not be coded in WHO's ATC/DDD Index 2021 system, was determined based on the recommended daily dosage in the manufacturers' instructions, as approved by the China Food and Drug Administration (WHO Collaborating Centre for Drug Statistics Methodology, 2021). The calculation of drug use is as follows:

$$Y = \sum_{i=1}^{n}\left(\frac{U_i P_i}{DDD_i} \times N_i\right) \quad (1)$$

where Y is DDDs and represents the consumed volume of a certain drug (or a group of drugs); DDD_i refers to the DDD value of drug product i; U_i refers to the unit ingredient of product i; P_i refers to the packing specification of product i; andN_i refers to the number of product i.

In addition to the primary volume indicator for drug use, four drug use structure indicators were included for measuring drug utilization by referring to government assessment documents (General Office of the State Council, 2019b; NHSA, 2019b) and relevant literature (Xie et al., 2021; Yang et al., 2022a; Luo et al., 2022; Wang et al., 2022), including the use proportion of bid-winning drugs, the proportion of generics, the proportion of bid-winning and originators, and the proportion of "4 + 7" List drugs. Also, an indicator—the "procurement completion rate"—was included as the *process* parameter according to the NHC documents (NHC, 2019a; NHC, 2019b).

$$\text{procurement completion rate} = \frac{\text{actual procurement volume of bid} - \text{winning drugs}}{\text{agreed procurement volume}} \times 100\% \quad (2)$$

In Eq. 2, the "agreed procurement volume" refers to the purchase volume to be completed by the pilot cities as published by the Joint Procurement Office (2018b), which is generated based on reports from medical institutions of each pilot city. The "actual procurement volume of bid-winning drugs" refers to the volume of drugs actually purchased by each pilot city during the one-year procurement cycle.

$$\text{bid} - \text{winning drugs}\% = \frac{\text{volume of bid} - \text{winning drugs}}{\text{volume of } ''4+7'' \text{ List INNs}} \times 100\% \quad (3)$$

$$\text{generics}\% = \frac{\text{volume of generics}}{\text{volume of } ''4+7'' \text{ List INNs}} \times 100\% \quad (4)$$

$$\text{bid} - \text{winning \& originators}\% = \frac{\text{volume of bid} - \text{winning \& originators}}{\text{volume of } ''4+7'' \text{ List INNs}} \times 100\% \quad (5)$$

$$''4+7'' \text{ List INNs}\% = \frac{\text{volume of } ''4+7'' \text{ List INNs}}{\text{volume of } ''4+7'' \text{ List and alternative INNs}} \times 100\% \quad (6)$$

In Eqs. 3–6, the "volume of "4 + 7" List INNs" refers to the volume of "4 + 7" List INNs purchased in a certain observation region in a certain time. The "volume of bid-winning drugs" refers to the volume of bid-winning drugs purchased in a certain observation region in a certain time. Next, the "volume of generics" refers to the volume of generic drugs in the "4 + 7" List purchased in a certain observation region at a certain time. The "volume of bid-winning and originators" refers to the overall volume of bid-winning drugs and non-winning original drugs in the "4 + 7" List purchased in a certain observation region at a certain time. Further, the "volume of "4 + 7" List and alternative INNs" refers to the overall volume of "4 + 7" List INNs and alternative INNs purchased in a certain observation region at a certain time, respectively.

Statistical analysis

Descriptive analysis

First, we applied the descriptive statistical methods to quantify the change in drug use volume of each category and drug use structure in the pre- and post-intervention periods, as well as stratified changes by healthcare settings, geographical regions, and ATC classes. Next, to visualize the policy's effects, we plotted monthly trends of drug use structure variables.

Difference-in-difference modeling

We adopted the DID approach to estimate the impact of the "4 + 7" pilot, where we performed generalized linear models to quantify the associations of policy intervention with the changes in the outcome indicators. The basic regression model is specified as follows:

$$Y_{it} = \alpha + \beta(D_i \cdot T_t) + \mu_{it} + \delta_{it} + \varepsilon_{it} \quad (7)$$

where Y_{it} refers to outcome variables of region i in month t. Next, D_i is a dummy variable of policy intervention groups, coded 1 if region i belongs to the treatment group and coded 0 in the control group. T_t is a dummy variable of policy intervention time, coded 0 in the month i before policy implementation (January 2018–February 2019) and coded 1 after policy intervention (March–December 2019). μ_{it} and δ_{it} are fixed effects of months and regions. ε_{it} refers to the random error term. $D_i \cdot T_t$ is the interaction term between study group and time, and its coefficient β refers to the DIDs effect associated with policy intervention.

Common pre-trend tests

Common trend refers to the idea that the treatment group would have evolved with the same trend as the control group with the absent of treatment, which is the premise of DID method to identify causal effects. Next, strictly, the common trend cannot be directly observed and tested, and it is usually done by common pre-trend tests to prove that the outcome variable demonstrates the same time-varying trend between the intervention group and control group in the pre-intervention period (Huang et al., 2022), with the following regression model:

$$Y_{it} = \alpha + \sum_{s=1}^{T_D-2} \beta_s^{pre}(D_i \cdot T_t^s) + \sum_{s=T_D}^{T} \beta_s^{post}(D_i \cdot T_t^s) + \theta W_{it} + \mu_{it} + \delta_{it} + \varepsilon_{it} \quad (8)$$

where Y_{it} refers to outcome variables. D_i is a dummy variable of policy intervention groups, with the intervention group ("4 + 7" pilot cities) being coded as 1 and the control group coded as 0. T_t^s is the time dummy of period s. β_s^{pre} and β_s^{post} refer to the differences of outcome variables between the intervention group and the control group before and after policy implementation in period s, compared with the differences of outcome variables in the base period (assigned to the first month of observation period). If the coefficient β_s^{pre} demonstrates no statistical significance, it indicates a common trend of the corresponding outcome variable in intervention and control group.

Results

Completion rate of agreed procurement quantity

We calculated the completion rate of pooled procured drugs based on the annual agreed procurement volume of each drug (by INN) in each pilot city (Joint Procurement Office, 2018b). During one-year policy implementation (April 2019–March 2020), the actual procurement volume of bid-winning drugs reached 2.37 billion DDDs in pilot cities, with a total procurement completion rate of 191.4%. Figure 3 indicates the completion rate of each "4 + 7" bid-winning drug. Except for Olanzapine (91.0%), the procurement completion rates of other 24 drugs exceeded 100%, ranging from 143.3 to 556.7%. Next, a completion rate of more than 200% was observed in twelve drugs (12/25). Also, the separated analysis of each pilot city indicated

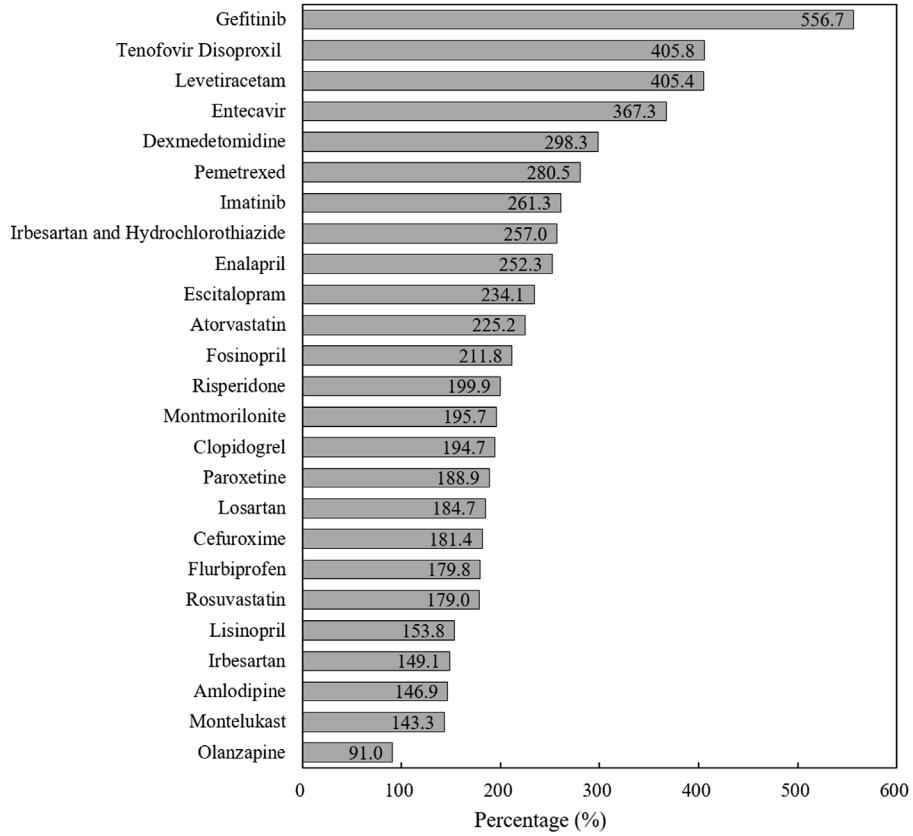

FIGURE 3
The completion rate of agreed procurement quantity of each "4 + 7" List drug during one-year agreement period.

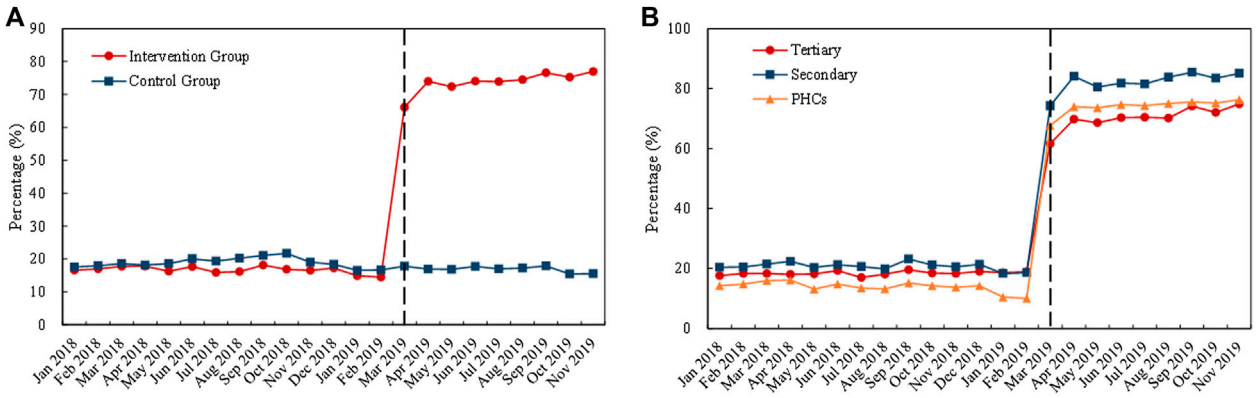

FIGURE 4
Trends in the volume proportion of bid-winning drugs during January 2018 to November 2019: **(A)** volume proportion of bid-winning drugs in the intervention group and control group **(B)** volume proportion of bid-winning drugs in intervention group by healthcare setting. *Note*: PHCs, primary healthcare centers.

TABLE 1 Impact of the "4 + 7" pilot on monthly volumes of bid-winning or non-winning drugs, stratified by healthcare settings.

Categories	Descriptive change (million DDDs)			DID estimate		
	Pre	Post	Change (%)	β	95% *CI*	Change (%)
Overall						
Bid-winning drugs	345.00	1690.00	389.86	1.62	(1.45, 1.79)***	405.31
Non-winning drugs	1681.00	606.00	−63.95	−0.98	(−1.21, −0.74)***	−62.28
Bid-winning%	17.03	73.61	56.58	1.48	(1.39, 1.57)***	337.54
Bid-winning drugs						
Tertiary hospitals	150.30	675.50	349.43	1.50	(1.32, 1.68)***	346.83
Secondary hospitals	64.34	297.40	362.20	1.02	(0.78, 1.25)***	175.94
PHCs	130.40	717.30	450.08	2.29	(1.99, 2.60)***	890.46
Non-winning drugs						
Tertiary hospitals	668.80	287.90	−56.95	−0.77	(−0.99, −0.55)***	−53.79
Secondary hospitals	239.10	64.90	−72.86	−1.97	(−2.23, −1.70)***	−86.00
PHCs	773.50	253.20	−67.27	−1.04	(−1.40, -0.68)***	−64.62
Bid-winning%						
Tertiary hospitals	18.35	70.12	51.76	1.29	(1.20, 1.39)***	264.01
Secondary hospitals	21.21	82.09	60.88	1.52	(1.41, 1.63)***	355.85
PHCs	14.43	73.91	59.48	1.83	(1.65, 2.01)***	523.39

Note: *p< 0.05.
**p< 0.01.
***p< 0.001.
Pre refers to March–November 2018; Post refers to March–November 2019; Bid-winning% refers to the volume proportion of bid-winning drugs in the "4 + 7" List drugs.
DDDs, defined daily doses; DID, difference-in-difference; CI, confidence interval; PHCs, primary healthcare lefts.

that all 11 pilot cities fulfilled their agreed procurement tasks in excess.

Drug utilization changes

Bid-winning and non-winning drugs

Figure 4 visualizes the trends in monthly volume proportion of bid-winning drugs. Before policy intervention, the proportion in the intervention group and control group generally remained the same level (about 20%). After policy intervention in March 2019, the proportion in the intervention group drastically increased to about 70%, while the proportion in the control group maintained at previous level (Figure 4A). Under policy intervention, in all three types of medical institutions, markable increases were found in the volume proportion of bid-winning drugs (Figure 4B).

As shown in Table 1, DID analysis revealed that the monthly volume of bid-winning drugs increased significantly (β = 1.62, p < 0.001) after policy intervention, with a 405.31% increment when some transformations of the coefficients were made (Kim and Skordis-Worrall, 2017; Zhang et al., 2017; Li et al., 2021). The volume of non-winning drugs was associated with a 62.28% reduction (β = −0.98, p < 0.001). The volume proportion of bid-winning drugs raised from 17.03% in the pre-intervention period to 73.61% in the post-intervention period, and the increase was detected with significance in the DID analysis (β = 1.48, p < 0.001).

Considering the type of medical institution, significant increases in bid-winning drugs were observed in the healthcare setting of tertiary hospitals (346.83%), secondary hospitals (175.94%), and PHCs (890.46%) (all p-values < 0.001). Significant decreases of non-winning drugs were observed in tertiary hospitals (−53.79%), secondary hospitals (−86.00%), and PHCs (−64.62%) (all p-values < 0.001). As for the volume proportion of bid-winning drugs, a prominent increase of 264.01, 355.85, and 523.39% were detected in tertiary hospitals (β = 1.29, p < 0.001), secondary hospitals (β = 1.52, p < 0.001), and PHCs (β = 1.83, p < 0.001), respectively.

Generic and original drugs

Figure 5 outlines the monthly trends of volume proportion of generic drugs. During the whole observation period, the proportion in the control group remained stable, while the proportion in the intervention group increased suddenly after the implementation of the policy in March 2019 (Figure 5A).

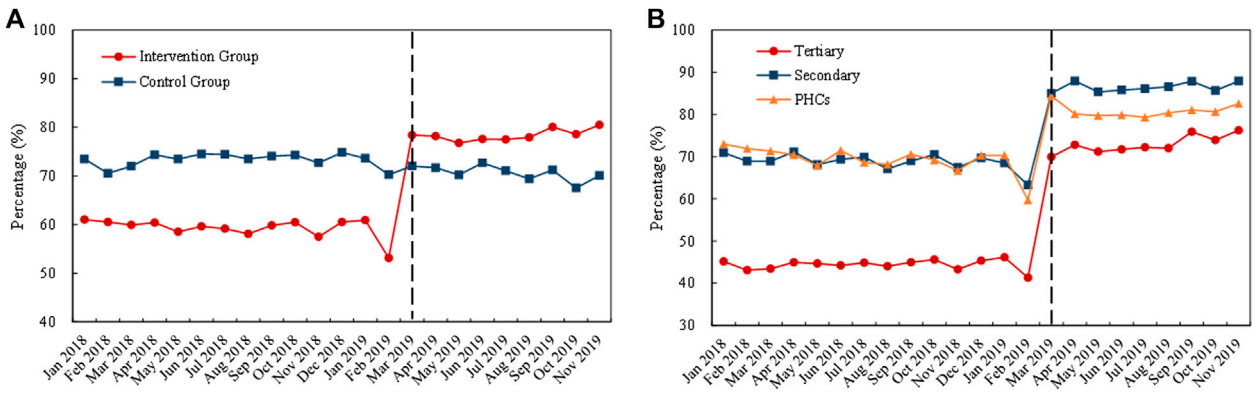

FIGURE 5
Trends in the volume proportion of generic drugs during January 2018 to November 2019: **(A)** volume proportion of generic drugs in the intervention group and control group **(B)** volume proportion of generic drugs in intervention group by healthcare setting. Note: PHCs, primary healthcare centers.

TABLE 2 Impact of the "4 + 7" pilot on monthly volumes of generic or original drugs, stratified by healthcare settings.

Categories	Descriptive change (million DDDs)				DID estimate	
	Pre	Post	Change (%)	β	95% *CI*	Change (%)
Overall						
Generics	1200.00	1801.00	50.08	0.52	(0.34, 0.69)***	67.53
Originators	826.80	495.00	−40.13	−0.31	(−0.54, −0.09)**	−26.88
Generics%	59.23	78.44	19.21	0.24	(0.20, 0.28)***	27.12
Generics						
Tertiary hospitals	363.90	701.90	92.88	0.61	(0.42, 0.79)***	83.68
Secondary hospitals	209.30	313.30	49.69	−0.12	(−0.35, 0.11)	−11.57
PHCs	626.60	786.00	25.44	0.60	(0.34, 0.86)***	81.85
Originators						
Tertiary hospitals	455.10	261.50	−42.54	−0.24	(−0.45, −0.04)*	−21.65
Secondary hospitals	94.13	48.98	−47.97	−1.17	(−1.43, 0.92)***	−69.06
PHCs	277.30	184.50	−33.47	−0.03	(−0.39, 0.34)	−2.57
Generics%						
Tertiary hospitals	44.43	72.86	28.42	0.31	(0.27, 0.34)***	35.66
Secondary hospitals	68.98	86.48	17.49	0.23	(0.17, 0.29)***	25.86
PHCs	69.32	80.99	11.67	0.11	(0.07, 0.16)***	12.08

*Note: $p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
Pre refers to March–November 2018; Post refers to March–November 2019; Generics% refers to the volume proportion of generic drugs in the "4 + 7" List drugs.
DDDs, defined daily doses; DID, difference-in-difference; *CI*, confidence interval; PHCs, primary healthcare lefts.

Among the medical institutions, the proportion of generic drugs was lower in tertiary hospitals than in secondary hospitals and PHCs, and the proportion increased remarkedly in all healthcare settings with the implementation of the "4 + 7" pilot (Figure 5B).

Table 2 demonstrates the changing pattern in generic and original drugs. After policy intervention, the procurement volume of generic drugs in the "4 + 7" List INN increased by 67.53% ($\beta = 0.52$, $p < 0.001$), while original drugs decreased by

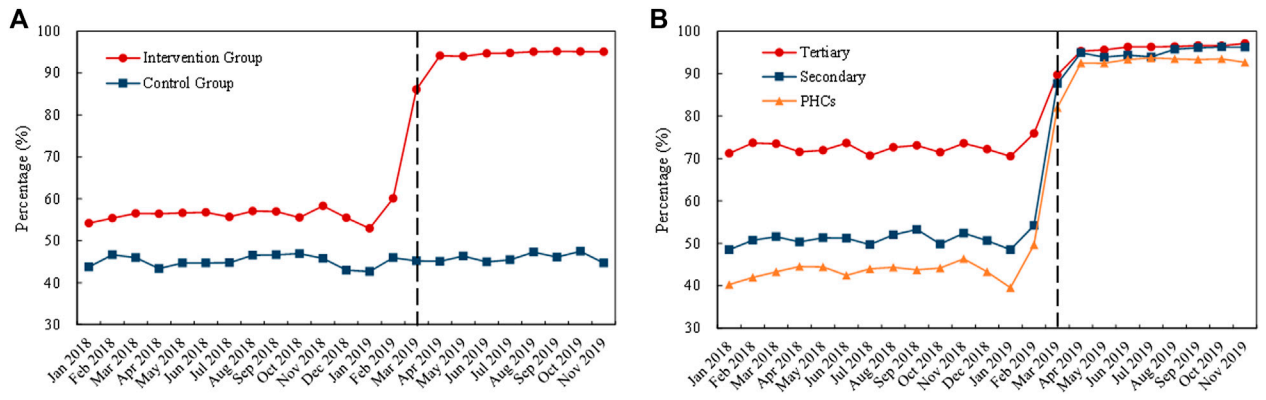

FIGURE 6
Trends in the volume proportion of bid-winning and originators during January 2018 to November 2019: **(A)** volume proportion of bid-winning and originators in the intervention group and control group **(B)** volume proportion of bid-winning and original drugs in intervention group by healthcare setting. Note: PHCs, primary healthcare centers.

TABLE 3 Impact of the "4 + 7" pilot on the volume proportion of bid-winning and originators, stratified by healthcare settings.

Categories	Descriptive change (million DDDs)			DID estimate		
	Pre	Post	Change (%)	*β*	95% *CI*	Change (%)
Overall	56.69	93.61	36.93	0.61	(0.57, 0.64)***	83.31
Tertiary hospitals	72.49	95.42	22.93	0.43	(0.41, 0.46)***	53.88
Secondary hospitals	51.32	94.13	42.82	0.64	(0.59, 0.69)***	89.27
PHCs	44.19	91.63	47.45	1.12	(0.97, 1.27)***	206.18

Note: *$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
Pre refers to March–November 2018; Post refers to March–November 2019.
DID, difference-in-difference; PHCs, primary healthcare lefts; *CI*, confidence interval.

26.88% ($\beta = -0.31$, $p = 0.006$). Next, the volume proportion of generic drugs in the "4 + 7" List INN increased from 59.23% in the pre-intervention period to 78.44% in the post-intervention period, and the increment was statistically significant ($\beta = 0.24$, $p < 0.001$).

Significant increases of 83.68% and 81.85% were associated with the volume of generic drugs in tertiary hospitals ($\beta = 0.61$, $p < 0.001$) and PHCs ($\beta = 0.60$, $p < 0.001$), respectively, while the change in secondary hospitals was not statistically significant ($\beta = -0.12$, $p = 0.296$). The volume of original drugs significantly decreased by 21.65% and 69.06% in tertiary ($\beta = -0.24$, $p = 0.022$) and secondary ($\beta = -1.17$, $p < 0.001$) hospitals, respectively, while the volume in PHCs exhibited no significant change ($\beta = -0.03$, $p = 0.890$). The volume proportion of generic drugs increased by 28.42 (tertiary hospitals), 17.49 (secondary hospitals), and 11.67 (PHCs) percentage points, and the increases were significant from the DID analysis (all p-values < 0.001).

Use proportion of bid-winning and original drugs

Figure 6 displays the monthly trends of volume proportion of bid-winning and original drugs. The proportion in the control group remained stable (about 45%) during the whole observation period. The proportion in the intervention group increased remarkedly with the implementation of the "4 + 7" pilot in March 2019 (Figure 6A). Among the medical institutions, before policy intervention, the highest proportion in the intervention group was observed in tertiary hospitals (about 70%), followed by secondary hospitals (about 50%) and PHCs (about 40%). With the implementation of the "4 + 7" pilot in March 2019, the

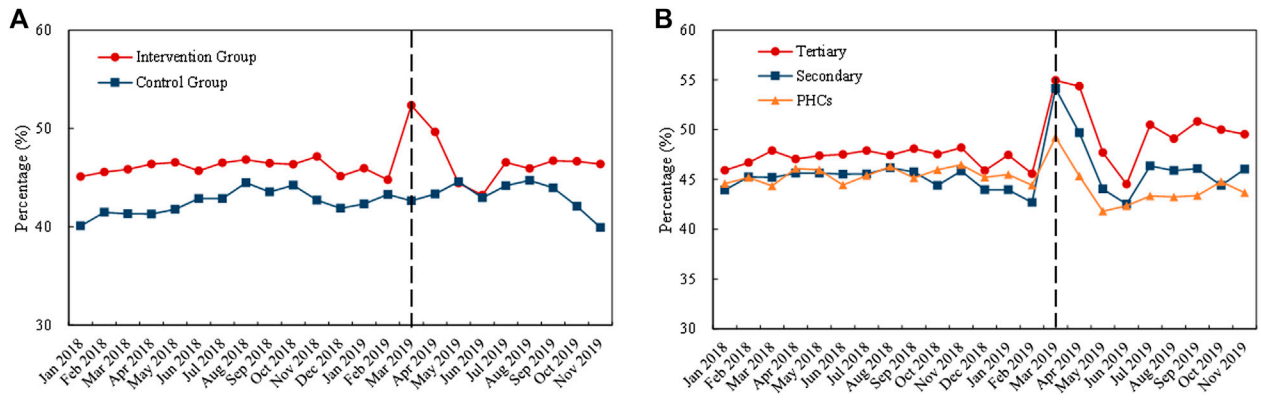

FIGURE 7
Trends in the volume proportion of "4 + 7" List drugs during January 2018 to November 2019: **(A)** volume proportion of "4 + 7" List drugs in the intervention group and control group **(B)** volume proportion of "4 + 7" List drugs in intervention group by healthcare setting. Note: PHCs, primary healthcare centers.

TABLE 4 Impact of the "4 + 7" pilot on monthly volumes of "4 + 7" List drugs and their alternative drugs, stratified by healthcare settings.

Categories	Descriptive change (million DDDs)			DID estimate		
	Pre	Post	Change (%)	*β*	95% *CI*	Change (%)
Overall						
"4 + 7" List INNs	2026.00	2296.00	13.33	0.30	(0.11, 0.48)**	34.45
Alternative INNs	2340.00	2591.00	10.73	0.01	(−0.16, 0.17)	0.50
"4 + 7" List INNs%	46.40	46.98	0.58	0.18	(0.15, 0.22)***	20.08
"4 + 7" List INNs						
Tertiary hospitals	819.00	963.40	17.63	0.32	(0.14, 0.51)**	37.99
Secondary hospitals	303.40	362.30	19.41	−0.36	(−0.59, −0.13)**	−30.44
PHCs	903.90	970.50	7.37	0.49	(0.23, 0.75)***	62.74
Alternative INNs						
Tertiary hospitals	898.00	952.60	6.08	0.14	(−0.04, 0.31)	14.57
Secondary hospitals	362.90	412.40	13.64	−0.58	(−0.79, −0.38)***	−44.23
PHCs	1079.00	1226.00	13.62	−0.02	(−0.27, 0.24)	−1.69
"4 + 7" List INNs%						
Tertiary hospitals	47.70	50.28	2.58	0.11	(0.08, 0.14)***	11.52
Secondary hospitals	45.53	46.77	1.24	0.18	(0.13, 0.22)***	19.12
PHCs	45.58	44.17	−1.41	0.40	(0.33, 0.47)***	48.59

Note: *$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
Pre refers to March–November 2018; Pos[a]efers to March–November 2019; "4 + 7" List INNs% refers to the volume proportion of "4 + 7" List INNs, in the total volume of "4 + 7" List and alternative INNs.
DDDs, defined daily doses; DID, difference-in-difference; *CI*, confidence interval; INN, international nonproprietary name; PHCs, primary healthcare lefts.

proportion in all types of medical institutions prominently increased, up to approximately 95% (Figure 6B).

As shown in Table 3, the volume proportion of bid-winning and original drugs in the "4 + 7" List INN increased from 56.69% in the pre-intervention period to 93.61% in the post-intervention period, with a significant increase of 83.31% ($\beta = 0.61$, $p < 0.001$). Further, an increase in bid-winning and original drugs' volume proportions were demonstrated in all types of medical institutions, and the figure

TABLE 5 Subgroup analyses on the impacts of "4 + 7" pilot on drug use structure by geographical region.

Regions	Bid-winning%			Generics%			Bid-winning & originators%			"4 + 7" list INNs%		
	Pre	Post	Change (%)	Pre	Post	Change (%)	Pre	Post	Change (%)	Pre	Post	Change (%)
Descriptive change												
East China	18.45	84.94	66.49	76.20	88.89	12.68	41.52	95.05	53.53	45.21	40.77	-4.44
North China	17.15	62.20	45.05	50.05	68.73	18.67	65.38	91.49	26.12	45.91	46.55	0.64
Central China	8.48	77.78	69.30	46.53	78.58	32.05	61.24	97.68	36.44	52.79	55.87	3.08
Northeast China	14.61	78.64	64.03	53.51	82.11	28.60	60.05	94.79	34.74	39.31	46.18	6.87
Southwest China	21.74	81.33	59.60	66.25	87.10	20.85	55.06	92.95	37.89	48.23	52.48	4.25
Northwest China	33.25	83.43	50.18	63.87	85.11	21.24	67.90	97.47	29.57	38.78	53.48	14.69
Regions	**Bid-winning%**			**Generics%**			**Bid-winning and Originators%**			**"4 + 7" List INNs%**		
	β	*p*	Change (%)	*β*	*p*	Change (%)	*β*	*p*	Change (%)	*β*	*p*	Change (%)
DID estimate												
East China	1.79	< **0.001**	496.55	0.21	< **0.001**	22.88	0.82	< **0.001**	126.82	0.03	0.572	2.74
North China	1.31	< **0.001**	269.14	0.21	< **0.001**	23.37	0.48	< **0.001**	62.09	0.18	< **0.001**	19.60
Central China	1.32	< **0.001**	272.48	-0.001	0.979	-0.10	0.86	< **0.001**	136.08	0.36	< **0.001**	42.62
Northeast China	1.42	< **0.001**	311.65	0.45	< **0.001**	57.46	0.37	< **0.001**	44.63	0.09	**0.002**	8.98
Southwest China	1.62	< **0.001**	404.30	0.31	< **0.001**	36.21	0.59	< **0.001**	79.68	0.20	< **0.001**	22.63
Northwest China	1.46	< **0.001**	330.60	0.34	< **0.001**	40.21	0.50	< **0.001**	64.38	0.29	< **0.001**	33.24

Note: Bold values indicate regression coefficients with statistical significance (p-value < 0.05). Pre refers to March–November 2018; Post refers to March–November 2019; Bid-winning% refers to the volume proportion of bid-winning drugs in the "4 + 7" List INNs; Generics% refers to the volume proportion of generic drugs in the "4 + 7" List INNs; Bid-winning & Originators% refers to the volume proportion of bid-winning products or original products in the "4 + 7" List INNs; "4 + 7" List INNs% refers to the volume proportion of "4 + 7" List INNs, in the total volume of "4 + 7" List and alternative INNs.
INN, international nonproprietary name; DID, difference-in-difference.

reached 95.42% (tertiary hospitals), 94.13% (secondary hospitals), and 91.63% (PHCs) in the post-intervention period. Next, DID analysis revealed that the proportion significantly increased by 53.88%, 89.27%, and 206.18% in tertiary hospitals ($\beta = 0.43$, $p < 0.001$), secondary hospitals ($\beta = 0.64$, $p < 0.001$), and PHCs ($\beta = 1.12$, $p < 0.001$), respectively.

"4 + 7" List and alternative drugs

Figure 7 demonstrates the monthly trends of volume proportion of "4 + 7" List drugs. The proportion in the intervention group prominently improved in the early periods of policy implementation (March to April 2019) (Figure 7A). Also, a similar increment was observed in three medical institution types in this period (Figure 7B).

Table 4 presents the change of "4 + 7" List drugs and their alternative drugs. After policy intervention, the volume of "4 + 7" List drugs significantly increased by 34.45% ($\beta = 0.30$, $p = 0.002$). The volume change of alternative drugs was not statistically significant ($\beta = 0.01$, $p = 0.956$). As for the proportion of "4 + 7" List drugs in the total volume of "4 + 7" List drugs and alternative drugs, a prominent increase was observed after intervention ($\beta = 0.18$, $p < 0.001$).

In different healthcare settings, the volume of "4 + 7" List drugs significantly increased by 37.99% in tertiary hospitals ($\beta = 0.32$, $p = 0.001$) and 62.74% in PHCs ($\beta = 0.49$, $p < 0.001$), and it significantly decreased by 30.44% ($\beta = -0.36$, $p = 0.002$) in secondary hospitals after policy intervention. The volume of alternative drugs significantly decreased by 44.23% in secondary hospitals ($\beta = -0.58$, $p < 0.001$), and no significant changes were seen in tertiary hospitals ($\beta = 0.14$, $p = 0.128$) and PHCs ($\beta = -0.02$, $p = 0.895$). The volume proportion of "4 + 7" List drugs increased by 11.52%, 19.12%, and 48.59% in tertiary hospitals ($\beta = 0.11$, $p < 0.001$), secondary hospitals ($\beta = 0.18$, $p < 0.001$), and PHCs ($\beta = 0.40$, $p < 0.001$), respectively.

Drug utilization changes by subgroup

Geographical region

Table 5 demonstrates the change in drug utilization among different geographical regions. After policy intervention, the

TABLE 6 Subgroup analyses on the impacts of "4 + 7" pilot on drug use structure by ATC classification.

ATC class	Bid-winning%			Generics%			Bid-winning & originators%			"4 + 7" list INNs%		
	Pre	Post	Change (%)	Pre	Post	Change (%)	Pre	Post	Change (%)	Pre	Post	Change (%)
Descriptive change												
ATC-C	13.21	72.65	59.44	57.90	77.35	19.45	54.32	93.83	39.51	49.35	48.52	−0.84
ATC-N	31.84	67.08	35.24	72.18	82.50	10.31	59.65	84.58	24.93	33.67	33.44	−0.23
ATC-L	25.96	65.91	39.96	72.43	59.17	−13.26	34.89	73.02	38.14	73.00	69.90	−3.10
ATC-J	28.32	84.57	56.25	78.00	89.85	11.85	50.32	94.70	44.39	53.58	68.23	14.64
ATC-A	2.68	73.46	70.78	71.15	93.01	21.87	31.53	80.44	48.91	19.40	17.42	−1.98
ATC-B	36.83	75.42	38.60	58.77	78.54	19.77	78.08	96.90	18.82	34.59	38.87	4.28
ATC-M	97.86	93.92	−3.94	2.14	6.08	3.94	97.86	93.92	−3.94	19.92	18.78	−1.14
ATC-R	0.00	69.99	69.99	39.43	76.73	37.29	60.57	93.26	32.69	78.28	73.25	−5.03

ATC class	Bid-winning%			Generics%			Bid-winning and Originators%			"4 + 7" List INNs%		
	β	*p*	Change (%)	*β*	*p*	Change (%)	*β*	*p*	Change (%)	*β*	*p*	Change (%)
DID estimate												
ATC-C	1.69	< **0.001**	444.12	0.26	< **0.001**	29.43	0.66	< **0.001**	92.90	0.14	< **0.001**	15.03
ATC-N	0.72	< **0.001**	104.83	0.01	0.541	0.90	0.57	< **0.001**	76.12	0.09	**0.003**	9.53
ATC-L	0.93	< **0.001**	153.96	−0.38	< **0.001**	−31.89	0.88	< **0.001**	141.09	−0.06	**0.002**	-5.73
ATC-J	0.87	< **0.001**	137.98	0.03	**0.004**	3.46	0.77	< **0.001**	116.84	0.11	< **0.001**	11.74
ATC-A	2.48	< **0.001**	1090.55	0.36	< **0.001**	43.19	1.02	< **0.001**	176.77	−0.23	< **0.001**	−20.55
ATC-B	1.05	< **0.001**	186.91	0.67	< **0.001**	96.21	0.16	< **0.001**	17.47	0.50	< **0.001**	65.37
ATC-M	0.12	< **0.001**	13.20	−0.39	0.249	−32.50	0.24	< **0.001**	26.87	0.71	< **0.001**	103.60
ATC-R	4.60	< **0.001**	9858.38	0.65	< **0.001**	91.17	0.47	< **0.001**	59.84	−0.01	0.709	−1.19

Note: Bold values indicate regression coefficients with statistical significance (p-value < 0.05). Pre refers to March–November 2018; Post refers to March–November 2019; Bid-winning% refers to the volume proportion of bid-winning drugs in the "4 + 7" List INNs; Generics% refers to the volume proportion of generic drugs in the "4 + 7" List INNs; Bid-winning & Originators% refers to the volume proportion of bid-winning products or original products in the "4 + 7" List INNs; "4 + 7" List INNs% refers to the volume proportion of "4 + 7" List INNs, in the total volume of "4 + 7" List and alternative INNs.

ATC, anatomical therapeutic chemical; INN, international nonproprietary name; DID, difference-in-difference.

volume proportion of bid-winning drugs significantly increased in all six regions: 496.55% (east China), 269.14% (North China), 272.48% (Central China), 311.65% (Northeast China), 404.30% (Southwest China), and 330.60% (Northwest China) (all p-values < 0.001). In the post-intervention period, bid-winning drugs' volume proportion reached between 62.20% and 84.94% in the six regions.

Among the six geographical regions, the change in volume proportion of generic drugs in central China was not statistically significant ($\beta = -0.001$, $p = 0.979$), while significant increases were observed in other five regions (all p-values < 0.001): 22.88% (east China), 23.37% (north China), 57.46% (northeast China), 36.21% (southwest China), and 40.21% (northwest China).

The volume proportion of bid-winning and original drugs significantly increased in all the six regions after policy intervention: 126.82% (east China), 62.09% (north China), 136.08% (central China), 44.63% (northeast China), 79.68% (southwest China), and 64.38% (northwest China) (all p-values < 0.001). Next, in the post-intervention period, the volume proportion of bid-winning and original drugs ranged from 91.49% to 97.68% among the six regions.

Among the six geographical regions, the change in volume proportion of "4 + 7" List drugs in east China was not statistically significant ($\beta = 0.03$, $p = 0.572$), while prominent increases were detected in other five regions (all p-values < 0.01): 19.60% (north China), 42.62% (central China), 8.98% (northeast China), 22.63% (southwest China), and 33.24% (northwest China).

ATC classification

In this study, the included drugs covered eight ATC classifications. As shown in Table 6, the volume proportion of bid-winning drugs significantly increased after policy intervention in all the ATC classes (all p-values < 0.001).

As for the volume proportion of generic drugs, no significant change was observed in ATC-N ($\beta = 0.01$, $p = 0.541$) and ATC-M (β = -0.39, p = 0.249). By contrast, significant increases were found in ATC-C (29.43%), ATC-J (3.46%), ATC-A (43.19%), ATC-B (96.21%), and ATC-R (91.17%), while a significant decrease was found in ATC-L (-31.89%).

For the volume proportion of bid-winning and original drugs, prominent increases were detected in all eight ATC classes (all p-values < 0.001), with the increment ranged from 17.47% to 176.77%. During the post-intervention period, the proportion of bid-winning and original drugs in eight ATC classes was between 73.02% and 96.90%.

In terms of the volume proportion of "4 + 7" List drugs, among the eight ATC classes, five (ATC-C, ATC-N, ATC-J, ATC-B, and ATC-M) demonstrated significant increases (all p-values < 0.05), two (ATC-L and ATC-A) showed significant decreases (all p-values < 0.05), and one (ATC-R) indicated no significant change ($\beta = -0.01$, p = 0.709).

Common pre-trends tests for DID

According to the direct observation of the monthly trend chart above, it can be shown that, to some extent, the monthly trends of change in drug use were similar between the intervention group and control group prior to the "4 + 7" pilot implementation. Furthermore, we conducted common pre-trends tests for each outcome variable based on Eq. 8. As shown in Supplementary Figure S1, the coefficients of the interaction terms were all statistically insignificant in the pre-intervention periods—the point estimates and 95% confidence intervals of the interaction terms' coefficients were not different from zero. Next, the results appeared that the outcome variables demonstrate the same time-varying trend between the intervention group and control group before policy implementation, thus clearly suggesting that the common trends assumption could not be rejected.

Discussion

In this study, we quantified the change in drug utilization in China's public medical institutions under the impact of the "4 + 7" centralized procurement policy, by using data of drug procurement order from an authoritative national database. Natural experimental design and difference-in-difference method were applied to estimate policy impacts. Overall, within the one-year agreed procurement period, the procurement tasks of bid-winning drugs were well completed in each "4 + 7" pilot city. After the implementation of the "4 + 7" policy, the use of policy-related drugs in China's public medical institutions significantly changed, where drug use became more concentrated on bid-winning drugs, generic drugs, quality-guaranteed drugs, and drug INNs covered by centralized procurement list. Besides, a gradually decreasing difference existed in drug use structure among different healthcare settings and geographical areas.

First of all, results of this study showed that the accumulative actual procurement volume of bid-winning drugs in "4 + 7" pilot cities during the one-year procurement period (April 2019–March 2020) reached about two times the agreed volume; the procurement of a majority of drug INNs were also over-fulfilled. The present findings are generally consistent with the findings reported by NHSA (2020), reflecting good policy acceptance and compliance of healthcare providers. However, our investigation revealed that the published agreed procurement volume in the 11 pilot cities only accounted for approximately 45% of the actual procurement volume in 2018 (Joint Procurement Office, 2018b), which is markedly lower than the projected amount of 60–70% (General Office of the State Council, 2019a), and the underreporting was particularly prominent in several pilot cities. This finding may implicate the phenomenon of underreporting of procurement demands in public medical institutions to relieve their pressure of assessment, which was also reported in a previous study (Yu, 2020). Next, the accurate identification of demands for drugs is the foundation for conducting centralized drug bidding and procurement, as well as for assessing the medical institutions. Therefore, in the future, to promote authentic reporting of drug use demands in medical institutions, a more comprehensive mechanism for reporting drug procurement volume and a reform of assessment approach are warranted.

Second, a significant increase was found in usage of bid-winning drugs following the policy intervention, while the opposite trend was observed in the non-winning drugs. As a consequence, bid-winning drugs became more dominant in use among the centralized procurement drugs, increasing from 14 to 74%. Also, these results are in line with the body of literature (Chen et al., 2020; Yang et al., 2021a; Chen et al., 2021; Wen et al., 2021; Yang et al., 2022a; Wang et al., 2022). In particular, such changes were found to be more prominent in PHCs, compared to those in secondary and tertiary hospitals, which indicated that the bid-winning drugs among the centralized procurement drugs may be more reflective to the drug demands at PHC level. Following the implementation of the "4 + 7" policy, the bid-winning drugs have become more accessible at community level (NHSA, 2022), which complies with the original policy intention of improving drug accessibility.

Third, we also observed a significant increase in usage of generic drugs under the impact of the "4 + 7" policy implementation, while the opposite trend was seen in the original drugs. The usage of generic drugs has become more dominant, increasing from 59% to 78%; the increment was the largest in tertiary hospitals, followed in order by secondary hospitals and PHCs. In China, the high reliance of use in original drugs has long existed, especially in large hospitals; also, an increasing use of original drugs is found year by year (Li et al., 2013; Zeng, 2013; Tang, 2016; Li et al., 2021; Huang et al., 2022), which appears to be contradicted to the situation in the United State where the generic drugs reached 90% of the prescriptions (FDA, 2019).

Next, the low utilization rate of the generic drugs in China could be attributed to a number of factors, including the lack of sufficient understanding in the trust to the quality and efficacy of domestic generic drugs among the physicians, pharmacists, and patients (Oncu et al., 2020; Li et al., 2021), as well as the incentives for markups or rebates of high-priced drugs (such as the imported original drugs) (Zeng et al., 2014). After the implementation of the "4 + 7" centralized procurement policy, the long-standing problem of low utilization rate of generic drugs in public hospitals has been reversed; also, the variations in the utilization rate of generic drugs among healthcare settings and geographical regions also gradually reduced. In the future, persistent publicity and education of knowledge on generic drugs are needed to further reverse the misunderstandings of the generic drugs among the general public (Qu et al., 2021). Moreover, further improving the establishment of drug quality standard is urgent, to promote the monitoring and evaluation on the efficacy and safety of generic drugs that passed the GCE using real-world data and to consolidate the foundation for the substitution use of generic drugs.

Forth, since the centrally procured bid-winning drugs and the imported original drugs are of relatively high quality assurance, in this study, they were regarded as quality-guaranteed drugs. Analysis of the current work revealed that a tremendous upsurge was found in the overall utilization of these quality-guaranteed drugs from 57 to 94% following the policy implementation, which is consistent with the reports released by NHSA (2020) and Wang et al. (2022). Of note, the increment was more prominent in PHCs, as compared to that in the secondary and tertiary hospitals. More importantly, the utilization rate of these quality-guaranteed drugs increased consistently in all geographical regions and all ATC classes. In China, there has been a long-standing concern on the quality of generic drugs, as well as among different brands, which impeded improvement in the quality of drugs used among the general public (Tian, 2014; Chen et al., 2021). Next, fortunately, following the implementation of the "4 + 7" centralized procurement policy, the utilization rate of the quality-guaranteed drugs, at least among the "4 + 7" List drugs, remarkably improved, reflecting an overall improvement of the quality of drugs used at the population level. Meanwhile, the increase in the market share of high quality generics under the influence of the centralized procurement policy would encourage the development of the Chinese domestic pharmaceutical industry (Mao et al., 2020). In the long run, the advance of the policy may be conducive to guiding pharmaceutical enterprises to pay more attention to drug quality and innovation. In light of this, we recommend to expand the coverage of centralized procurement drugs in order to benefit more patients and, meanwhile, to get rid of the use of low-quality drugs, such as generic drugs that failed to pass the GCE assessment.

Moreover, the quantity and proportion in use of the "4 + 7" List drugs significantly increased after the policy intervention, which might be ascribed to the release of some previously unmet drug demands after drug price reduction. Besides, we found that the increment in the utilization proportion of "4 + 7" List drugs took place mostly during early months of the policy implementation, which then generally returned to the pre-intervention level. These results suggested that excessive procurement and use of related drugs might be found in medical institutions in the early stage of policy implementation, (Yang et al., 2021b), which deserves a full attention in policy monitoring in the future.

Centralized public procurement is an effective approach to redress the imbalance in pharmaceutical market leverage between supply and demand, with the logical underpinnings that the consolidation of purchasing power produces economies of scale and brings many benefits such as price reduction, improved quality assurance, rationalized choice, etc. (Huff-Rousselle, 2012). The principle for the impact of centralized procurement on hospitals' drug utilization lies in the reshaping of the market pattern under the alliance mechanism—the influence of the centralized procurement mechanism on drug market varied by existing competition patterns, drug attributes, and buyers' demands (Dubois et al., 2021; Wang and Zahur, 2022). Existing literature noted that centralized procurement mechanism demonstrated no limit on product choices of healthcare providers (Callea et al., 2017; Wang and Zahur, 2022), nor did we observe in this study; therefore, reasons exist to believe that changes in drug utilization may be largely derived from the increased efficiency of the procurement system and improved rationality of decision-making about drug procurement (Bandiera et al., 2008; Huff-Rousselle, 2012). In China's current public procurement practice, our findings indeed indicated significant changes in drug utilization of policy-related drugs after the implementation of the centralized drug procurement policy, and the variations in drug use structure among healthcare settings and geographical regions were gradually diminished. Next, the promotion of overall quality of drugs used and the homogenization of drug use structure might be conducive to hierarchical diagnosis and treatment, as well as enhancement in the fairness of drug usage at population level in China.

This study demonstrates a few limitations. First, provincial procurement data (i.e., population level data), rather than the clinical medicine use of patients (such as prescriptions), were analyzed in this study. Although the research method for drug utilization is internationally accepted, the resulting DDD data cannot be followed back to the demand in individual patients. Therefore, in the future, patient- and prescriber-level research might be needed to identify the direct causes behind the observed changes in drug utilization under the "4 + 7" policy. Second, due to the lack of city-level data from non-pilot areas, in this study, we matched the control group by province (rather than by city), which might be an imperfection regarding the establishment of the control group. Also, it should be noted that the "4 + 7" pilot cities are China's top developed areas; therefore, it is difficult to assign a control group in mainland China that completely matched the pilot group in terms of population size, economic development, medical resources, etc. In this study, we made further explorations based on our previous work (Wang et al., 2022), such as the TOPSIS matching and the stratified

matching by geographical region, in an attempt to improve the comparability between intervention and control group to the greatest extent. Next, luckily, the common trends tests supported our hypothesis. Despite that, the present findings might also be confronted with the risk of bias, and one should be cautious when interpreting the results.

Conclusion

During the 1-year contracted procurement period, the agreed procurement tasks of medical institutions were mostly well fulfilled in pilot cities, with an overall completion rate of 191.4%. After policy intervention, the drug utilization of China's public medical institutions significantly changed, and the consumption became more concentrated to bid-winning drugs and generic drugs. Next, the variations in drug use among healthcare settings and geographical regions were gradually narrowed. Moreover, "4 + 7" centralized procurement policy significantly promoted the use proportion of quality-guaranteed drugs consistently in all regions, healthcare settings, and ATC classes. In the future, policy improvement is still needed to expand the influence coverage on drug utilization and promote equity in drug use in China.

Data availability statement

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

Author contributions

Conception and design: JL, YY, ZM, and JL. Collection and assembly of data: JL, YS, JW, HL, and ZM. Statistical analysis: HL, XG, YY, and ZM. Interpretation: JL, HL, XG, YY, ZM, and JL. Manuscript preparation: JL, HL, YS, JW, XG, and YY. Manuscript review: YS, JW, ZM, and JL.

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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.2022.923209/full#supplementary-material

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Clinical and economic impact of changing reimbursement criteria for statin treatment among patients with type 2 diabetes mellitus in South Korea

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Aim: Patients with type 2 diabetes mellitus (T2DM) in South Korea can be reimbursed for statins if they have a low-density lipoprotein cholesterol (LDL-C) level of ≥100 mg/dL. We aimed to explore the clinical and economic benefit received by T2DM patients when easing the current criteria for statin treatment by lowering the LDL-C threshold from 100 mg/dL to 70 mg/dL.

Methods: We used a static course model with a 5-year period to compare the following two scenarios in T2DM patients with no history of cardiovascular (CV) events: the current criteria covering LDL-C ≥100 mg/dL and the revised criteria covering LDL-C ≥70 mg/dL. The number of target patients was estimated based on previous Korean studies on patients with T2DM. The current mix of treatments used for T2DM and costs involving CV events were estimated using the National Health Insurance Service–National Health Screening Cohort database. The baseline CV event rates and case fatality were estimated using NHIS Customized database, including 50% patients who were prescribed atorvastatin and 100% who were not prescribed statins between 2009 and 2012 among patients with T2DM in the entire Korean population. After propensity score matching, patients with T2DM not prescribed statins were followed up until 2018 to estimate the incidence rates of coronary heart disease (CHD) and stroke. The efficacy of atorvastatin for the primary prevention of CV events in patients with T2DM was derived from a pivotal clinical trial. The outcome measures were the number of CV events prevented after the change in criteria and the consequent cost savings.

Results: In South Korea, the current and revised criteria covered 2,434,379 and 3,446,149 patients with T2DM, respectively. The change in criteria resulted in the prevention of 726 CV events and cost savings of US dollars (USD) 5.5 million at the national level and USD 0.0089 per member per month in the fifth year.

Conclusion: Easing the reimbursement criteria for statin treatment among patients with T2DM was associated with a reduction in CV events and their related costs; therefore, changing the reimbursement criteria is worth further consideration to mitigate the burden of CV disease.

KEYWORDS
cardiovascular event, diabetes, economic impact, reimbursement criteria, statin

1 Introduction

Cardiovascular disease (CVD) is associated with an enormous burden, including a high mortality rate and healthcare cost, worldwide (Leal et al., 2006; Deaton et al., 2011; Fox et al., 2016). Elevated low-density lipoprotein cholesterol (LDL-C) levels are a major risk factor for CVD and are associated with an increased risk of cardiovascular (CV) events and CVD-associated mortality (Pekkanen et al., 1990; Wong et al., 1991; Wilson et al., 1998). Therefore, statin therapy is recommended for the management of LDL-C levels in patients with CVD or those at high risk of CVD (Grundy et al., 2019). Patients with type 2 diabetes mellitus (T2DM) are considered to be at a high risk of CVD, which accounts for 20–49% of the total healthcare cost of T2DM (Einarson et al., 2018).

As T2DM and CVD are the leading causes of the burden of illness in South Korea (Oh et al., 2011; Jung et al., 2021), LDL-C management is recommended based on LDL-C goals stratified by patient risk levels (Kim et al., 2016). In South Korea, the reimbursement criteria for statin treatment are also based on patients' LDL-C levels and risk levels and can be summarized as follows: 1) LDL-C ≥70 mg/dL in patients with acute coronary syndrome; 2) LDL-C ≥100 mg/dL in patients with coronary artery disease (CAD) or equivalent risk (i.e., diabetes mellitus, peripheral artery disease, abdominal aortic aneurism, and carotid disease); 3) LDL-C ≥130 mg/dL in patients with two or more risk factors (i.e., smoking, hypertension, HDL-C <40 mg/dL, family history of premature CAD, and age ≥45 years in men and ≥55 years in women); and 4) LDL-C ≥130 mg/dL in patients with one or no risk factors (Health Insurance Review and Assessment Service, 2014). Accordingly, patients with diabetes can be reimbursed for statin treatment if they have LDL-C levels ≥100 mg/dL.

Several previous studies have suggested the benefit of intensive treatment goals in preventing CV events among patients with T2DM with relatively low LDL-C levels, such as those with <100 mg/dL (Fleg et al., 2008; Itoh et al., 2018; Wang et al., 2020; Shinohara et al., 2021). In a phase 3 randomized clinical trial of atorvastatin treatment in patients with T2DM with no history of CVD, a post-hoc analysis revealed that atorvastatin was associated with a 26% reduction in CV events among patients with baseline LDL-C <100 mg/dL (Colhoun et al., 2004). Moreover, the American College of Cardiology/American Heart Association has suggested approaches for lipid management based on risk reduction benefits rather than specific LDL-C goals, recommending that adult patients with T2DM start statin treatment regardless of their LDL-C levels (Stone et al., 2014; Grundy et al., 2019).

Considering the existing evidence, statin treatment in a broader group of patients with T2DM, including those with relatively low LDL-C levels, might have an additional benefit regarding the prevention of CVD and its related costs. Therefore, we assessed the clinical and economic benefit of CV event prevention when easing the reimbursement criteria for statin treatment in patients with T2DM in South Korea.

2 Methods

2.1 Study design and data source

We estimated the clinical and economic impact of changes in reimbursement criteria using a static course model with a 5-year period from a Korean payer's perspective, assuming that the epidemiology of the disease remains unchanged over time. Two reimbursement scenarios were compared: current criteria, covering patients with T2DM with LDL-C ≥100 mg/dL and revised criteria, covering patients with T2DM with LDL-C ≥70 mg/dL. We assumed that atorvastatin is the only drug used in both scenarios, given that only atorvastatin and simvastatin are indicated for diabetes, and the prescription of atorvastatin is far more frequent than that of simvastatin in South Korea (Kim and Rhew, 2021). The study population included patients with T2DM with LDL-C ≥70 mg/dL and no previous history of CV events.

The input parameters used in this model are listed in Table 1. Most input values were based on the National Health Insurance Service (NHIS) database and published literature. We utilized two types of NHIS databases: the NHIS-National Health Screening Cohort (NHIS-HEALS) database and the NHIS Customized database. The former includes information on sociodemographic characteristics, healthcare resource use, disease diagnosis, health screening results, and death during 2002–2015, which was collected from a 10% random sample of all patients who participated in health screening during 2002–2003, assuring the representativeness of laboratory test results, such as LDL-C (Seong et al., 2017). Having a data structure similar to that of the NHIS-HEALS, the NHIS Customized database consists of data on diabetes patients among the entire Korean population between 2009 and 2012, with 50% diabetes patients who were prescribed atorvastatin and 100% with no statin prescriptions. We were able to obtain 50% of the sample rather than all patients with diabetes who were prescribed atorvastatin because this was the maximum sample that could be utilized under the limited data size imposed by the NHIS. The data period of the NHIS Customized database was 2008–2018, and patients with cancer diagnoses (International Classification of Diseases, 10th revision [ICD-10] codes of

TABLE 1 Input parameter values and data sources used in the model.

Parameter	Value	Source
Population		
Total Korean population in 2020	51,780,579	KOSIS
Prevalence of T2DM, %	8.4	Koo et al. (2014)
Proportion of patients without previous CV events among patients with T2DM, %	89.2	Rhee et al. (2011)
LDL-C distributions of patients with T2DM, %		Kim et al. (2019)
70–99 mg/dL	26.1	
≥100 mg/dL	62.7	
The current mix of treatments		NHIS-HEALS DB
Proportion of patients taking atorvastatin, %	11.6	
CV event costs, USD		NHIS-HEALS DB
Non-fatal CHD	7,440	
Fatal CHD	4,674	
Non-fatal stroke	8,057	
Fatal stroke	4,802	
Efficacy		
Baseline CV event rates, per 100 PYs		NHIS Customized DB
CHD	0.59	
Stroke	0.85	
Hazard ratio of CV events		Colhoun et al. (2004)
CHD	0.640	
Stroke	0.520	
Case fatality, %		NHIS Customized DB
CHD	12.2	
Stroke	5.5	

CHD, coronary heart disease; CV, cardiovascular; DB, database; KOSIS, Korean Statistical Information Service; LDL-C, low-density lipoprotein cholesterol; NHIS, National Health Insurance Service; NHIS-HEALS, National Health Insurance Service–National Health Screening cohort; PYs, person-years; T2DM, type 2 diabetes mellitus; USD, United States Dollar.

C00–C97) from 2008 to 2018 were excluded from the database. In this study, we utilized the NHIS Customized database to estimate the efficacy of atorvastatin in the primary prevention of CV events, given that this database contains the largest sample of the population of interest and appropriate controls. However, the patients included in the database were not representative of all patients with diabetes in Korea but were limited to a subgroup of patients with diabetes. Therefore, we estimated the current mix of treatments used for T2DM and CV event costs using the NHIS-HEALS database, which provided a 10% sample of health-screening participants in Korea.

2.2 Population

To estimate the number of target patients in the current and revised reimbursement criteria, we started from the entire Korean population and narrowed them down to the target population of the reimbursement criteria. The number of T2DM patients in South Korea in 2020 was estimated by applying the prevalence of T2DM estimated from a previous study using the Health Insurance Review and Assessment Service data (Koo et al., 2014). The proportion of patients with T2DM with no history of CVD was derived from the results of the Korean National Diabetes Program cohort (Rhee et al., 2011). The LDL-C distributions among patients with T2DM with no history of CVD were derived from a previous study using the NHIS Customized database, which reported the proportion of patients with LDL-C <70 mg/dL, 70–99 mg/dL, 100–129 mg/dL, 130–159 mg/dL, and ≥160 mg/dL as 11.2, 26.1, 31.5, 20.4, and 10.9%, respectively (Kim et al., 2019). Because we used a static course model, the number of target patients was assumed to be the same for the 5-year period.

2.3 The mix of treatments

We analyzed the NHIS-HEALS database to estimate the proportion of patients prescribed atorvastatin among patients with T2DM with LDL-C levels ≥100 mg/dL (Figure 1A). Patients satisfying all of the following criteria were selected: 1) LDL-C ≥100 mg/dL at the first health examination they received between 1 January 2009 and 31 December 2012; 2) diagnosed with T2DM (ICD-10 codes E11, E14, and E14 up to the fifth

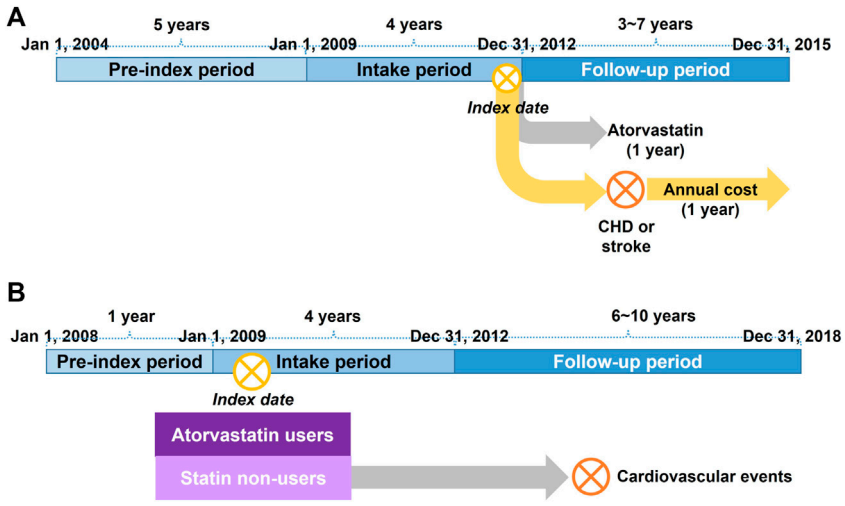

FIGURE 1
(A) Schematic diagram of the analysis of treatment mix and cost of cardiovascular events using the NHIS-HEALS database **(B)** Schematic diagram of the analysis of baseline cardiovascular event rates and case fatality using the NHIS Customized database. CHD, coronary heart disease; NHIS, National Health Insurance Service.

TABLE 2 Diagnosis codes of cardiovascular events.

Cardiovascular event	ICD-10 code*	Description	Source
Myocardial infarction	I21	Acute myocardial infarction	Kimm et al. (2012)
Unstable angina	I20.0	Unstable angina	
Cardiac arrest	I46	Cardiac arrest	
Stroke	G46	Vascular syndromes of brain in cerebrovascular diseases	Park and Choi, (2016)
	I60	Subarachnoid hemorrhage	
	I61	Intracerebral hemorrhage	
	I63	Cerebral infarction	
	I64	Stroke, not specified as hemorrhage or infarction	

ICD-10, International Classification of Diseases, 10th revision; *In any position.

position) and prescribed anti-diabetics within 1 year before the index date; 3) no history of lipid-lowering therapy, such as statins, ezetimibe, fibrates, nicotinic acid, and omega-3-acid ethyl esters, within 1 year before the index date; and 4) no history of CV events within 5 years before the index date (Table 2). The index date was defined as the first date of receiving a health examination between 1 January 2009, and 31 December 2012. The definition of CV events was based on previous studies that validated CV events in Korean national health insurance claims data (Kimm et al., 2012; Park and Choi, 2016). Eligible patients were followed-up for 1 year from the index date. As a result, 11.6% of the patients were prescribed atorvastatin.

Because the NHIS-HEALS database includes only claims data generated under the current reimbursement criteria, we were unable to measure the proportion of patients prescribed atorvastatin among patients with diabetes with LDL-C <100 mg/dL. Therefore, the proportion of patients with LDL-C levels between 70 and 100 mg/dL was assumed to be the same as that of patients with LDL-C ≥100 mg/dL. Consequently, in the reimbursement scenario with the revised criteria, the proportion of patients with LDL-C between 70 and 100 mg/dL increased from 0 to 11.6% over the 5 years. This assumption was confirmed by an expert elicitation by an endocrinologist in South Korea.

2.4 Cost of CV events

The annual costs of coronary heart disease (CHD) and stroke were estimated using the same database as that of the treatment

mix analysis (Figure 1A). We selected patients who underwent LDL-C examination between 1 January 2009, and 31 December 2012, with T2DM diagnosis and anti-diabetics within 1 year before the index date, and experienced CV events with hospitalization between the index date and 31 December 2014 (Table 2). The total medical costs incurred in 1 year from the first date of the CV event were measured from a Korean payer's perspective. CV events were classified into fatal and non-fatal events, where fatal events were defined as cases of death within 28 days after the occurrence of a CV event (Xie et al., 2018). Costs were converted into US dollars (USD) using the average exchange rate in 2020 between Korean won and USD (1 USD = 1,180.11 Korean won).

2.5 Efficacy

The baseline CV event rates and case fatality among patients with T2DM who were not treated with statins were estimated from the NHIS Customized database (Figure 1B). First, patients treated with atorvastatin were selected according to the following criteria: 1) patients with an outpatient prescription with T2DM diagnosis (ICD-10 codes E11, E14, and E14 up to the fifth position), anti-diabetics, and atorvastatin between 1 January 2009, and 31 December 2012; 2) patients who were prescribed atorvastatin with a proportion of days covered ≥80% for 3 months after the index date; 3) patients with no history of atorvastatin in an outpatient setting within 1 year before the index date; 4) patients who received an LDL-C examination within 1 year before the index date; and 5) patients with no history of CV events within 1 year before the index date (Table 2). The index date was defined as the first date of outpatient prescription with T2DM diagnosis, antidiabetics, and atorvastatin between 1 January 2009, and 31 December 2012. Second, patients not treated with statins were selected according to the following criteria: 1) patients with an outpatient prescription with T2DM diagnosis and antidiabetics without any statin prescription between 1 January 2009, and 31 December 2012; 2) patients matched to the patients treated with atorvastatin by age and sex (up to 1:10 ratio); 3) patients who received an LDL-C examination within 1 year before the index date, the same as the index date of the matched atorvastatin users; and 4) patients with no history of CV events within 1 year before the index date. Lastly, patients treated with atorvastatin and those not treated with statins were matched using a 1:1 ratio according to the propensity scores. The propensity score was estimated by logistic regression, including age, sex, LDL-C, blood pressure, fasting blood sugar, smoking status, Charlson Comorbidity Index, and concomitant medication (antihypertensive and antiplatelet) as covariates. Greedy matching was conducted with calipers of 0.2 of the standard deviation of the logit of the propensity score (Austin, 2011). After propensity score matching, patients who were not treated with statins were followed up from the index date to the first date of CV events with hospitalization (Table 2), death, or 31 December 2018, whichever came first. The incidence rates of CHD and stroke were measured using the incidence density method. The case fatality of CHD and stroke was measured as the proportion of fatal events (i.e., death within 28 days) among all events (Xie et al., 2018). Further details of the analysis of the NHIS Customized database will be presented elsewhere (Kim and Suh, 2022).

The efficacy of atorvastatin in the primary prevention of CV events was derived from a pivotal clinical trial that compared atorvastatin with placebo among patients with T2DM without previous CV events (Colhoun et al., 2004).

2.6 Outcome measures

We measured the clinical and economic outcomes by comparing the two reimbursement scenarios. The clinical outcome was the number of CV events prevented after the change in the reimbursement criteria. The economic outcomes included total costs and per member per month (PMPM) costs resulting from the reduction in CV events. Total costs included annual medical costs related to CV events measured from a Korean payer's perspective and were calculated at the national level by multiplying the annual cost of CV events per patient by the number of target patients in the reimbursement criteria. The PMPM costs were calculated on a monthly basis by dividing the total costs by the total Korean population in 2020.

2.7 Analyses

To determine the impact of uncertainty related to cost parameters, we conducted a sensitivity analysis by measuring the costs of CV events among patients with T2DM with no history of CV events within 5 years before the index date, whereas the costs were measured among all patients with T2DM regardless of CV event history in the base case. We also changed the baseline CV event rates based on published literature that assessed the risk of CV events according to LDL-C levels among patients with T2DM in South Korea (Kim et al., 2019). In the study, the baseline event rates of CHD and stroke in patients with LDL-C between 70 and 100 mg/dL were 0.32 and 0.56 per 100 person-years (PYs), respectively, and those in patients with LDL-C ≥100 mg/dL were 0.36 and 0.57 per 100 PYs, respectively.

An analysis with a static course model that assessed the clinical and economic impact of reimbursement criteria changes was conducted using Microsoft Excel (Microsoft, Redmond, WA, United States). The NHIS database was analyzed using the SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, United States). This study was exempt from full review by the

TABLE 3 Calculating the population size of target patients of reimbursement criteria for statin treatment for type 2 diabetes mellitus.

Category	Value	Population size
Total Korean population in 2020	51,780,579	51,780,579
Prevalence of T2DM, %	8.4	4,349,569
Proportion of patients without previous CV events among patients with T2DM, %	89.2	3,879,815
LDL-C distributions of patients with T2DM, %		
70–99 mg/dL	26.1	1,011,770
≥100 mg/dL	62.7	2,434,379
Current criteria (covering LDL-C ≥100 mg/dL)		2,434,379
Revised criteria (covering LDL-C ≥70 mg/dL)		3,446,149

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

TABLE 4 Clinical and economic outcomes before and after the change in reimbursement criteria for statin treatment for type 2 diabetes mellitus.

Category	Current criteria	Revised criteria				
		Year 1	Year 2	Year 3	Year 4	Year 5
Number of CV events	47,621	47,476	47,330	47,185	47,040	46,895
Non-fatal CHD	17,178	17,135	17,091	17,048	17,004	16,960
Fatal CHD	2,387	2,381	2,375	2,369	2,363	2,357
Non-fatal stroke	26,513	26,422	26,332	26,242	26,151	26,061
Fatal stroke	1,543	1,538	1,533	1,527	1,522	1,517
Total costs (USD)	359,984,234	358,878,362	357,772,491	356,666,619	355,560,747	354,454,875
PMPM costs (USD)	0.5793	0.5776	0.5758	0.5740	0.5722	0.5704

CHD, coronary heart disease; CV, cardiovascular; PMPM, per member per month; USD, United States Dollar

Institutional Review Board of Pusan National University (PNU IRB/2020_04_HR).

3 Results

3.1 Population size of the target patients in South Korea

Starting from the total Korean population in 2020, the patient group was narrowed to the target patients for the reimbursement criteria for statin treatment for T2DM (Table 3). Among patients with T2DM with no previous history of CV events, 1,011,770 had LDL-C levels between 70 and 100 mg/dL, and 2,434,379 had LDL-C levels ≥100 mg/dL. As a result, the current and revised criteria cover 2,434,379 and 3,446,149 patients, respectively, in South Korea. This change in reimbursement resulted in an approximately 40% increase in the number of patients with T2DM receiving reimbursement for statin treatment. When applying the mix of atorvastatin treatment to the target patients, 282,261 and 399,573 patients were estimated to be treated with atorvastatin before and after the change in reimbursement criteria, respectively.

3.2 Clinical outcomes

A static course model estimated that 47,621 CV events occurred annually in the status quo among all patients with T2DM in South Korea (Table 4). After the change in reimbursement criteria, the number of CV events decreased to 46,895 in the fifth year after the change, resulting in the prevention of 726 CV events among all patients with T2DM in South Korea. Among the types of CV events, non-fatal stroke showed the largest number of events prevented followed by non-fatal CHD, fatal CHD, and fatal stroke (Figure 2).

3.3 Economic outcomes

The annual cost of CV events at the national level was estimated to be USD 360 million under the current criteria, and the reduction in CV events decreased the cost to USD 354 million in the fifth year after the change in the reimbursement criteria (Table 4). As a result, the estimated cost savings were USD 5,529,359 at the national level and USD 0.0089 PMPM in the fifth year (Figure 3).

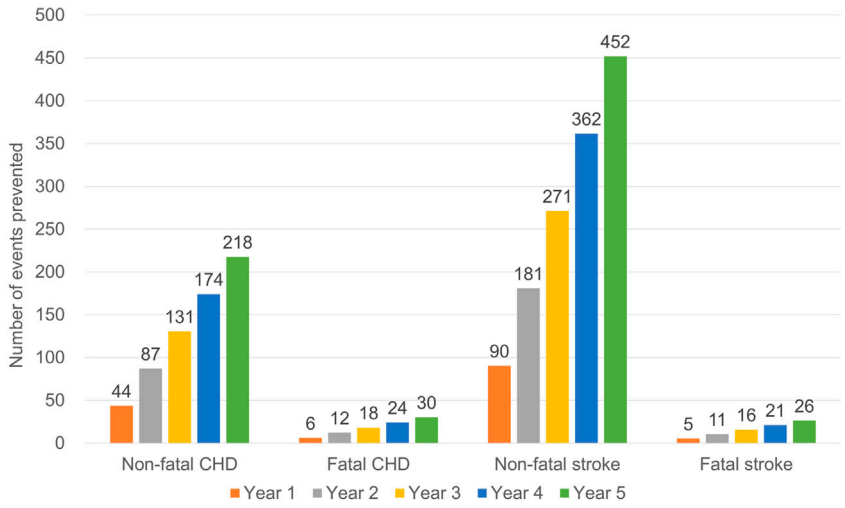

FIGURE 2
Predicted number of cardiovascular events prevented after the change in reimbursement criteria for statin treatment for type 2 diabetes mellitus. CHD, coronary heart disease.

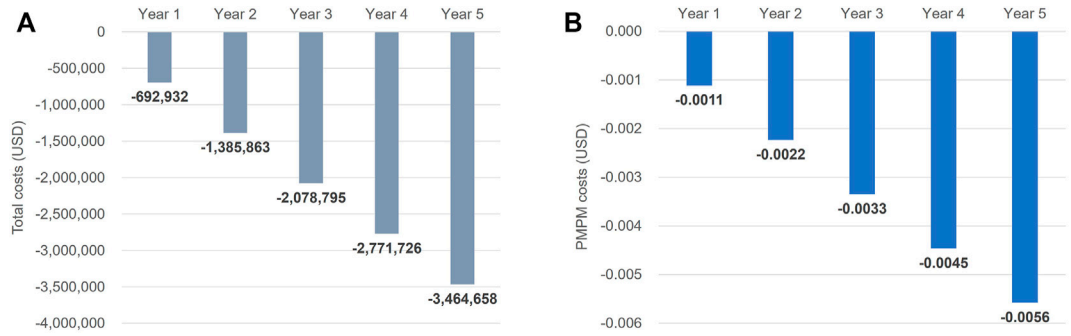

FIGURE 3
(A) Total cost savings and **(B)** per member per month cost savings resulted from the reduction of cardiovascular events after the change of reimbursement criteria for statin treatment for type 2 diabetes mellitus. PMPM, per member per month; USD, United States dollar.

In a sensitivity analysis using an alternative approach to measure the costs of CV events, which measured the costs among patients with T2DM with no history of CV events within 5 years, the cost of each CV event except for fatal CHD was slightly higher than that of the base-case analysis: USD 7,535, 4,375, 8,117, and 5,071 for non-fatal CHD, fatal CHD, non-fatal stroke, and fatal stroke, respectively. Consequently, the cost savings in the fifth year of change increased by <1% from the base-case analysis (USD 5,575,050 at the national level and USD 0.0090 PMPM in the fifth year of change). When changing the baseline CV event rates derived from published literature, the number of CV events prevented after the change in reimbursement criteria decreased compared to those of base-case analysis: 120, 17, 300, and 17 events for non-fatal CHD, fatal CHD, non-fatal stroke, and fatal stroke, respectively. This resulted in a 37% decrease in cost savings compared to the base-case analysis (USD 3,464,658 at the national level and USD 0.0056 PMPM in the fifth year of change).

4 Discussion

This study demonstrated that changing the current reimbursement criteria for statin treatment among patients with T2DM by lowering the LDL-C threshold from 100 mg/dL to 70 mg/dL was associated with a reduction in CV events and related costs. The change in reimbursement criteria allowed an

additional 1,011,770 patients with T2DM to be reimbursed for statin treatment, corresponding to 23% of all patients with T2DM and 2% of the entire population in South Korea. By using statins in these patients, we could expect 726 CV events to be prevented and USD 5.5 million to be saved at the national level in terms of annual disease-related costs.

A previous systematic review and meta-analysis showed that LDL-C reduction was associated with a decrease in the risk of major CV events by 19% per 1 mmol/L (Wang et al., 2020). The effect of LDL-C reduction was consistent across various baseline LDL-C levels, and patients with LDL-C <80 mg/dL showed a 17% risk reduction per 1 mmol/L. This finding was also consistent in both diabetes and non-diabetes patients (relative risk [RR] = 0.83, 95% confidence interval [CI] = 0.79–0.88 in diabetes patients; RR = 0.84, 95% CI = 0.78–0.90 in non-diabetes patients). Therefore, the study suggested a benefit for LDL-C management regardless of patient baseline LDL-C levels, even in patients with relatively low LDL-C levels who are generally not treated with lipid-lowering therapies.

In the Asian population, the EMPATHY study suggested the benefit of treating patients with intensive goals (LDL-C <70 mg/dL) compared to that in the standard goal (LDL-C between 100 and 120 mg/dL) among patients with diabetic retinopathy and hypercholesterolemia (Itoh et al., 2018). Although the primary outcome (i.e., CV events and CV-related deaths) did not show statistical significance (hazard ratio [HR] = 0.84, 95% CI = 0.67–1.07), cerebral events were significantly decreased in the intensive group (HR = 0.52, 95% CI = 0.31–0.88). In the sub-analysis of the EMPATHY study, in patients with blood pressure ≥130/80 mmHg, the intensive goal was associated with a significant decrease in the risk of the primary outcome compared to that in the standard goal (HR = 0.70, p-value = 0.015), whereas there was no significant association in patients with blood pressure <130/80 mmHg (Shinohara et al., 2021). These findings suggest that an intensive treatment goal is advantageous in Asian populations with T2DM, especially in patients with additional risk factors such as elevated blood pressure.

In most countries, statin treatment is recommended based on baseline risk assessment considering various patient risk factors. For example, the National Institute for Health and Care Excellence in the United Kingdom recommends patients with T2DM to use atorvastatin 20 mg if they have a ≥10% 10-years risk of CVD, as assessed by the QRISK2 risk calculator (National Institute for Health and Care Excellence, 2014). In contrast, the Korean guidelines for the management of dyslipidemia still recommend the use of LDL-C goals because of the lack of evidence regarding CV risk prediction and the impact of high- or moderate-intensity statin treatment in Asian patients (Kim et al., 2016). In a recent study exploring the association between LDL-C levels and the risk of CVD in Korean patients with T2DM who had no history of CVD and were treated with statins, the risk of myocardial infarction and stroke was significantly increased in those with an LDL-C level of 70–99 mg/dL compared to those with an LDL-C level <70 mg/dL (HR = 1.07, 95% CI = 1.03–1.12 for myocardial infarction; HR = 1.07, 95% CI = 1.03–1.11 for stroke) (Kim et al., 2019). This suggests the unmet needs for the prevention of CV events among patients with T2DM with LDL-C levels between 70 and 100 mg/dL. Further studies on CVD risk and statin effectiveness in the Korean population are warranted, and recent evidence from the Korean population should be considered in the lipid management of patients with T2DM.

Despite of the guidelines on CVD prevention developed by the European Society of Cardiology (ESC), two large-scale cross-sectional surveys in European countries revealed that a large proportion of patients with CHD received suboptimal management for CVD risk factors (Kotseva et al., 2009; Kotseva et al., 2016; Piepoli et al., 2016). Optimizing the management of CVD risk factors in these patients, such as using statins to achieve the LDL-C goals and smoking cessation, was found to be cost-effective (De Smedt et al., 2012; De Smedt et al., 2018). Our study also suggested that the CVD risk management at a national level can lead to decrease in the costs of CVD. To relieve the global burden of CVD, proactive strategies for the CV risk management need to be sought by considering the country-specific healthcare policies.

The findings of this study can be generalized to the Korean population by using Korea-specific data as extensively as possible. In particular, we utilized two types of real-world big data: the NHIS-HEALS and NHIS Customized databases. The NHIS-HEALS database is a representative sample of all patients who participated in health screening, thereby ensuring the representativeness of the clinical laboratory data. The NHIS Customized database contains patients of interest extracted from the entire Korean population. Therefore, the results obtained from the database can be generalized to the entire population. We also verified the appropriateness of the patient definitions and assumptions used in the model through expert elicitation.

However, the results should be interpreted with caution due to several limitations. First, we assumed that the proportion of atorvastatin prescriptions in patients with LDL-C between 70 and 100 mg/dL would be the same as that in patients with LDL-C ≥100 mg/dL because there was no evidence of the proportion of atorvastatin prescription in patients with T2DM with LDL-C between 70 and 100 mg/dL under the current reimbursement criteria. We also considered that the proportion of atorvastatin prescriptions in patients with LDL-C between 70 and 100 mg/dL would not exceed that in patients with LDL-C ≥100 mg/dL and therefore assumed a proportion between 0 and 11.6%. This assumption is partly supported by expert elicitation. Second, the efficacy of statin treatment was not specific to the Korean population owing to a lack of evidence. Third, although we matched patient groups by propensity scores when estimating baseline CV event rates, unmeasured

confounders might exist. Lastly, the baseline LDL-C levels used in this study were derived from biennial health screening data, and therefore the levels might vary from the actual LDL-C levels at the initiation of statin treatment. However, we defined the baseline LDL-C level as the most recent value measured before the start of statin treatment. Fourth, the databases used in this study did not include the entire patients with diabetes in Korea, which might limit the generalizability of our findings. Fifth, the efficacy of statins in the primary prevention of CV events might vary depending on the baseline LDL-C level. However, in a previous meta-analysis conducted by the Cholesterol Treatment Trialists' Collaborators, there was no difference in the effects of statin therapy among subgroups having different baseline LDL-C levels (Cholesterol Treatment Trialists' Collaborators et al., 2008).

5 Conclusion

In patients with T2DM without a history of CV events, easing the current reimbursement criteria for statin treatment by lowering the LDL-C threshold from 100 mg/dL to 70 mg/dL was associated with a reduction in CV events and related costs in South Korea. Changing the reimbursement criteria is likely to have an additional benefit in terms of the clinical and economic burden of CVD in patients with T2DM and therefore requires further consideration by policymakers.

Data availability statement

The datasets presented in this article are not readily available because this study data was extracted and analyzed from the National Health Insurance Service (NHIS) claims database, and additional data may be obtained from a third party (with appropriate authorization approval) but are not publicly available. Requests to access the datasets should be directed to National Health Insurance Sharing Service, https://nhiss.nhis.or.kr/

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Pusan National University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SK: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript; KC: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content; JK: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content; HSS: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

JK is a full-time employee of Viatris Korea Ltd. SK, KC, and HSS received research grant from Viatris Korea Ltd.

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Performance of a pharmaceutical services regionalization strategy policy in Minas Gerais, Brazil: Pre-post analysis from ERAF project

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Background: In 2016, the Brazilian state of Minas Gerais (~20 million people), implemented the ERAF policy ("Regionalization Strategy of Pharmaceutical Services") in an effort to improve medicine procurement and distribution within primary care. We evaluated the impact of the policy on three main goals: price reductions, volume increases, and expansion of therapeutic options.

Methods: We analyzed the procurement data from the Integrated System of Management of Pharmaceutical Services database in 2012 and 2018. We estimated the volume, drug mix, and expenditure indicators for all major therapeutic classes, and, in detail, for cardiovascular and nervous system drugs. We evaluated the expenditure drivers using decomposition analyses.

Results: Overall, the expenditure increased by 14.5%, drug mix almost doubled, while the volume decreased by a third. Cardiovascular and neurological system drugs followed similar patterns. Decomposition analyses showed that prices and drug mix had positive effects while the volume had negative effects, resulting in an overall increase in expenditure.

Conclusion: Our findings suggest that the ERAF policy cannot be considered effective as it has not fulfilled its intended purposes so far. Strategies to address the identified problems and to build a platform for a more sustainable long-lasting policy should be put in place by the government.

KEYWORDS

pre-post study, pharmaceutical policy, medicines, procurement, decomposition analysis

Introduction

The Brazilian National Health Care System (SUS), established more than 30 years ago, covers around 75% of the population for health care services (160 million people) (Brazil, 1998; Andrade et al., 2018). The Pharmaceutical Services based on Primary Care (PHCPS) is a program, part of SUS, funded jointly by the federal, state, and municipal governments. This program was designed to guarantee free access to medicines for patients treated at primary care facilities in Brazil (Costa et al., 2017).

Following the decentralization of health care coverage under SUS, PHCPS is coordinated by municipal governments which are responsible for program management, procurement, distribution of medicines, and provision of care (Brazil, 2017a). Over the past decade, substantial investments in medicine funding have been made in Brazil. The federal government contributed BRL 9.5 billion (~USD 2.9 billion) toward the program between 2010 and 2016 (Vieira, 2018). It is estimated, however, that the growth in expenditures is more pronounced for the municipalities. For example, Cunha (2014) showed an increase in spending of approximately 230% between 2009 and 2012, with the expenditure increasing from BRL 660 million (~USD 379 million) to BRL 2.2 billion (~USD 1.1 billion).

Regardless of these significant financial investments in the PHCPS program, challenges remain with respect to access of medicines for PHCPS patients. Prior studies have suggested deficiencies in the program planning, organization, infrastructure, human resources, and procurement system (Paniz et al., 2016; Luz et al., 2017a, 2017b; Carvalho et al., 2017; Gerlack et al., 2017; Leite et al., 2017; Barbi et al., 2019; Mattos et al., 2019; Soares et al., 2019; Bueno et al., 2021). Problematic sale prices and the failure of suppliers to comply with deadlines and legal documentation requirements have been widespread (CONASS - Conselho Nacional de Secretários de Saúde, 2014; Brazil, 2018a). This has, at least in part, contributed to the resulting shortages of medicines for the population (Helena et al., 2015; Nascimento et al., 2017; Bueno et al., 2021).

In response to these concerns, the state of Minas Gerais implemented a policy known as the Regionalization Strategy of Pharmaceutical Services in Minas Gerais—ERAF (*Estratégia de Regionalização da Assistência Farmacêutica*). This 2016 policy aims to promote technical cooperation between the State and municipal governments to improve medicine procurement and distribution within the PHCPS program. The policy rationale is to promote the purchasing of high-quality products with reliable suppliers obtaining economies of scale at the lowest-possible prices and transaction costs, through a competitive bidding process (SES/MG - Secretaria de Estado de Saúde de Minas Gerais, 2016; Souza Filho et al., 2016). Therefore, under ERAF, the state-level purchasing body is responsible for overarching functions, such as aggregating medication demand from the municipalities, coordinating tenderers eligibility, establishing the contractual instrument (price registration minutes/ata de registro de preços) to record prices, suppliers, and conditions to be applied, and the procurement time frame. Each municipality independently runs their procurement processes and takes buying decisions according to their individual plan and budget, benefiting from the conditions established in the State price registration minute (SES/MG—Secretaria de Estado de Saúde de Minas Gerais, 2016; Souza Filho et al., 2016).

Despite the fact that almost all the municipalities in Minas Gerais joined the ERAF policy (851/853 or 99%), to date, there has not been an evaluation of its impact on the major goals. Therefore, we examined whether the main three goals of the ERAF policy were achieved: reductions in prices, increases in volumes, and an expansion of therapeutic options that were accessed through the PCHPS program.

Methods

Research context and study area

This study is part of the ERAF Project, which is part of a mixed-methods study designed to conduct a retrospective, situational, and prospective evaluation of the ERAF Policy in Minas Gerais. This project included both primary data collection and secondary database analyses and qualitative and quantitative methods. The study focused on the State of Minas Gerais, located in the Southeast, Brazil. Within the country, this state has the highest number of municipalities (n = 853), the second highest population (20,997,560), and the third largest economy as measured by the gross domestic product (IBGE - Instituto Brasileiro de Geografia e Estatística, 2021). Around two-thirds of the disease burden in Minas Gerais is non-communicable diseases, followed by infectious and parasitic diseases, road injuries, and interpersonal violence (DATASUS - Departamento de Informática do SUS, 2021).

Data source

This study is based on data extracted from the Integrated System of Management of Pharmaceutical Services (*Sistema Integrado de Gerenciamento da Assistência Farmacêutica*—SIGAF) database. SIGAF is a health information system designed to collect, store, and manage pharmacoepidemiologic and pharmacoeconomic data from the municipalities in the State of Minas Gerais. SIGAF was established as the standard system for planning and monitoring medicine quantification and procurement for all the adherent municipalities within the ERAF Policy. The Minas Gerais State Secretary of Health manages the system and data are made available to researchers upon request

(SIGAF - Sistema Integrado de Gerenciamento da Assistência Farmacêutica, 2021).

Data regarding medicine procurement in SIGAF from 2012 and 2018 were analyzed. These 2 years were chosen for comparison purposes considering the data availability, accuracy, completeness, and consistency of the database (Elseviers et al., 2016). Registries were extracted on medicine purchases by municipalities, including drug names, dosage form, strength, purchase date, purchase price, and the number of pharmaceutical units (e.g., tablets, capsules, liquid solutions/suspensions, eye/ear drops, inhalers, suppositories, parenteral injections, transdermal patches, etc.).

The World Health Organization's Anatomical, Therapeutic, and Chemical (ATC) system was used to classify the medicines into therapeutic groups (WHOCC - WHO Collaborating Centre for Drug Statistics Methodology, 2021). The drugs were aggregated at different ATC levels: the main anatomical group (ATC first level), therapeutic subgroup (ATC second level), and chemical substance (ATC fifth level). Data on the purchasing prices and expenditures were adjusted for inflation using the Extended National Consumer Price Index (IPCA) produced by the Brazilian Institute of Geography and Statistics (IBGE) with 31 December, 2018 as the reference date (IBGE - Instituto Brasileiro de Geografia e Estatística, 2021). The IPCA value for a given month was divided by the IPCA value for 31 December 2018, resulting in the deflation factor for that month. The prices paid in purchases in that month were then multiplied by the deflation factor to give the inflation-adjusted price for each entry in the SIGAF database (over 350,000 entries). These prices were then multiplied by the respective purchasing quantities and totalized to provide the inflation-adjusted expenditure for each month. Expenditure and unit prices were measured in US Dollars (USD) (1 USD = 3,874 Brazilian Reais (BRL) on 31 December 2018). Purchases were aggregated by volume (number of pharmaceutical units purchased) and expenditure (number of pharmaceutical units purchased multiplied by unit purchase price) for 2012 and 2018.

Pre-post analysis

The pre-post analysis was conducted under three premises: 1) The ERAF Policy is a government intervention directed toward the procurement process of medicines (SES/MG - Secretaria de Estado de Saúde de Minas Gerais); 2) the policy goals are decreasing medicines prices while increasing their acquisition volumes and the expansion of the mix of products (SES/MG - Secretaria de Estado de Saúde de Minas Gerais, 2016); and 3) the understanding of the pharmaceutical spending and its drivers must be considered in formulating and reinforcing pharmaceutical policies (Mousnad et al., 2014). Therefore, two types of analyses were performed as described below. First, the analyses considered all the main anatomical groups (ATC first level) that were purchased, the corresponding chemical substance, and the pharmaceutical products, i.e, all the chemical substances in their different dosage forms and strengths. Following that, the two most relevant therapeutic classes in terms of expenditure and volume—cardiovascular and nervous system drugs, respectively–were evaluated. Microsoft Excel 2007 (Microsoft Corp. United States) was used for the statistical analyses.

1) Medicines profile

For the analysis of the medicine profile, absolute and relative indicators for both 2012 and 2018 were constructed, based on previous studies and guidelines (WHO, 2009; Elseviers et al., 2016; Alves et al., 2018; Barbi et al., 2019; Soares et al., 2019; Carvalho et al., 2021).

Three types of absolute indicators were computed: 1) drug mix (D), based on the total number of chemical substances and pharmaceutical products purchased; 2) drug volumes (Annual Volume—AV) by the total number of units of the pharmaceutical products purchased in millions; and 3) drug expenditures (Annual Expenditure—AE) based on the total costs of the pharmaceutical products purchased in millions. The correspondent accumulated totals were also estimated.

In addition, percentage variations were estimated for D, AV, and AE using Eq. 1:

$$Variation_{(D,AV\,or\,AE)} = \left[\frac{\Sigma 2018 - \Sigma 2012}{\Sigma 2012}\right] * 100 \qquad (1)$$

The distribution of D, AV, and AE by the major classes of medicines was estimated, as well as the percentage of injectable solutions by the pharmaceutical products purchased.

2) Decomposition analysis

The Expenditure Variation Index (E) was estimated by using the decomposition analysis, a technique that detects the driving factors of changes in the pharmaceutical expenditures (Alves et al., 2018; Vieira, 2021).

The analysis is a process of breaking down the expenditure variation into its three components: drug price effects (P), volume effects (V), and drug mix effects (or therapeutic choice or residual effects, D) (Gerdtham et al., 1998; Addis and Magrini, 2002; Alves et al., 2018; Vieira, 2021).

The expenditure variation index (E) was calculated using the following equation:

$$E = PxVxD = \frac{\sum P_1 V_0}{\sum P_0 V_0} X \frac{\sum V_1}{\sum V_0} X \frac{(\sum P_1 V_1 / \sum V_1)}{(\sum P_1 V_0 / \sum V_0)} \qquad (2)$$

In Eq. 2, P1 and P0 represent the average prices, weighted by purchased quantities, for each pharmaceutical product in periods 1 (2018) and 0 (2012). V1 and V0 represent the volumes in

TABLE 1 Major classes of medicines, drug mix, annual volume, and expenditure in 2012 and in 2018 and variations in the period. Minas Gerais, Brazil.

Major classes of medicines[a]	Drug mix								Annual volume (millions)			Annual expenditure USD (millions) [b]		
	Chemical substance			Pharmaceutical products[c]										
	2012	2018	Variation[d] (%)	2012		2018		Total variation[d] (%)	2012	2018	Variation[d] (%)	2012	2018	Variation[d] (%)
				Total	% IS [e]	Total	% IS [e]							
A-alimentary tract and metabolism	8	10	25	9	0	26	15	189	237.67	153.67	−35.34	2.64	3.26	23.54
B-blood and blood forming organs	5	9	80	6	0	14	50	133	82.72	78.12	−5.56	0.58	1.15	96.98
C—cardiovascular system	18	24	33	24	0	47	13	96	816.59	543.50	−33.44	8.85	8.90	0.56
D—dermatologicals	2	8	300	2	0	11	0	450	1.72	0.84	−50.99	0.30	0.34	13.37
G—genito-urinary system and sex hormones	6	6	0	6	33	7	0	17	37.44	0.67	−98.21	1.52	0.24	-84.47
H—systemic hormonal preparations, excl. Sex hormones and insulins	3	6	100	6	0	14	28	133	37.05	51.89	40.08	1.29	1.75	35.49
J—anti-infectives for systemic use	12	13	8	18	11	27	22	50	57.59	40.02	−30.52	4.14	5.21	25.85
M—musculo-skeletal system	3	3	0	6	0	6	0	0	37.84	25.18	−33.45	0.96	0.88	−8.51
N—nervous system	19	24	26	32	6	52	27	63	346.11	256.81	−25.80	7.61	10.51	38.13
P—anti-parasitic products, insecticides, and repellents	6	4	−33	10	0	7	0	-30	9.57	5.38	−43.81	0.37	0.36	−2.75
R—respiratory system	5	8	60	9	0	17	12	89	17.97	15.40	−14.27	1.99	2.15	7.68
S - sensory organs	3	6	100	3	0	7	0	133	0.15	0.09	−41.97	0.13	0.06	−54.88
V—various	1	6	500	1	0	8	75	700	0.10	0.23	123.25	0.05	0.05	4.45
Total	91	127	40	132	5	243	20	84	1,682.51	1,171.80	-30.35	30.43	34.84	14.50

[a]ATC, first level.
[b]1USD, 3.8742 BRL.
[c]Pharmaceutical products including all chemical substances in their different dosage forms and strengths.
[d]Variation = [(∑2018-∑2012)/∑2012]∗100.
[e]IS: Injectable Solution.

10.3389/fphar.2022.953990

periods 1 (2018) and 0 (2012), respectively. Drugs with the same chemical substance but with different dosage forms and strengths were treated as different products.

In this analysis, an expenditure index greater than one means that the expenditures grew, while values equal to or lower than 1 show stability or a decrease in spending, respectively. When analyzing each component (P, V, or D), a similar interpretation can be applied. Therefore, values greater than 1 indicate that the component contributed to the increase in drug spending; values equal to 1 indicate that no impact from the component was observed and values less than 1 indicate that the component contributed to a decrease in drug spending.

Ethical considerations

Ethical approval for the ERAF Project was granted by the Ethics Committee of the René Rachou Institute/Fiocruz (Reference: 3.746.752).

Results

Our study dataset included 801 municipalities in Minas Gerais (94% of all municipalities who adopted the ERAF Policy). In 2012, a total of 1.7 billion pharmaceutical units from 13 different anatomical main groups (ATC first level), 38 therapeutic groups (ATC second level), and 92 chemical substances (ATC fifth level) were purchased by these municipalities. In contrast, in 2018, the total was lower as there were 1.2 billion pharmaceutical units purchased. These purchases, however, were from more ATC sub-groups: 13 different anatomical main groups (ATC first level), 51 therapeutic groups (ATC second level), and 138 chemical substances (ATC fifth level).

Medicines profile

As shown in Table 1, the total inflation-adjusted medicine expenditures were USD 30.4 million (BRL 117.9 million) in 2012 and USD 34.8 million (BRL 135.0 million) in 2018. This represented a 14.5% increase over these 6 years. The drug classes that had the highest increases in expenditure were, blood and blood-forming organs (+97%), nervous system drugs (+38%), and systemic hormonal preparations (+36%).

Along with expenditures, the mix of drugs in terms of the chemical substances purchased also increased. As shown in Table 1, there was a 40% increase between 2012 and 2018, and in terms of pharmaceutical products, i.e, chemical substances in their different dosage forms and strengths, we observed a near doubling in numbers from 132 to 243 products. Dermatologicals and alimentary tract and metabolism classes showed the highest variation (450 and 189%, respectively). In terms of dosage forms, around 20% of the purchases were injections and this rate varied by the therapeutic group. For example, they represented 13% of cardiovascular drugs and 50% of blood and blood-forming organs.

Finally, despite the increase in costs and drug mix, the volume of units purchased between 2012 and 2018 decreased by almost one third, from 1.7 billion to 1.2 billion units (Table 1). Overall, we found reductions in the purchases of 11 out of 13 classes and these reductions varied from -5% to -98%. The most substantial drop in volume was observed for genito-urinary drugs (98%), followed by dermatologicals (51%), and anti-parasitic products (44%).

Figure 1 shows the drug mix, volume, and expenditure indicators for the major classes of medicines for 2012 and 2018. As shown in the figure, purchasing was concentrated largely with a few classes of medicines. For instance, nervous system, cardiovascular, and systemic anti-infectives were responsible for more than half of the drug mix in 2012 and 2018. In terms of volume, cardiovascular, nervous system, and alimentary tract and metabolisms were the main classes (more than 80% of the total). We did find some difference in the classes for expenditures. In 2012, the cardiovascular, nervous system, and systemic anti-infectives were responsible for 67.7% of the total spending. By 2018, nervous system drugs changed position and led the spending, followed by cardiovascular, and systemic anti-infective medications. Together, these three major classes amounted to 70.6% of the financial resources in 2018.

Decomposition analysis

The results of the decomposition analysis by major classes of medicines are presented in Table 2. Overall, the analysis suggests negative volume effects, while drug prices and drug mix had positive effects. In sum, this resulted in the increased expenditure we observed in 2018 compared to 2012. The expenditure index was positive for nine of the 13 major therapeutic classes, and the impacts largely arose from changes in prices and drug mixes. We observed positive volume effects for only two classes: systemic hormonal preparations and various (ATC V).

Cardiovascular drugs

The overall findings for the cardiovascular class are presented in Table 3. Seven therapeutic subgroups of cardiovascular drugs were purchased in both 2012 and 2018. This corresponded to a volume of around 1.4 billion units and a total expenditure of US$17.8 million (BRL 69.0 million). While the mix of

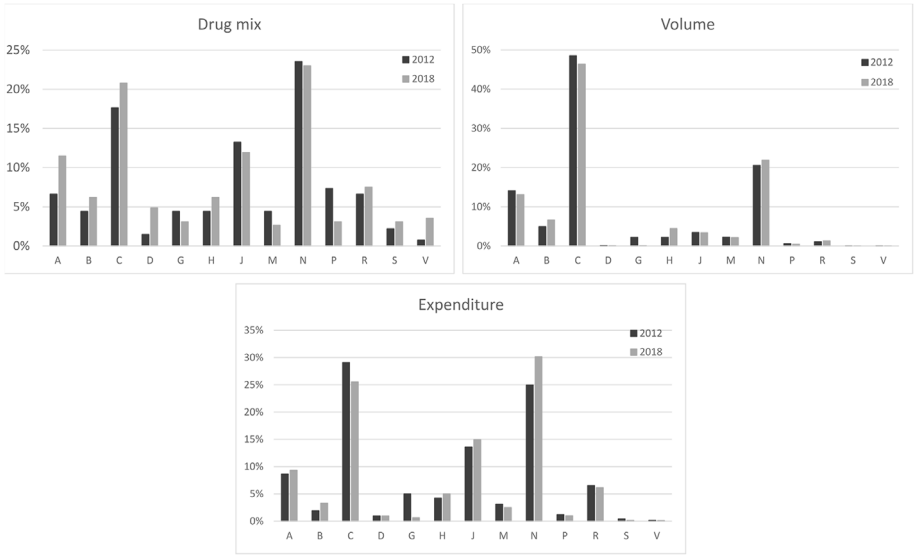

FIGURE 1
Distribution of the drug mix, volume, and expenditure by the major classes of medicines in 2012 and in 2018. Minas Gerais, Brazil.

TABLE 2 Results of the decomposition analysis by the major classes of medicines. Minas Gerais, Brazil, 2012-2018.

Major classes of medicines[a]	Drug price effects (P)	Volume effects (V)	Drug-mix effects (D)	Expenditure index (E)[b]
A—alimentary tract and metabolism	1.37	0.65	1.39	1.23
B—blood and blood-forming organs	1.31	0.94	1.59	1.97
C—cardiovascular system	0.98	0.66	1.55	1.01
D—dermatologicals	1.13	0.49	2.65	1.47
G—genito-urinary system and sex hormones	0.22	0.02	38.69	0.15
H—systemic hormonal preparations, excl. Sex hormones and insulins	1.33	1.40	0.88	1.65
J—anti-infectives for systemic use	1.65	0.69	1.09	1.25
M—musculo-skeletal system	1.17	0.66	1.16	0.91
N—nervous system	1.36	0.74	1.31	1.32
P—anti-parasitic products, insecticides, and repellents	1.18	0.56	1.42	0.94
R—respiratory system	1.18	0.85	1.12	1.13
S—sensory organs	1.10	0.58	0.70	0.45
V—various	0.53	2.23	0.89	1.05
TOTAL	1.20	0.70	1.41	1.18

[a]ATC, first level.
[b]$E = P \times V \times D = \frac{\sum P_1 V_0}{\sum P_0 V_0} X \frac{\sum V_1}{\sum V_0} X \frac{(\sum P_1 V_1 / \sum V_1)}{(\sum P_1 V_0 / \sum V_0)}$

cardiovascular drugs doubled between 2012 and 2018, volumes dropped by 33% and expenditures remained similar.

In terms of specific therapeutic groups, beta blocking agents, agents acting on the renin–angiotensin system (RAS), and cardiac therapy accounted for almost 60% of the drug mix in 2012. In 2018, the drug mix was dominated by cardiac therapy and beta-blocking agents. In terms of volume, three groups were most relevant in this order: RAS-acting agents, diuretics, and beta-blocking agents. These groups corresponded to 80 and 73% of the volume purchased in 2012 and 2018, respectively. In terms

TABLE 3 Cardiovascular and nervous system groups, drug mix, annual volume, and expenditure in 2012 and in 2018 and variations in the period. Minas Gerais, Brazil.

Therapeutic group[a]	Drug mix						Annual volume (millions)			Annual expenditure USD (millions)[b]		
	Chemical substance			Pharmaceutical products[c]								
	2012	2018	Variation[d] (%)	2012	2018	Variation[d] (%)	2012	2018	Variation[d] (%)	2012	2018	Variation[d] (%)
C—Cardiovascular system												
C01—Cardiac therapy	3	7	167	4	12	200	26.09	12.50	−52.11	0.51	0.77	52.78
C02—antihypertensives	2	3	50	3	5	67	22.48	15.46	−31.20	1.16	1.01	−13.10
C03—diuretics	3	3	0	3	5	67	185.68	106.13	−42.84	0.99	1.16	17.64
C07—beta blocking agents	4	4	0	5	12	140	133.95	98.61	−26.38	2.62	2.84	8.18
C08—calcium channel blockers	2	3	50	2	5	150	51.05	52.65	3.12	0.32	0.44	38.47
C09—agents acting on the renin–angiotensin system	3	3	0	5	5	0	353.29	193.20	−45.31	2.53	1.50	−40.48
C10—lipid modifying agents	1	1	0	2	3	50	44.05	64.95	47.44	0.73	1.18	60.77
Total	18	24	33	24	47	96	816.59	543.50	−33.44	8.85	8.90	0.56
N—Nervous system												
N01—anesthetics[e]	0	4	-	0	6	-	0	0.01	-	0	0.02	-
N02—analgesics	2	3	50	3	6	100	52.80	33.13	−37.25	0.86	0.97	12.33
N03—antiepileptics	5	5	0	9	12	33	113.48	87.79	−22.64	3.00	3.24	7.96
N04—anti-parkinson drugs	3	3	0	4	5	25	20.13	18.83	−6.49	0.73	2.25	207.24
N05—psycholeptics	4	5	25	10	14	40	78.49	40.05	−48.97	1.29	1.68	30.28
N06—psychoanaleptics	5	4	−20	6	9	50	81.21	76.99	−5.19	1.72	2.35	37.12
Total	19	24	26	32	52	63	346.11	256.81	−25.80	7.61	10.51	38.13

[a]ATC, second level.
[b]1USD, 3.8742 BRL.
[c]Pharmaceutical products including all chemical substances in their different dosage forms and strengths.
[d]Variation = [(∑2018-∑2012)/∑2012]∗100.
[e]N01-anesthetics were only acquired in 2018.

10.3389/fphar.2022.953990

TABLE 4 Results of the decomposition analysis by cardiovascular and nervous system groups. Minas Gerais, Brazil, 2012–2018.

Therapeutic group[a]	Drug price effects (P)	Volume effects (V)	Drug-mix effects (D)	Expenditure index (E)[b]
C—cardiovascular system				
C01—cardiac therapy	2.77	0.48	1.15	1.52
C02—anti-hypertensives	0.60	0.55	2.16	0.72
C03—diuretics	1.42	0.57	1.45	1.17
C07—beta-blocking agents	0.75	0.74	1.97	1.08
C08—calcium channel blockers	1.26	1.03	1.07	1.39
C09—agents acting on the renin–angiotensin system	0.82	0.55	1.34	0.60
C10—lipid-modifying agents	1.01	1.47	1.08	1.60
Total	0.98	0.66	1.55	1.01
N—Nervous system [c]				
N02—analgesics	1.85	0.63	0.97	1.12
N03—antiepileptics	1.01	0.77	1.42	1.12
N04—anti-parkinson drugs	0.82	0.93	3.49	2.69
N05—psycholeptics	1.16	0.51	1.55	0.92
N06—psychoanaleptics	1.39	0.95	1.06	1.40
Total	1.36	0.74	1.31	1.32

[a]ATC, second level.
[b] $E = P \times V \times D = \frac{\sum P_1V_0}{\sum P_0V_0} X \frac{\sum V_1}{\sum V_0} X \frac{(\sum P_1V_1/\sum V_1)}{(\sum P_1V_0/\sum V_0)}$
[c]N01-anesthetics were only acquired in 2018 and because of that there is no decomposition analyses for this group.

of expenditures, beta-blocking agents, RAS-acting agents, and anti-hypertensives, in this order, accounted for 71.2% of the total (USD 6.31 million) in 2012. In 2018, lipid-modifying agents replaced anti-hypertensives for third position.

The decomposition analysis results for cardiovascular medications are presented in Table 4. We found that expenditures increased for five therapeutic subgroups, while they decreased for two. Of the underlying factors driving these changes, drug mix had positive effects for all the seven subgroups, while price had positive effects for four. Volume increased for only lipid-modifying agents and calcium channel blockers. The most pronounced positive effect of price (p = 2.77) and negative effect of volume (V = 0.48) for the expenditure index was observed for cardiac therapy drugs, while drug mix had the strongest effect on anti-hypertensives (D = 2.16).

Nervous system drugs

Table 3 also shows the breakdown of therapeutic groups for nervous system drugs, where six different therapeutic groups were purchased. These purchases were for a volume of 603 million pharmaceutical units and a total expenditure of USD 18.1 million (BRL 70.1 million). Anti-epileptics, psychoanaleptics, and psycholeptics were responsible for nearly 80% of both the total volume purchased and total expenditures. These drugs also accounted for 80% of the drug mix, with a slightly different ordering: psycholeptics, psychoanaleptics, and anti-epileptics, respectively.

Across the subgroups of nervous system drugs, our decomposition analysis showed that the expenditure index was positive for four subgroups and negative for one subgroup (Table 4). Prices also increased for the four subgroups (analgesics, anti-epileptics, psycholeptics, and psychoanaleptics), and this increase was most pronounced for analgesics (p = 1.85). At the same time, volumes decreased across all of the subgroups. Psycholeptics had the greatest reduction in volume (V = 0.51). Changes in the drug mix also had positive effects on the expenditures for four subgroups, particularly anti-Parkinson drugs (D = 3.49).

Discussion

In general, many pharmaceutical policies are intended to improve the provision and use of medicines (Morrow, 2015). The ERAF policy was launched as a state-level policy to improve medicine procurement within the PCHPS program in Minas Gerais. This policy established a new decentralized procurement system, in which decision making, responsibility, and control was moved from a centralized

system to municipal managers starting in 2016 (SES/MG - Secretaria de Estado de Saúde de Minas Gerais, 2016). This decentralization in the public procurement process is not new and is supported by the theory that local managers are more familiar with their programmatic needs, and thus can increase the efficiency of purchasing processes (McCue et al., 2000). It was hoped that the policy would lead to the provision of quality medicines at public facilities, in the right quantities, at the right time (Fausto et al., 2017, Paim et al., 2011, Brazil, 2006a, b).

Our evaluation focused on the operational goals of the policy: price reductions, volume increases, and drug mix expansions. Overall, medicine expenditure increased by 14.5% after ERAF implementation while the quantities purchased decreased 30%. The only indicator showing an alignment with the policy goals was the drug mix.

It is important to note, that just the three therapeutic classes—nervous system, cardiovascular, and systemic anti-infectives—accounted for 70% of the total financial resources invested by the municipalities. This suggests a discrepancy between purchasing and the PHCPS' goal of covering treatments for various conditions. Notably, this concentration leaves comparatively little spending for major causes of diseases, including diabetes mellitus, chronic respiratory conditions, parasitic diseases, iron-deficiency anemia, and gynecological conditions (GBD 2016 Brazil Collaborators, 2018). Importantly, several of these diseases with less expenditure focus are among the leading non-communicable causes of mortality in Brazilian municipalities (Cardoso et al., 2021), creating inequity in access to medicines. Our results are in line with a nationwide survey with a representative sample of 12,725 adults aged 20 years or more, which have shown that free access to cardiovascular treatments was favored, while those medicines acting on the respiratory system were more often paid out-of-pocket (Tavares et al., 2016).

One of the main arguments favoring the implementation of the ERAF policy was to enhance the quantification process, avoiding risks of shortages of specific treatments and wastages, problems pointed out by a report from the State Audit Court in 2013 (TCE/MG - Tribunal de Contas do Estado de Minas Gerais, 2013). Indeed, several studies have highlighted that about half of the essential medicines were available at PHCPS in Minas Gerais (Barbosa et al., 2021, 2017; Luz et al., 2017a; Lima et al., 2019). Our findings, however, do not support the rationale that decentralization of quantification to municipalities would improve the process since there was a significant drop in volume associated with the investments in few therapeutic classes. Instead, our findings corroborate the studies based on data collected after ERAF implementation showing that low availability of medicines has continued to impact medicine access to primary care patients (Nascimento et al., 2020; Bueno et al., 2021).

Considering that the ERAF policy was established to better coordinate procurement in an effort to reduce costs, our findings do not support its success in that regard. The decomposition analysis confirmed a spending growth in 2018 in comparison with 2012. Expenditure drivers were the increase-in-the-price component by 20% and in the drug mix by 41%, whereas the quantity component decreased by 30%. The same behavior for each therapeutic class was observed individually: positive effects of the price and of the drug mix, and negative effects of volume. These findings indicate that, from 2012 to 2018 there was a shift toward more expensive products and higher prices were paid for the existing ones. This likely contributed to the lower volumes purchased, considering the annual cap on the PHCPS budget (Brazil, 2017b).

Medicines costs are rising faster worldwide. Although Brazil implemented pharmaceutical policies for more than 20 years (Brazil, 2004,1998) on top of a large body of legislation and guidelines around public procurement of medicines, transparency, accountability, and functioning of the PHCPS (Brazil, 2012, 2017a, 2017c; Kohler et al., 2015; Rida et al., 2017; Bermudez et al., 2018), the evidence does not support their effectiveness in reducing prices and increasing medicine availability (Brazil, 1998; Kohler et al., 2015; Tavares et al., 2016; Nascimento et al., 2017; Bueno et al., 2021).

Lack of governance, insufficient monitoring, poor implementation of regulations, along with a restricted number of producers and suppliers in the pharmaceutical market are possible reasons for the failure of the pharmaceutical pricing policies, especially in developing countries (Kohler et al., 2015; Rida et al., 2017). Additionally, pricing interventions in healthcare systems where the government procures medicines are limited to applying competitive bidding for a restricted list of medicines. Furthermore, robust generic substitution policies are not usually in place, neither are policies focusing on innovation and strategies to stimulate the local pharmaceutical industry (Gray, 2015). It is reasonable to assume that a combination of these factors influences the price increase observed in our study. Drug prices may also have increased due to the ERAF requirement that states that deliveries are to be made to municipalities rather than to the state's central warehouse.

The observed increase in drug mix likely resulted from the ERAF-initiated change to municipalities following the Brazilian national list of essential medicines–RENAME–as the reference list (SES/MG - Secretaria de Estado de Saúde de Minas Gerais, 2016), which is more comprehensive than the prior municipal lists (Assunção et al., 2013). Even here, however, the observed rise of the drug mix was uneven across therapeutic classes and resulted more from the number of pharmaceutical products rather than chemical substances.

Our further analyses allowed us to enhance our understanding about the spending patterns on cardiovascular and nervous system drugs, groups that accounted for 55% of the expenditure both in 2012 and in 2018.

The cardiovascular group includes anti-hypertensives, cardiac therapy, beta-blocking agents, RAS-acting agents among others, while the nervous system group contains, for example, analgesics, anxiolytics, antidepressants, hypnotics, and sedative drugs. Thus, the relevance of these groups among all the therapeutic groups procured was, at a certain degree, predictable, since they incorporate drugs to treat a wide variety of prevalent illnesses and acute conditions. In Minas Gerais, for instance, a cross-sectional study with a representative sample of primary care patients aged 18 years or older in 104 municipalities found that hypertension (50.3%), dyslipidemia (31.2%), depression (28.0%), and arthritis/arthrosis or rheumatism (20.4%), in this order, were the most prevalent diseases (Moreira et al., 2020).

Although the expenditure on the cardiovascular group remained the same in 2018 compared to 2012, of particular note is the significant decrease in the volume and expansion of the drug mix. Noteworthily, the growth in the drug mix was due to changes not in terms of incorporation of novel cardiovascular therapies, but regarding pharmaceutical products, i.e., it was purchasing the same drugs in different dosage forms and strengths. This was particularly relevant for beta-blocking agents, drugs acting on the renin–angiotensin system (RAS), lipid-modifying agents, and diuretics. For example, almost 50% of the spending was centralized on beta-blocking agents and RAS-acting agents, and the main changes on the drug mix in 2018 were the purchase of products such as carvedilol tablets (6.25 and 25 mg), metoprolol tablets (25 and 100 mg), and propranolol tablet 10 mg among the beta-blocking agents, and enalapril tablet 5 mg among the RAS drugs.

The marked reduction in the volume of cardiovascular drugs purchased may significantly compromise millions of patients' well-being and quality of life. Taking hypertension as an example and considering the risks of heart, brain, and kidney diseases (Hevesi et al., 2018; Volpe and Savoia, 2018) that accompany patients if untreated, the Brazilian guideline recommends anti-hypertensives, diuretics, beta-blocking agents, calcium channel blockers, and RAS-acting agents for the treatment (Brazil, 2013). Our findings highlighted that, except for calcium channel blockers which had a quite small increase in the volume in 2018 compared to 2012, all the other groups had lessened their quantities by figures ranging from 26 to 45%. These results are consistent with (Mengue et al. (2016)), who found that only 56% of patients could access their anti-hypertensive treatment through the National Health Care System (SUS).

With respect to nervous system drugs, the expenditure increased by 40% and this finding contrasts with our previous study on neuropsychiatric drug procurement in Minas Gerais (Carvalho et al., 2021). Unlike the investigation that included several institutions and purchases made by the Minas Gerais state-level management, this study focused only on medicines procured within the PHCPS program, which may explain the difference in the results.

The expenditure drivers were price and drug mix increases (36 and 31%, respectively) and volume decrease (26%), which means that the municipalities are paying more for less and choosing products that are, on average, more expensive. As in cardiovascular drugs, the mix did not expand due to the inclusion of new therapies, but mostly because of purchasing different dosage forms and strengths for the existing drugs. This was the case, for instance, of anti-epileptics (e.g., addition of phenytoin 50 ml/ml injection, phenobarbital 100 mg/ml injection, sodium valproate 500 mg tablet, and carbamazepine 400 mg tablet); psycholeptics (e.g. chlorpromazine 5 mg/ml injection, diazepam 5 mg/ml injection, and haloperidol 1 mg tablet); and psychoanaleptics (e.g., amitriptyline 75 mg tablet, clomipramine 10 mg tablet, nortriptyline 75 mg capsule, and nortriptyline 10 mg capsule).

Anti-Parkinson drugs presented the highest expenditure variation (207%) and the most significant effect on expenditure was caused by the drug mix (increase by a factor of 3.5). The findings on anti-Parkinson drugs are also consistent with the results from our previous study (Carvalho et al., 2021), where we observed an upward trend in pharmaceutical spending on these drugs. In that study, the drug mix also played a leading role in the expenditure, although not exclusively (in that case, the volume was the strongest factor).

The changes in the drug mix we observed in this investigation were due to pharmaceutical products (e.g., incorporation of biperiden 5 mg/ml injection) and also to the purchase of greater volumes of more expensive products, such as levodopa 200 mg plus benzerazide 50 mg, again, another common finding with our previous study (Carvalho et al., 2021). These products were responsible for 20% of the volume purchased in 2018. Although biperiden injection is classified for primary care use at the RENAME (Brazil, 2018b), this product is not recommended at the Brazilian national protocol for Parkinson disease (PD) (Brazil, 2017d), which sets the biperiden tablet (2 and 4 mg) for the initial treatment phase of the disease. Levodopa in combination with benzerazide is at RENAME and at the official guideline, which supports its effectiveness in the symptomatic control of PD (Brazil, 2017d).

Strengths and limitations

To the best of our knowledge, this is the first study examining the performance of the ERAF policy considering its goals of price reduction, volume increase, and drug mix expansion through the PCHPS program. Some limitations, however, deserve consideration. We opted to measure volumes in units of the drugs purchased instead of DDDs because several drugs registered in the SIGAF database were not classified in the ATC-DDD system, thus limiting some comparisons. Although we outlined several pharmaceutical

products to discuss the study findings, our unity of analysis was the aggregated therapeutic classes purchased, not the individual drugs. Furthermore, we could only estimate direct drug expenditures (volume x price) and no other costs to the healthcare system, for instance, such as the costs associated with distribution and storage. Nevertheless, our study relied on comprehensive data from SIGAF from almost every municipality in Minas Gerais (only 5.8% of non-differentiated losses), meaning our external validity and generalizability are likely very high.

Implications for policy and practice

The evidence provided by this study suggests some avenues to develop a more sustainable long-term policy in this area. First, the adoption of the Brazilian national medicines list–RENAME–could be reconsidered since this list, from 2012 on, has changed its purpose from indicating essential medicines to specifying medicines financed by the public system (Osorio-de-Castro et al., 2018). Second, the option for a more limited number of drugs selected should lead to a better supply at lower costs (Management Sciences for Health, 2012). Third, employing evidence-based sources for medicine selection, such as scientific literature and national and international therapeutic guidelines and protocols could also support the process (Management Sciences for Health, 2012). Finally, to reduce the risk of treatment non-adherence, it would be preferable to select, whenever possible, oral pharmaceutical formulation instead of injections, as they are more convenient and preferred routes of administration by patients (Stewart et al., 2016).

Investments could be made, by the municipalities, to improve the quantification process, which should be combined with monitoring and periodic reviews by state-level managers and policymakers (Management Sciences for Health, 2012).

Regarding prices, our results suggest that more attention should be paid to the bidding processes, and policies focusing on increasing the value for money (UK-Government, 2020), i.e., providing medicines of appropriate quality and effectiveness at the least possible cost. Contracting authorities in the municipalities should ensure regular feedback to state managers about the suppliers' performance, creating a monitoring network to exclude those that do not have the capability to deliver quality products on time.

Conclusions

This study evaluated the performance of a new and unique pharmaceutical policy in Brazil, implemented by one of its most populous states. Overall, our findings suggest that the intervention proposed by the Minas Gerais Government–the ERAF policy–cannot be considered effective regarding its outputs, as it has not made an empirical contribution to the achievement of the intended purposes so far (OECD - Organisation for Economic Co-operation and Development, 2009).

Running a public healthcare system of this magnitude is challenging, especially considering the goal of supplying medicines free of charge to the population. The ERAF policy can be revised to deal with the drawbacks we identified to maximize procurement practices. The experiences and lessons learned in Minas Gerais are useful for countries where health systems aim to allow appropriate and sustainable access to medicines to their populations.

Data availability statement

The dataset supporting this article can be made available upon request after approval by the corresponding author.

Ethics statement

The ERAF Project was reviewed and approved by the Ethics Committee of the René Rachou Institute of the Oswaldo Cruz Foundation (Fiocruz-Minas) (Reference: 3.746.752). The participants provided their written informed consent to participate in the project. This study, particularly, analysed only medicines data from secondary database and did not involve human subjects.

Author contributions

TL was responsible for funding acquisition, study conception, design, manuscript writing, and final manuscript review and contributed to the data analysis and interpretation. IM contributed with database cleaning and preparation. AC, IM, and BC contributed to the data interpretation and critically revising the manuscript for intellectual content. JA and ML were responsible for data analysis and interpretation and for critically revising the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

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Conflict of interest

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

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Economic burden of opioid misuse focused on direct medical costs

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Background: Since their development, synthetic opioids have been used to control pain. With increased opioid use, problematic opioid prescription has also increased, resulting in a growing economic burden. However, there is a paucity of research studies on the economic burden of prescription opioid misuse in Asia, especially South Korea.

Objectives: To estimate the incremental economic burden of prescription opioid misuse for the South Korean population.

Methods: The National Health Insurance Service-National Sample Cohort database, covering 2% of the South Korean population between 2010 and 2015, was analyzed. Outpatients aged 18 or older who took one or more prescription opioids were selected. Based on their opioid prescription patterns, patients were classified into opioid misuse and non-misuse groups. The direct medical costs per person per year (PPPY) and the incremental economic burden of the opioid misuse group were explored using an exponential conditional model with a suitable distribution and log link function. All analyses were performed using SAS® Enterprise Guide version 9.4, and $p < 0.05$ was considered statistically significant.

Results: The number of patients who had ≥1 opioid prescription was 345,020 including 84,648 (24.53%) in the opioid misuse group and 260,372 (75.47%) in the non-misuse group. The adjusted mean direct medical costs PPPY were estimated to be USD 401 for the opioid misuse group, which is 1.49 times significantly higher than that for the non-misuse group ($p < 0.0001$). The incremental economic burden of the opioid misuse group in the South Korean population was estimated to be approximately USD 0.52 billion for the period 2010–2015.

Conclusion: Prescription opioid misuse was significantly associated with the increased economic burden. Along with proper policies for using opioids, it is necessary to monitor opioid prescription patterns to prevent opioid misuse and reduce the related economic burden.

KEYWORDS

opioid, opioid misuse, opioid abuse, economic burden of disease, burden of disease (BOD)

Introduction

For decades, opioids have been used all over the world to manage pain. Since the identification of various opioid receptors led to the development of synthetic opioids, their prescription has steadily increased (Cherny, 1996; Sullivan et al., 2008; Trescot et al., 2008). Opioids are effective analgesic drugs that do not have a ceiling effect—a pharmacological phenomenon in which a drug's effect reaches a plateau; however, this attribute can lead to adverse effects including sedation, nausea, vomiting, and respiratory depression (Trescot et al., 2008). In addition, with the increased use of opioids in pain management, problematic prescription opioid incidents such as overdose, dependence, and addiction have also increased (Vowles et al., 2015). Furthermore, in 2014, the reported total number of non-medical prescription opioid users was 10.3 million (Abuse and Administration, 2014). In terms of non-medical prescription opioid use, the rate of heroin use increased by approximately 140% between 2002 and 2004 and the period of 2011–2013 (Compton et al., 2016). The rate of death from prescription opioid overdose approximately quadrupled between 2000 and 2014. From 2019 to 2020, the rate increased by over 16% (CDC National Center for Health Statistics, 2021).

Prescription opioid misuse and abuse create not only public health issues, including overdose and death, but also a growing economic burden globally (Meyer et al., 2014). Birnbaum et al. (2006) and Birnbaum et al. (2011) revealed that healthcare costs related to prescription opioid abuse in the US rose from $2.6 billion in 2001 to $25.0 billion in 2007. While the authors investigated the overall costs of opioid abuse in the US, some studies analyzed the average costs per person adjusting for differences in patient demographics. After matching the opioid abuse group with the non-abuse group, the average cost for each group was calculated (White et al., 2005). However, they did not appropriately manage the skewness of cost data, which could lead to incorrect average cost estimates, nor did they examine the relationship between costs and patient characteristics.

In South Korea, health insurance is a universal public insurance system covering over 97% of the entire population (Seong et al., 2017; Kwon, 2009). Owing to this health insurance system, access to healthcare in South Korea is easier than in other Organization for Economic Co-operation and Development (OECD) member nations. The number of doctor consultations per person in Korea is the highest among OECD member nations (14.7 in Korea vs. 5.9 in OECD nations on average in 2020) (OECD.Stat, 2022). Access to opioids is no exception. In Korea, all forms of opioids can only be obtained *via* prescription under the Narcotics Control Act (Korean Law Information Center, 2022). Despite strong regulations, the rate of opioid prescription has increased. According to South Korean studies on prescription patterns, the opioid prescription rate per 1,000 persons almost doubled from 347.5 in 2009 to 531.3 in 2019 (Cho et al., 2021). Specifically, cases of opioid prescription have soared since 2010 (Kim et al., 2022). However, there is a paucity of evidence on the economic burden of opioid prescription use in Asia, including South Korea. Moreover, to the best of our knowledge, no studies have been conducted to estimate the size of opioid abuse and its associated economic burden in Asia.

Therefore, using econometric models, our study estimated the total economic burden of prescription opioid misuse adjusting for non-cancer patients considering the skewness of cost data and seeks to fill the evidence gap in the Asian population. We also estimated the incremental costs related to opioid misuse in comparison with non-misuse in South Korea.

Materials and methods

Data source and study population

Data were drawn from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database version 2.0 from 2002 to 2015. The NHIS-NSC is a representative database that covers 2.2% of the South Korean population (Lee et al., 2017). The study period ranged from 1 January 2002 to 31 December 2015 (Figure 1). The eligible study population comprised outpatients aged 18 years or older who took one or more prescription opioids between 1 January 2010 and 1 January 2015. Patients with cancer diagnoses who had ICD-10 codes C00–C97, except C44 [other malignant neoplasms of the skin], were excluded from our study during the entire study period. Prescription opioids were defined based on the US Drug Enforcement Administration's Schedule II–IV opioids and the Korean guideline's category; they can be enumerated as follows (Sullivan et al., 2008; Kim et al., 2017; Carey et al., 2018; Kim et al., 2021): buprenorphine, codeine, dihydrocodeine, fentanyl, hydromorphone, hydrocodone, meperidine, morphine, oxycodone, pentazocine, and tramadol.

The eligible study population was classified into opioid misuse and non-misuse groups based on the patients' opioid prescription patterns. Since the definition of opioid misuse is not straightforward using claims data, the most widely used indicators for opioid misuse are opioid shopping and overlapping prescriptions (Sullivan et al., 2008; Yang et al., 2015; Kim et al., 2017; Carey et al., 2018; Kim et al., 2021). Yang et al. (2015) found that opioid prescription patterns—more than four different pharmacies within 90 days—was significantly associated with an increased risk of overdose. The index date was defined as the first date of opioid prescription between 1 January 2010 and 1 January 2015. The opioid misuse group was defined as outpatients who met at least one of the following criteria prior to the index date within 1 year: 1) they visited more than four different hospitals to obtain prescription opioids during any 90-day period (Sullivan, 2013; Yang et al., 2015; Carey et al., 2018;

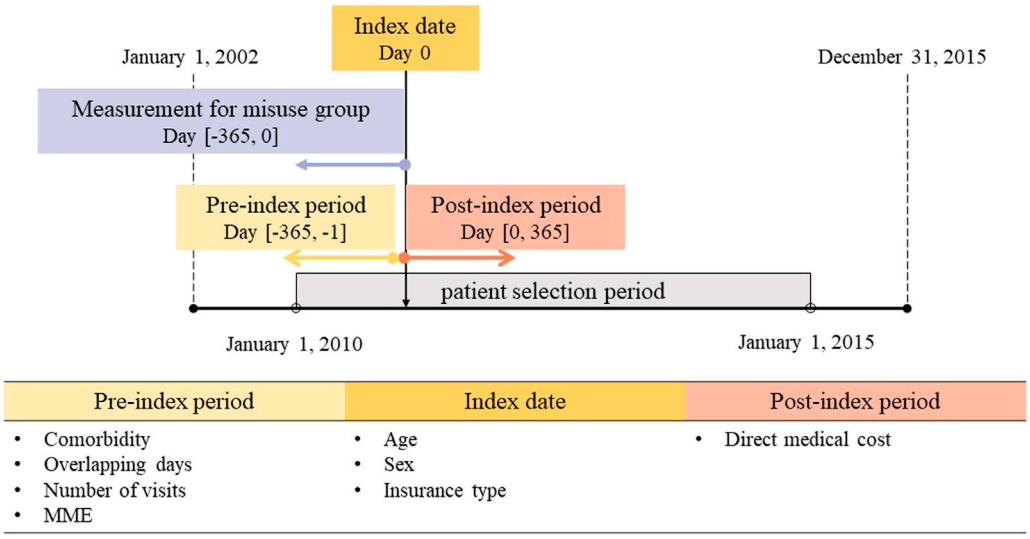

FIGURE 1
Study scheme. MME, morphine milligram equivalent.

Kim et al., 2021) and 2) they had prescriptions with more than 25% overlapping days with the next prescription for opioids containing the same active ingredient (Yang et al., 2015; Kim et al., 2021). The non-misuse group was defined as the cohort of opioid users that did not fulfill the aforementioned criteria.

Covariates and outcome measures

The baseline characteristics included sex, age, insurance type, the Charlson comorbidity index (CCI) score, the mean overlapping days with the next prescription, the mean number of opioid-related visits by outpatients, and the morphine milligram equivalent (MME). MME is a measurement that converts an opioid dose to its equivalent morphine dose. The CCI score, mean overlapping days, and mean number of visits were evaluated in the pre-index period 1 year before the index date, whereas the others were assessed on the index date. In South Korea, there are two types of health insurance, and the ratio of the co-payment depends on patients' income levels: the National Health Insurance (NHI), in which the co-payment ranges from 30% to 60%, and the Medical Aid Program, available for people with low incomes, in which the co-payment ranges from 10% to 30% (Chun et al., 2009). The major diagnoses for the misuse group were examined according to the total medical cost and frequency.

We explored the direct medical costs per person per year (PPPY) as the outcomes. These were assessed by analyzing opioid prescriptions during 1 year after the index date. To avoid overestimation of outcomes, prescriptions accompanied by surgery were excluded. This was because opioids are essential during surgery for both the opioid misuse and non-misuse groups. For both groups, the direct medical cost was comprised of outpatient costs and hospitalization costs. Outpatient costs were the sum of the outpatient visit costs and the outpatient drug costs. Outpatient visit costs included the doctors' visiting costs and the cost of drugs that patients were administered at the institutions. Outpatient drug costs included the total opioid and non-opioid costs charged at pharmacies. Hospitalization costs included all expenses for services provided during hospitalization, such as room rates, medical imaging fee, laboratory test fee, nursing fee, and drug costs. All costs were the incurred costs paid by the NHIS and patients.

Mean direct medical costs PPPY were estimated for each group and were used to calculate the incremental costs PPPY. The incremental economic burden of the opioid misuse group in the South Korean population during the period 2010–2015 was calculated using the following equation:

$$\begin{aligned}&\textit{The incremental economic burden of opioid misuse in the South Korean population in } 2010-2015\\ &= (\textit{The adjusted mean incremental cost per person per year of the opioid misuse group})\\ &\times (\textit{the prevalence of opioid misuse in the NHIS}\text{–NSC population in } 2010-2015)\\ &\times (\textit{the average total number of South Korean population in } 2010-2015). \qquad (1)\end{aligned}$$

The prevalence of opioid misuse was calculated by dividing the number of patients in the misuse group by the total number of the NHIS-NSC population from 2010 to 2015. Data on the South Korean population were obtained from the Korean Statistical Information Service (Korean Statistical Information Service, 2021).

TABLE 1 Baseline characteristics of the study population.

Characteristic	Misuse (n = 84,648) No. (%) or mean (SD)	Non-misuse (n = 260,372) No. (%) or mean (SD)	p-value[a]
Female	51,156 (60.43)	141,457 (54.33)	<0.0001
Age, years	54.03 (15.30)	44.49 (15.38)	<0.0001
Age group			<0.0001
18–29 years	5,718 (6.76)	49,025 (18.83)	
30–39 years	10,044 (11.87)	55,694 (21.39)	
40–49 years	15,838 (18.71)	59,362 (22.80)	
50–59 years	20,839 (24.62)	51,807 (19.90)	
60–69 years	17,132 (20.24)	26,544 (10.19)	
70–79 years	12,250 (14.47)	14,196 (5.45)	
≥80 years	2,827 (3.34)	3,744 (1.44)	
Insurance			<0.0001
NHI program	80,034 (94.55)	253,689 (97.43)	
Medical Aid program	4,614 (5.45)	6,683 (2.57)	
CCI score[b]	0.67 (0.89)	0.42 (0.72)	<0.0001
Overlapping days[b]	0.81 (1.64)	0.01 (0.10)	<0.0001
No. of outpatient visits[b]	26.01 (39.92)	5.19 (8.34)	<0.0001
MME, mg	27.85 (112.68)	16.63 (63.00)	<0.0001
MME group			<0.0001
20 mg >	51,232 (60.52)	235,478 (90.44)	
20–49 mg	28,581 (33.76)	23,157 (8.89)	
50–89 mg	3,090 (3.65)	663 (0.25)	
≥90 mg	1,745 (2.06)	1,074 (0.41)	

SD, standard deviation; CCI, Charlson comorbidity index; MME, morphine milligram equivalent; NHI, National Health Insurance.
[a]The chi-squared test was used for categorical variable analysis, and both the t-test and Wilcoxon rank sum test were used for continuous variable analysis.
[b]These were evaluated in the pre-index period.

Statistical analysis

To compare the baseline characteristics between the opioid misuse and non-misuse groups, the chi-squared test was used for categorical variables, and the student's t-test and Wilcoxon rank sum test were used to for continuous variables. To consider the property of cost data characterized by the positively skewed distribution, we first confirmed the normality using a histogram and the Kolmogorov–Smirnov test. The mean cost was estimated using an exponential conditional model (ECM), which has the structure of a generalized linear model (GLM) (Manning and Mullahy, 2001). The GLM can estimate the cost with a suitable distribution and link function and can identify the association between covariates and cost. The suitable distributions for cost were selected based on a modified Park test. The Akaike information criterion (AIC) was used to compare regression models in terms of goodness of fit (Manning and Mullahy, 2001; Barber and Thompson, 2004; Nixon and Thompson, 2004). In the case of including a zero value, we selected the GLM with the Tweedie distribution and log link function (Lord et al., 2005;Kurz, 2017). When modeling the GLM, the following covariates were included: age, sex, insurance type, CCI score, comorbid diseases, and MME.

Costs were recorded in Korean won (KRW), which was converted to United States dollar (USD) using the average 2020 exchange rate (1 USD = 1,180.27 KRW). All analyses were performed using SAS® Enterprise Guide version 9.4, and the statistical significance was set at $p < 0.05$. The Institutional Review Board of Pusan National University granted an exemption from an Institutional Review Board review for this study (PNU IRB/2020_76_HR).

Results

Baseline characteristics

Of the NHIS-NSC population from 2010 to 2015, the number of patients who had one or more opioid prescriptions was estimated to be 345,020, of which 84,648 (24.53%) belonged to the opioid misuse group and 260,372 (75.47%) to the non-misuse group (Table 1). Among the opioid misuse group, 60.43%

TABLE 2 Observed mean direct medical cost and adjusted mean direct medical cost by modeling[a].

		Misuse		Non-misuse		
	AIC	Adjusted mean cost (USD)	SE	Adjusted mean cost (USD)	SE	Δ mean
Observed cost	—	256.48[b]	691.98[c]	122.65[b]	387.27[c]	+133.83
GLM, inverse Gaussian distribution	3919294	401.18	7.33	268.81	4.98	+132.37
GLM, gamma distribution	4072729	402.30	3.58	263.67	2.43	+138.63
GLM, normal distribution	6128952	386.49	25.72	241.51	18.76	+144.98

AIC, Akaike information criterion; SE, standard error; GLM, generalized linear model with the log link function.
[a]We estimated the mean direct medical cost per person per year under following control covariates: sex, age, insurance type, the Charlson comorbidity index score, comorbid diseases, and morphine milligram equivalent.
[b]Arithmetic mean cost.
[c]Standard deviation.

were female, and the mean age was 54.03 ± 15.30 (mean ± standard deviation). The proportion of Medical Aid recipients in the opioid misuse group was higher than that in the non-misuse group (5.45% vs. 2.57%). The CCI score was significantly higher in the opioid misuse group than in the non-misuse group (0.67 ± 0.89 vs. 0.42 ± 0.72, $p < 0.0001$). The mean value of overlapping days in the former group was higher than that in the latter (0.81 ± 1.64 vs. 0.01 ± 0.10 days, $p < 0.0001$). The opioid misuse group visited clinics or hospitals for opioid prescriptions on an average of 26.01 ± 39.92 times per year and consumed a significantly larger amount of MME (27.85 ± 112.68 vs. 16.63 ± 63.00 mg, $p < 0.0001$) than the non-misuse group during this period. The medical costs of dorsalgia accounted for the highest proportion of the total medical costs related to opioids for the misuse group, at 7.75%, followed by arthrosis of the knee (7.5%) and other spondylopathies (5.97%). The list of the diagnoses according to the total medical cost and frequency is presented in the Supplementary Appendix SA1.

Direct medical costs and the incremental burden of the opioid misuse group

The distribution of the observed direct medical costs was severely skewed to the right with a long tail. The arithmetic mean of the direct medical costs PPPY (USD 155.48) was substantially greater than its medians (USD 58.87). Based on the Kolmogorov–Smirnov test results, the null hypothesis that the data were sampled from a normal distribution was rejected ($p < 0.0001$). As seen in Table 2, the unadjusted mean direct medical costs PPPY, not controlling for any covariates, were USD 256.48 and USD 122.65 in the misuse and non-misuse groups, respectively. A large standard deviation was observed for both groups (691.98 vs. 387.27).

The modified Park test results suggested that the distribution of the direct medical costs PPPY lay somewhere between the gamma and the inverse Gaussian distribution (variance function powers $\lambda = 2.21$). The direct medical costs PPPY were best fitted by the GLM with the inverse Gaussian distribution and log link function because the AIC was the lowest. The adjusted mean direct medical costs PPPY with the GLM were estimated as USD 401.18 ± 7.33 for the opioid misuse group. The adjusted mean incremental cost PPPY of this group relative to the non-misuse group was USD 132.37 (Table 2).

Using the GLM with the inverse Gaussian distribution and log link function that had the lowest AIC, all components of the total direct medical costs were found to be higher in the opioid misuse group than in the non-misuse group (Figure 2). The outpatient costs PPPY were USD 275.72 ± 2.37 and USD 181.36 ± 1.70 in the misuse and non-misuse groups, respectively. Of the outpatient costs, the outpatient drug costs PPPY were USD 139.85 ± 1.34 and USD 74.20 ± 0.74 in the misuse and non-misuse groups, respectively. The outpatient drug costs were best fitted by the GLM with the gamma distribution and log link function.

A total of 2.97% of the overall study population had been hospitalized more than once (4.28% and 2.54% for the misuse and non-misuse groups, respectively). The hospitalization costs PPPY were USD 100.21 ± 4.57 and USD 71.79 ± 3.45 in the misuse and non-misuse groups, respectively. The drug costs PPPY incurred during hospitalization were USD 20.73 ± 1.10 and USD 13.71 ± 0.77 for the misuse and non-misuse groups, respectively. Both were estimated using the GLM with the Tweedie distribution and log link function.

The prevalence of opioid misuse in the NHIS-NSC population between 2010 and 2015 was calculated to be 7.76%. The total number of patients in the NHIS-NSC population during the period was 1,091,257, and the number of patients in the misuse group was 84,648. During the same

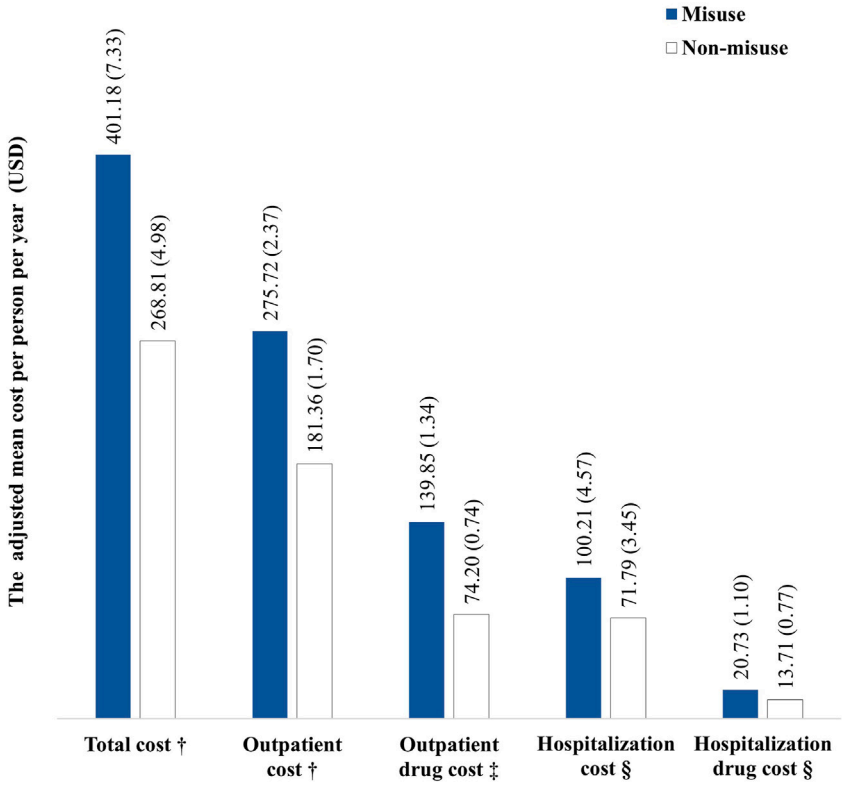

FIGURE 2
Adjusted mean costs per person per year in the misuse and non-misuse groups. †The generalized linear model (GLM) with the inverse Gaussian distribution and log link function. ‡The GLM with the gamma distribution and log link function. §The GLM with the Tweedie distribution and log link function. Note: the total cost was the sum of the outpatient and hospitalization costs. Outpatient costs were the sum of the outpatient visits and drug costs. Hospitalization costs included room rates, medical imaging fee, laboratory test fee, nursing fee, and drug costs.

period, the average population of South Korea was estimated to be 50,313,517 (Korean Statistical Information Service, 2021). The total economic burden of the opioid misuse group was estimated to be approximately USD 1.57 billion, and the incremental economic burden of the opioid misuse group compared to the non-misuse group was 0.52 billion USD.

Association between total direct medical cost and patient characteristics

As previously shown, the mean direct medical costs were estimated using the GLM with the inverse Gaussian distribution and log link function since it showed the lowest AIC. The coefficients of covariates estimating the mean direct medical costs are reported in Table 3. Almost all the coefficients were significantly associated with the direct medical costs ($p < 0.0001$), except for chronic obstructive pulmonary disease ($p = 0.7288$), dementia ($p = 0.6141$), myocardial infarction ($p = 0.9721$), and paraplegia ($p = 0.8058$). The mean direct medical costs for the misuse group were 1.49 times significantly higher than those for the non-misuse group. Those for males were 1.05 times significantly higher than those for females. Moreover, such costs were 1.48 times significantly higher for Medical Aid patients than for NHI patients. Additionally, older age, higher CCI scores, and higher MME were significantly associated with increased costs. The following comorbidities were significantly associated with increased costs: back pain, cerebrovascular disease, congestive heart failure, diabetes, liver disease, peptic ulcer, peripheral vascular disease, and rheumatic disease.

Discussion

This study estimated the incremental direct medical burden of opioid misuse. We estimated the mean direct medical costs PPPY in the opioid misuse and non-misuse groups after adjustments based on the econometric model. The former group incurred significantly higher direct medical costs than the latter group. The estimated mean direct medical costs PPPY for the misuse group were approximately 1.5 times higher than those for the non-misuse group.

TABLE 3 Association between the direct medical cost and patient characteristics measured by GLM with the inverse Gaussian distribution and log link function.

Covariate	Estimate	SE	95% confidence limit		*p*-value
Intercept	4.2754	0.0056	4.2644	4.2865	<0.0001
Group (ref. non-misuse)					
Misuse	0.4004	0.0073	0.3860	0.4147	<0.0001
Sex (ref. female)					
Male	0.0534	0.0049	0.0438	0.0631	<0.0001
Age (ref. 18–29 Y)					
30–39 Y	0.1304	0.0069	0.1169	0.1439	<0.0001
40–49 Y	0.2770	0.0070	0.2633	0.2908	<0.0001
50–59 Y	0.5299	0.0078	0.5146	0.5453	<0.0001
60–69 Y	0.6644	0.0103	0.6442	0.6846	<0.0001
70–79 Y	0.8890	0.0143	0.8609	0.9171	<0.0001
≥80 Y	1.0790	0.0292	1.0218	1.1363	<0.0001
Insurance (ref. NHI)					
Medical Aid	0.3904	0.0184	0.3543	0.4264	<0.0001
CCI score (ref. CCI=0)					
CCI = 1	0.1238	0.0063	0.1114	0.1362	<0.0001
CCI = 2	0.3285	0.0130	0.3030	0.3540	<0.0001
CCI = 3	0.5780	0.0221	0.5347	0.6214	<0.0001
MME (ref. 20 mg>)					
20–49 mg	0.0781	0.0076	0.0631	0.0931	<0.0001
50–89 mg	0.2445	0.0316	0.1826	0.3065	<0.0001
≥90 mg	0.8375	0.0493	0.7408	0.9342	<0.0001
Comorbid disease dummy					
Back pain	0.1428	0.0080	0.1272	0.1585	<0.0001
CERE	0.a1384	0.0318	0.0760	0.2007	<0.0001
CHF	0.1965	0.0465	0.1053	0.2878	<0.0001
COPD	0.0032	0.0091	−0.0147	0.0211	0.7288
Dementia	0.1643	0.3260	−0.4745	0.8032	0.6141
DM	0.1198	0.0208	0.0789	0.1606	<0.0001
Liver	0.1548	0.0147	0.1261	0.1836	<0.0001
MI	0.0030	0.0857	−0.1649	0.1709	0.9721
Paraplegia	−0.0282	0.1148	−0.2533	0.1969	0.8058
PUD	0.0344	0.0095	0.0158	0.0530	0.0003
PVD	−0.0689	0.0300	−0.1277	−0.0101	0.0216
RM	0.2859	0.0301	0.2270	0.3448	<0.0001
Scale	0.1269	0.0002	0.1266	0.1272	

Number of observations = 345,020. Dependent variable = the mean direct medical cost. GLM, generalized linear model; CCI, Charlson comorbidity index; MME, morphine milligram equivalent; NHI, National Health Insurance; CERE, cerebrovascular disease; CHF, congestive heart failure; COPD, chronic pulmonary disease; DM, diabetes; Liver, liver disease; MI, myocardial infarction; PUD, peptic ulcer disease; PVD, peripheral vascular disease; RM, rheumatic disease.

The estimated prevalence of opioid misuse during the period 2010–2015 was 7.76%. We were not able to compare this estimate with others since none of the previous studies reported the prevalence of opioid misuse in South Korea. Studies conducted in the US have determined opioid misuse rates between 2.0% and 56.3% (Vowles et al., 2015). Although differences between countries may exist, the estimated prevalence of opioid misuse in this study is likely to be reasonable. Considering the estimated prevalence and the average population of South Korea, the economic burden of opioid misuse for the South Korean population was estimated to be approximately USD 1.57 billion in 2010–2015. The incremental economic burden of opioid misuse was estimated to be approximately USD 0.52 billion during the same period.

According to the National Health Insurance Statistical Yearbook in South Korea in 2015, the NHIS financing expenditure was USD 40.81 billion. According to the results of studies on disease burdens in South Korea in 2015, the direct medical costs were estimated to be approximately USD 2.65 billion for stroke, USD 0.32 billion for hepatitis B, and USD 0.15 billion for depression (Baik et al., 2020; Cha, 2018; Chang et al., 2012). In the current study, the incremental economic burden of opioid misuse per year was estimated to be approximately USD 86 million, which is noteworthy compared to other disease burdens. The annual opioid prescriptions in South Korea increased continuously from 2009 to 2019 (Cho et al., 2021). According to this trend, the economic burden of opioid prescriptions is expected to increase, especially in the misuse group, implying that the opportunity cost of opioid misuse is expected to steadily increase as well.

Previous studies defined opioid misuse from healthcare claims data by using specific patterns of opioid prescriptions. The most widely used indicators for opioid misuse are opioid shopping and overlapping prescriptions. Yang et al. (2015) revealed that an opioid misuse defined by both indicators (i.e., pharmacy shopping and overlapping prescriptions) was significantly associated with an increased risk of overdose. In this study, we used both indicators to differentiate between patients with and without opioid misuse and compared these two groups to assess the incremental economic burden of opioid misuse.

Rice et al. (2012) determined that the probability of opioid abuse in the US was associated with the number of opioids, antipsychotics, or hypnotics as concomitant medication and mental illness as comorbid conditions. Patient characteristics affecting the probability of opioid misuse were generally similar between the US and South Korea (Noh et al., 2022). In contrast with the US (odds ratio (OR) = 0.59 for older people, 60–64 years old), the risk of an inappropriate prescription of opioids in South Korea was higher in females and older people (OR = 2.12 for older people, ≥ 65 year old). Notably, polypharmacy (≥10 medications) was significantly associated with the inappropriate prescription of opioids in South Korea (OR = 18.5) (Noh et al., 2022). Kim et al. (2014) revealed that over 80% of people of age 65 years and above had polypharmacy in South Korea. In other words, polypharmacy in older people in South Korea may be associated with the probability of opioid misuse.

South Korea has various programs, regulations, and policies for preventing opioid misuse. The Korean Association Against

Drug Abuse is the nation's only private organization that carries out comprehensive projects for the prevention of drug abuse such as the construction of community networks and the undertaking of research activities and educating high-risk groups (Korean Association Against Drug Abuse, 2022). Since 2018, all individuals who handle narcotics in South Korea have been mandated to legally report the narcotic details (e.g., product name, the quantity consumed, stock, and serial number) and patients' information to the web-based Narcotics Information Management System (NIMS): exporter and importer, manufacturer, wholesaler, pharmacist, healthcare provider, and researcher. The NIMS can contribute to the identification and management of opioid prescription patterns to prevent its misuse. In addition, the "Network System to Prevent Doctor-shopping for Narcotics" was implemented by the NIMS in 2021 to verify previous narcotic prescriptions and evaluate the risk of abuse. The healthcare provider can access the patient's narcotic history from the NIMS database and examine the previous narcotic prescriptions. This system has been assessed to be a cost-effective method for preventing opioid abuse (Kim et al., 2021). We recommend that the NIMS should be actively utilized to evaluate prescription opioid patterns and prevent opioid misuse. For this, we suggest an additional policy, the compulsory assessment of the patient's opioid history, before prescribing opioids. The compulsory assessment can help reduce the risk of misuse and provide appropriate treatment for patients who need pain control. Moreover, a decrease in the healthcare expenditure is expected.

By matching differences in patient characteristics between patients with and without opioid abuse, White et al. (2005) demonstrated that the direct medical costs of opioid abuse were approximately eight times higher than those of opioid non-abuse. They calculated the average costs per person, regardless of the nature of the cost data in terms of distribution. Since most cost data are right-skewed, it may violate the assumptions of a normal distribution required to calculate the average costs, resulting in inaccurate estimates. Skewed data are the main issue in statistical models in healthcare costs which tend to be skewed to the right. This occurs because a large number of costs cluster around a lower range of values (left-hand side), whereas a few high-cost values are present in the tail (right-hand side) (Manning and Mullahy, 2001; Thompson and Barber, 2000). In other words, the right-skewed distribution cost means that the number of patients with low expenditure is high; those with high expenditure are relatively rare. Since the mean is typically greater than the median in this case, we need to be cautious when estimating the mean to obtain unbiased and precise estimates. To do so, we used the ECM, which can estimate the unbiased and precise mean even with non-symmetric data. Although the linear regression model with logarithmic transformation can make the skewed data symmetric, the transformation creates the problem of retransformation of estimates back to an economically meaningful scale. In contrast, ECM assumes a nonlinear relationship for the cost regression; therefore, it allows avoiding retransformation. In summary, to consider the distribution of costs, we used the GLM, which has a distribution family function for the dependent variable and the link function that describes the relationship with covariates. This flexibility allows for the estimation of non-normal distributions (Afifi et al., 2007; Barber and Thompson, 2004; Dodd et al., 2006). In our direct medical costs data, the variance function power was 2.21, and the inverse Gaussian distribution showed the lowest AIC.

The present study has several notable strengths. First, we estimated an incremental economic burden for the opioid misuse group in Asia. This is expected to be useful in forecasting the incremental economic burden of such groups in Asian countries, where the rate of opioid misuse is different from that of Western countries. Health policymakers would be able to understand the magnitude of the burden related to opioid misuse. Moreover, the results provide evidence for comparison with the burden of other diseases so that health policymakers would be able to prioritize certain policies over others. Second, we estimated the economic burden by using real-world data representing the entire population of South Korea. Third, we considered a skewed distribution of cost data and estimated the economic burden more accurately by adjusting for patient characteristics.

There are several limitations that should be acknowledged. First, it was difficult to clearly define opioid misuse. Although some characteristics, such as overdose and addictions, are distinguishable based on their diagnosis codes, we were not able to use these codes because these were masked in the NHIS-NSC database to protect personal information. However, we overcame this limitation by classifying opioid users into the opioid misuse and non-misuse groups based on their opioid prescription patterns related to overdose or shopping. To classify opioid prescription misuse patterns, we applied an operational definition based on previous studies (Sullivan, 2013; Yang et al., 2015; Carey et al., 2018; Kim et al., 2021). Second, we were unable to determine the exact prevalence of opioid misuse in the entire South Korean population. Instead, we used the estimated prevalence in the NHIS-NSC population because it contains representative data based on an entire population with a single-insurer system, which is similar to the overall population of South Korea. Third, the claims database did not include clinical variables such as laboratory values and clinical markers. However, to overcome this limitation, comorbidities were assessed by the CCI score as well as the comorbid disease dummy. Fourth, we estimated the economic burden for the period 2010–2015, since it was the latest available population-based sample data. Further research with more recent data is warranted to examine the economic burden of prescription opioid misuse. Finally, we did not include patients with cancer who might be exposed to the high risk of opioid misuse, and 34% of cancer survivors may have chronic pain which is 20% of the general US population (Dahlhamer et al.,

2018; Jiang et al., 2019). Since the focus of this study was to evaluate the opioid misuse in non-cancer patients, we excluded patients with cancer. To understand the burden of opioid misuse in the total Korean population, including patients using opioid with or without cancer, further studies examining the opioid misuse in the patients with cancer would be needed.

Conclusion

We estimated the incremental direct medical burden of prescription opioid misuse for non-cancer patients using healthcare claims data. Such misuse was significantly associated with an increased economic burden. This result suggested that if we pay attention to opioid misuse, the healthcare expenditure burden can be efficiently managed. Along with appropriate policies to prevent opioid misuse and reduce its economic burden, it is necessary to monitor opioid prescription patterns. Furthermore, the effectiveness of the policies on opioid use should be continuously evaluated.

Data availability statement

The datasets presented in this article are not readily available because the datasets are not accessible and were analyzed only in a remote analysis space provided by the National Health Insurance Service and it is not possible to take out a generated dataset. Requests to access the datasets should be directed to https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Pusan National University (PNU IRB/2020_76_HR). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MK: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; SK: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content; and HS: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.928890/full#supplementary-material

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An analysis of the essential medicines policy in primary care: Findings from MedMinas project

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Background: Essential Medicines Policy (EMP) has been adopted in Brazil to improve the provision and use of pharmaceuticals. This mixed methods study aims to bring evidence of the EMP implemented in municipalities in the context of primary care in Minas Gerais (20,997,560 inhabitants), Southeast Brazil.

Methods: We analysed the core output of the EMP, i.e., the municipal essential medicines lists (MEML) and the effects of the policy on the procurement and availability of medicines. Data sources included a sample of 1,019 individuals (patients, health managers and health professionals), 995 prescriptions, 2,365 dispensed medicines and policy documents from 26 municipalities. Data were collected between April and October 2019. Document analysis and thematic content analysis were performed, and four availability indexes were estimated.

Results: The findings suggest an overall lack of standardised and methodologically sound procedures to elaborate the MEML. Funding and public purchasing processes were found to be the major obstacles to medicine procurement. Only 63% of medicines were available at public community pharmacies and just 46.2% of patients had full access to their pharmaceutical treatment.

Conclusion: This study reveals weaknesses in the implementation of EMP and a clear disconnection between medicines selection, procurement, and availability, the three core elements of the supply system. These findings contribute to informing future policy improvement actions to strengthen this system. Other countries aiming to advance towards universal health coverage may learn from the challenges that primary care in Brazil still needs to address.

Abbreviations: BNMP: Brazilian's National Medicines Policy; MEML/REMUME, Municipal lists of Essential Medicines (Relação Municipal de Medicamentos Essenciais, in Portuguese); EML, Essential Medicines List; EMP, Essential Medicines Policy; ERAF, Pharmaceutical Care Regionalization Strategy; MHS, Municipal Health Secretariats; NEML/RENAME, Brazilian National Essential Medicines List (Relação Nacional de Medicamentos Essenciais, in Portuguese); PCPs, Public community pharmacies; PHCPS, Pharmaceutical Services based on Primary Care; REM, Rapid Evaluation Methods; SUS, Brazilian National healthcare system (Sistema Único de Saúde, in Portuguese).

KEYWORDS

essential medicines policy, medicines supply, mixed-methods study, primary health care, pharmaceutical services

Introduction

Brazil has a national healthcare system known as SUS—*Sistema Único de Saúde*, established more than 30 years ago, run by the government, funded through taxes, and covering the entire population of more than 210 million inhabitants (Paim et al., 2011; Brasil, 2021a).

The Brazilian's National Medicines Policy (BNMP) was launched in 1998 (Brasil, 1998) as a fundamental component of SUS. Pharmaceutical Services based on Primary Care (PHCPS) are a programme, part of BNMP, involved in activities of regulation, planning, procurement, distribution, and dispensing of essential medicines in primary care related facilities, mostly public community pharmacies (PCPs) (Barreto and Guimarães, 2010; Brasil, 2013).

In accordance with the SUS principle of decentralization to subnational entities, Primary Care, and consequently the PHCPS, are coordinated by each of the 5,570 Brazilian municipalities, who are responsible for the development of local policies, health system management, and service provision (Facchini et al., 2018). Funding, on the other hand, is under shared responsibility of the federal, state, and municipal levels (Costa et al., 2017).

Despite significant incentives and guidance included in the Brazilian medicines-related legal framework throughout more than 20 years of the BNMP publication (Bermudez et al., 2018), there is still great difficulty in achieving the goals of the PCHPS in the country, especially regarding medicine supply and logistics. A nationwide study found an average availability of tracer medicines in PCHPS of only 52.9% (Nascimento et al., 2017), while a state-level study found an availability index verified by stock levels of 61.0% (Barbosa et al., 2021). To 9.7% of Municipal Health Secretaries the financial resources are perceived as sufficient to cover medicines demanded by patients (Faleiros et al., 2017). Additionally, PCHPS pharmacist managers reported lack of financial autonomy (61.5%), knowledge gaps on the financial resources available (81.7%), and lack of procedures for medicines selection, forecasting, and procurement (50%) (Gerlack et al., 2017). Considering that in Brazil universal access to medicines is constitutionally guaranteed to all citizens, litigation has been increasingly used by individuals to ensure their rights, which, in turn, affects health financing (Oliveira et al., 2020).

The PCHPS deem medicines to be the central element in guaranteeing comprehensive and continuous care for the population's health needs and problems, both individually and collectively (OPS, 2013). Thus, two complementary systems must operate: 1) the supply system, encompassing medicines selection, procurement, and delivering; and 2) the pharmaceutical care system, including dispensing, counselling and monitoring, pharmacotherapeutic follow-up of patients and health education activities (Brasil, 2006a, 2009).

The Essential Medicines Policy (EMP) is embedded in the BNMP and isa cross-cutting dimension for the PHCPS management system in Brazil, as its main purpose is to promote free access to the population to efficacious, cost-effective, quality, and safe medicines (Bermudez et al., 2018). The main output following the EMP implementation is the Essential Medicines List (EML). The Brazilian National Essential medicines list—NEML—is known as RENAME (*Relação Nacional de Medicamentos Essenciais)*. The policy requires that states and municipalities develop their own lists based upon the NEML and conduct periodic reviews (Brasil, 1998). The pharmaceutical products selected in their lists must have adequate public sector financing and be continuously available to the healthcare system patients (Brasil, 1998, 2007; Bermudez et al., 2018; Brasil, 2021c).

Based on the premise that the EML constitute the benchmark for procurement processes and, consequently, for the availability of essential medicines in the healthcare system, this study brings evidence of EMP implemented in the municipalities. We examined the core output of EMP, i.e., the municipal lists of essential medicines—MEML– (*Relação Municipal de Medicamentos Essenciais,* REMUME). Also, we discussed the effects of the policy on its primary process and outcome, respectively: procurement effectiveness and barriers, and medicines availability at public community pharmacies (PCPs).

Materials and methods

Design and setting

This investigation is part of MedMinas Project (Luz, 2017), a mixed-methods study conducted in medium to large size-sized municipalities (35,000 to 900,000 inhabitants) from all 13 macro regions (Malachias et al., 2010) in the State of Minas Gerais (20,997,560 inhabitants) in the Southeast region of Brazil.

MedMinas adopted the principles of Rapid Evaluation Methods (REM) (Anker et al., 1993; McNall and Foster-Fishman, 2007), which recommends a sample of at least 20 health care facilities and 30 patients per facility. For the quantitative component, MedMinas used a multistage sampling technique in three levels of stratification: 1) macro-regions of the State of Minas Gerais; 2) municipalities within the macro-region; and 3) PHCPS facility. A sample size of 26 municipalities was estimated to guarantee the representativeness of the entire state. In each municipality, one service—a public community pharmacy was selected.

Considering that 30 patients should be interviewed in each of the 26 services, a sample of 780 patients was selected. To this number a percentage of 20% was added to compensate for losses, totalling 936 patients of both sexes and aged 18 years or older and who were patients from the PCPs for at least 6 months.

For the qualitative component, a purposeful sample was estimated, totalling five key actors per municipality, divided in two subgroups: healthcare system managers, including the Municipal Health Secretary (1), the Director/Coordinator of Primary Health Care Services (1) and the Municipal Coordinator of Pharmaceutical Services (1); and health workers from the public community pharmacy, including a pharmacist (1) and a dispensary assistant (1).

Data sources and data collection

Data were collected between April and October 2019, by a trained field team in each selected municipality. Data sources included in MedMinas comprised individuals (patients and professionals), prescriptions and dispensed medicines, and policy documents. Specific semi-structured, multidimensional, pre-tested, and piloted questionnaires were applied to each respondent profile. Face-to-face interviews were conducted at the public community pharmacies (PCPs) and at Municipal Health Secretariats (MHS). Patients were interviewed after dispensing, where information on their prescribed and dispensed medicines were also collected. Healthcare workers and managers were interviewed at their workplace. Policy documents were collected at the MHS. More details about MedMinas methods can be found in another publication (Luz et al., 2022).

Data analysis

Document analysis of the Municipal Essential Medicines lists–MEML/REMUME

Copies of the current MEML were provided by the municipalities. A database was prepared combining the content of the lists. We classified all pharmaceutical products in accordance with the WHO-ATC/DDD system (WHO, 2021) and in accordance with the Brazilian Common Name (*Denominação Comum Brasileira*–DCB) that identifies the pharmaceutical substance or active pharmaceutical ingredient approved by the Brazilian Health Regulatory Agency–ANVISA (Brasil, 2021b). We also cross-referenced MEML with the Brazilian National Essential Medicines List (NEML/RENAME) (Brasil, 2018a).

In order to gain understanding and to be able to triangulate data (Bowen, 2009), we evaluated the MEML in two phases:

A) Appraisal of the overall content (WHO 2010; Rashid, 2016), estimating the following yes-no indicators: 1) presentation of the review committee members; 2) presentation of the criteria adopted for medicines' inclusion/exclusion; 3) organization by level of care, indicating whether the proposed medicine should be listed for use (e.g., primary care, secondary care, tertiary care); 4) organization by dispensing facility (e.g., public community pharmacy, emergency care unit, psychosocial care centres, etc); 5) organization by therapeutic or pharmacologic classes (e.g., medicines listed by pharmacological or therapeutic groups); 6) organization by funding components (Basic, Strategic, and Specialized Component).

B) We included at this phase only medicines related to Primary Care. We used information provided by the MEML and, when the MEML did not specify, by the NEML. We excluded several products, such as those for hospital, specialized care and for internal use in health facilities. We also excluded items that are not considered medicines, such as food supplements and formulas, sunscreen, reagent strips, and lancets, among others. We estimated the indicators (mean/SD, minimum and maximum): 1) average number of medicines (i.e., pharmaceutical products defined by active ingredient/s, route of administration and strength); 2) average number of chemical substances. We aggregated medicines by therapeutic group and estimated the indicator "proportion of medicines listed in the MEML by anatomical main group (ATC 1st level)."

Additionally, we analysed managers and professionals' responses to the following questions (yes/no answers), regarding primary care medicines, using descriptive statistics: *"In your opinion, the MEML is updated?"*; *"Do patients look for drugs that are not included in the MEML?"* We also analysed responses to the question *"In your opinion, is the MEML adequate to patients' needs?"* (adequate/partially adequate/inadequate).

Medicines procurement effectiveness and barriers

Concerns and experiences of managers and professionals may remain invisible if they are not properly acknowledged; hence, we investigated medicines procurement effectiveness and barriers, according to their perceptions. We analysed responses to the following questions (yes/no answers), using descriptive statistics: "*Has your municipality been able to procure primary care medicines*?"; "*Are there any difficulties purchasing these medicines*?" If the respondent stated "yes" to the latter, we asked an additional open-ended question: "*Could you explain why the municipality is not being able to purchase the medicines*?" Answers were analysed by Thematic Content Analysis (Bardin, 2011; Patton, 2015), which included codification of the answers in *units of meanings*. In sequence, similar codes were grouped to generate themes and categories. A coding frame was developed based on a Brazilian guideline and a technical note (Brasil 2006a; Brasil, 2014). Each final category was organized into larger

themes following the coding frame and then that coding frame was applied to all data.

Medicines availability at public community pharmacies

To estimate medicines availability at PCPs we considered four sources of information per municipality: patients' data, prescriptions, dispensed medicines, and the MEML.

We asked patients if they had obtained the prescribed medicines and, if so, if they were given the amount needed for the duration of their treatment. We extracted from prescriptions and medicines dispensed the products' names, dosage forms, and strengths. For analysis, we included only medicines prescribed and dispensed that were listed on the MEML. We classified the included products according to the WHO-ATC/DDD system (WHO, 2021).

We built four availability indexes (Bueno et al., 2021): 1) Overall medicines availability, 2) Medicines availability by therapeutic groups, 3) Prescription availability, and 4) Pharmaceutical treatment availability.

The analyses were conducted according to the following steps:

1) First, each prescribed medicine was classified "available" or "unavailable" to build the index "Overall medicines availability". To be considered "available", the product should be dispensed in the correct quantity for treatment duration. We estimated the index by using the formula:

$$\frac{Number\ of\ medicines\ available\ at\ the\ PCP}{Total\ number\ of\ prescribed\ medicines}$$

2) Then, medicines were aggregated by their main therapeutic groups and the proportions of prescribed and dispensed drugs were estimated (by ATC 1st level) to build the index "Medicines availability by therapeutic groups" by the formula:

$$\frac{Number\ of\ medicines\ available\ at\ the\ PCP\ by\ their\ main\ ATC\ group}{Total\ number\ of\ prescribed\ medicines\ by\ their\ main\ ATC\ group}$$

3) We built the index "Prescription availability", considering each patients' prescriptions. Each prescription was classified in one of the three following categories: "Totally filled" (if all prescribed medicines were considered available); "Partially filled" (if at least one prescribed medicine was considered unavailable) and "Unavailable" (if all prescribed items were unavailable). The index was estimated by the formula:

$$\frac{Number\ of\ prescriptions\ (totally\ filled/partially/unavailable)}{Total\ number\ of\ prescriptions}$$

4) Next, we built the index "Pharmaceutical treatment availability" considering all the prescriptions dispensed per patient (sometimes patients receive multiple prescriptions). Each treatment was classified in one of the three following categories: available (if all prescriptions were considered totally filled), partially available (if at least one prescription was considered partially filled) and unavailable (if all prescriptions were considered unavailable). The index was estimated by the formula:

$$\frac{Number\ of\ treatments\ (available/partially/unavailable)}{Total\ number\ of\ patients}$$

Results

MedMinas included 26 municipalities varying from 37,784 to 409,341 inhabitants totalling 3,874,247 people. A total sample of 1,019 individuals participated in the study from three groups: managers (n = 77), health professionals (n = 50), and primary care patients (n = 892). The group of managers was represented by 24 municipal health secretaries, 27 coordinators of primary health care services and 26 coordinators of pharmaceutical services. One municipal health secretary refused to participate and another one asked to be replaced by the Municipal Director of Health Care. The group of health professionals consists in 26 dispensary assistants and 24 pharmacists, because in two municipalities, at the time of data collection, the coordinators of pharmaceutical services were also responsible for the public community pharmacies investigated, reducing the number of pharmacists in the study. Most study participants were women, with mean age ranging from 36.8 to 53.0 years, depending on the study group (Table 1).

The municipal essential medicines lists

The EMP is implemented in the totality of municipalities included in the study (n = 26), but one municipality did not provide a copy of the MEML for our analysis. The evaluation of the content of the MEML showed that around a third presented the review committee members and only two lists provided the criteria adopted for medicines' inclusion/exclusion. One quarter of the lists were organized by level of care, 48% were organized by dispensing facility, and 44% by therapeutic or pharmacologic classes. Three MEML were organized by funding components (Table 2).

The total number of pharmaceutical products listed for primary care, considering all the MEML, was 3957 (mean 158.3 [SD ± 38.0]), while the total number of chemical substances was 2641 (mean 105.6 [SD ± 22.9]). Medicines from the nervous system (N), cardiovascular system (C), anti-infectives for systemic use (J), and alimentary tract and metabolism (A) were the most frequently included in the lists (64.8%) (Table 2).

TABLE 1 Sociodemographic profile of study participants. MedMinas Project, 2019.

Characteristic	n (% or SD)		
	Managers (n = 77)	Health professionals (n = 50)	Patients (n = 892)
Sex (female)	54 (70.1)	40 (80.0)	561 (62.9)
Age [mean (SD)]	42.7 (10.8)	36.8 (9.7)	53.0 (15.5)
Educational level (years of study)			
0 ≥ 9	-	-	582 (65.3)
10 to 13	1 (1.3)	16 (32.0)	236 (26.5)
≥14	76 (98.7)	34 (68.0)	73 (8.2)

TABLE 2 Findings from the Municipal Lists of Essential Medicines (REMUME) evaluation in accordance with the document analysis. MedMinas Project, 2019.

REMUME evaluation	n (%)
Document analysis	
Presentation of the review committee members (yes)	7 (28.0)
Presentation of the criteria adopted for medicines' inclusion/exclusion (yes)	2 (8.0)
Frequency of REMUMEs organized by level of care[a]	7 (28.0)
Frequency of REMUMEs organized by dispensing facility[b]	12 (48.0)
Frequency of REMUME organized by therapeutic/pharmacologic classes	11 (44.0)
Frequency of REMUME organized by funding components[c]	3 (12.0)
Average number of medicines	
Mean (SD)	158.3 (38.0)
Minimum	95.0
Maximum	242.0
Average number of chemical substances	
Mean (SD)	105.6 (22.9)
Minimum	67
Maximum	159
Proportion of medicines by anatomical main group (ATC 1st level) (n = 3957)	
Nervous system (N)	954 (24.1)
Cardiovascular system (C)	661 (16.7)
Anti-infectives for systemic use (J)	530 (13.4)
Alimentary tract and metabolism (A)	419 (10.6)
Respiratory system (R)	266 (6.7)
Genito urinary system and sex hormones (G)	196 (5.0)
Systemic hormonal preparations (H)	194 (4.9)
Blood and blood forming organs (B)	168 (4.2)
Antiparasitic products, insecticides, and repellents (P)	162 (4.1)
Musculo-skeletal system (M)	142 (3.6)
Other[d]	265 (6.7)

[a]Level of care: primary care, secondary care, tertiary care.
[b]Dispensing facility: public community pharmacy, emergency care unit, psychosocial care centres, etc.
[c]Funding components: basic, strategic, and specialized component.
[d]Other: Dermatologicals (D), Sensory Organs (S) Various (V), Antineoplastic and Immunomodulating Agents (L), herbal medicines.

TABLE 3 Managers and health professionals' perceptions regarding the Municipal Lists of Essential Medicines (REMUME). MedMinas Project, 2019.

REMUME evaluation	n (%)
Perceptions of managers and health professionals	
Updated medicines list (yes)	
Managers (n = 77)	48 (64.9)
Health professionals (n = 23)[a]	19 (82.6)
Demands for medicines not covered by the list	
Managers (n = 77)	70 (95.9)
Health professionals (n = 50)	48 (100.0)
Adequacy to patients' needs (yes)	
Managers (n = 77)	52 (70.3)
Health Professionals (n = 23)[a]	19 (82.6)

[a]Questions not applied to dispensary assistants since these are out of the scope of their responsibilities at PCPs.

Considering professionals' perceptions regarding the MEML, the lists were updated for 64.9% of the managers and 82.6% of health professionals. However, 95.9% of health managers and 100% of health professionals declared that there is a demand from patients for medicines not covered by their lists. Regarding the adequacy of the lists in relation to patients' needs, most managers (70.3%) and health professionals (82.6%) considered their lists adequate (Table 3).

Medicines procurement effectiveness and barriers

Regarding medicines procurement effectiveness, most managers and a portion of health professionals stated that their municipality has been able to procure primary care medicines (63.2% and 40.0% of respondents, respectively). Coincidently, a similar proportion of managers recognized difficulties to purchase medicines (62.3%) and 47 of them reflected on these difficulties. The major themes regarding procurement barriers yielded during thematic analysis and frequency of appearance are presented in Table 4. Funding (61.7%) and purchasing processes at SUS (38.3%) appeared in most of the responses.

Theme 1: Funding

Two subthemes emerged from this category: transfer of resources allocated to PHCPS and overall programme funding. In Brazil, federal, state and municipal government share the responsibility for funding the PHCPS programme. The resources allocated to PHCPS is transferred on a regular basis to the Municipal Health Fund. Most managers (18/47) were consistently concerned about the transfer of resources allocated to PHCPS by the State Government. They also complained about the poor financial situation of the municipalities (12/47).

"*Most of all, is the financial situation of the municipality. . . we have the State of Minas Gerais with an extremely complicated situation, from the financial point of view, in terms of transferring resources to the municipalities, especially in matters of healthcare. So, the municipality ends up paying for many things that were, previously, under the responsibility of the state. We have been suffering a lot from this!* (*Municipal Health Secretary, 24*).

"*What makes it difficult [medicines procurement] is the debt of the government of State of Minas Gerais with us. They are not transferring the funds. (Municipal Health Secretary, 16).*"

"*The problem that we're going through is due to the lack of financial resources. We purchase medicines, but there are delays in the payment, and then the suppliers suspend the deliveries. . .*" *(Municipal Coordinator of PHCPS, 11)*

TABLE 4 Managers and health professionals' perceptions regarding medicines procurement. MedMinas Project, 2019.

Procurement	n (%)	
	Managers (n = 77)	Health professionals (n = 50)
Municipality being able to procure medicines (yes)	48 (63.2)	20 (40.0)
Difficulties to purchase medicines[a] (yes)	48 (62.3)	-
Major themes regarding difficulties to purchase medicines[a,b]		
Funding	29 (61.7)	-
Purchasing processes at SUS	18 (38.3)	-
Pharmaceutical market	7 (14.9)	-
Litigation	2 (4.3)	-
Governance	1 (2.1)	-

[a]Questions not applied to health professionals since these are out of the scope of their responsibilities at PCPs.
[b]Response percentages exceed 100% because questions allowed respondents to mention multiple themes.

"*Financial resources! Our biggest challenge here is financial resources, we don´t have any money!" (Municipal Coordinator of PHCPS, 22)*

The underfunded situation of the PHCPS programme, however, was stressed by some managers.

"*The financial resources for the PHCPS programme are not enough. We are not being able to purchase several anti-hypertensives, antidiabetics, antidepressants. . .*" *(Municipal Coordinator of PHC Services, 27)*

"*I'm talking about the amount of money that comes, I mean, I'm considering the amount of money available to fund the programme. We have been working with the given budget, of course, but if we could increase the funding from the three levels of government, right, it would be great! We could expand our capacity of supply and everything. . .*" *(Municipal Health Secretary, 2)*

Theme 2: Purchasing Processes at Sistema Único de Saúde (SUS)

Several constrains and challenges still exist and affect the capacity of the purchasing process of medicines by SUS. Managers (19/47) complained about difficulties in preparing public procurement tender documents, excessive bureaucracy, significant delay in public procurement tenders and bidding processes, and about the fact that many suppliers decide not to respond to public procurement tenders or not deliver the medicines at the end of the processes.

"*Well, the Statement of Requirements [the document that defines the product or service, that is, being put to tender] preparation is exhausting! We write it every single year and every year there is something to be changed! So, this document goes to City Hall because we need the feedback of the legal team and it keeps coming back and forth several times. . .*" *(Municipal Coordinator of PHCPS, 8)*

"*. . . bidding here is extremely slow, there are so many bids for the municipality to handle, so the processes are quite slow. I've participated in the preparation of a public bidding months ago, and so far, it has not been published yet.*" (*Municipal Coordinator of PHCPS*, 24)

"*The main difficulty is to involve the suppliers; we often cannot find them, biddings fail. . . we need the medicines, but they do not offer them for us to buy, there just are no suppliers!*" *(Municipal Coordinator of PHCPS, 15)*

One manager stated that the Brazilian legal rules on public procurement bidding (Brasil, 1993) need to be updated.

"Umm, well, the great difficulty is the law itself, right, law 8666/93 [number of the Law], which is a total obstacle in the country, not just for purchasing medicines. We need something different, something newer, less bureaucratic, because the more bureaucratic the easier the deviations and errors, right? (*Municipal Coordinator of PHCPS*, 6)

Other managers complained about the policy *Pharmaceutical Care Regionalization Strategy* (ERAF) published by the State Health Secretariat, that pre-select the suppliers for a comprehensive list of primary care medicines. The municipalities can, then, purchase direct from these suppliers. However, some managers believe that this policy adversely affected the effectiveness of the procurement processes.

"*We adhered to the ERAF policy, but the scarcity of the financial resources from the State is making us purchase small quantities of medicines. Maintaining such a low stock is leading us to re-do purchases within a very short time. Additionally, due to the lack of items in the State list, we run out of medicines we need." (Municipal Health Secretary, 22)*

. . ."*Some suppliers were not willing to adhere to the State pharmaceutical pricing when selling the medicines to us. . .we had to re-specify ceiling prices to be able to purchase primary care medicines" (Municipal Health Secretary, 21)*

Theme 3: Pharmaceutical market

Medicines procurement is a complex process and negotiations highly depend on market constraints. Managers (7/47) emphasized obstacles such as unreliable suppliers or lack of competitiveness.

"*We are having problems with the suppliers that win the bids because some of them do not have the medicines that were solicited in the public bidding, so we do not receive these medicines. Additionally, they are dividing deliveries over multiple delivery points, without our consent. . .so, you do purchase, you do plan, you do think about your deadline and at the end of the day there is no agreement between the supplier and you. . .*" *(Municipal Coordinator of PHCPS, 7)*

"*The problem of having just one supplier sometimes is they leave us in the lurch!" (Municipal Health Secretary, 17)*

"*They win the bid but don´t want to deliver the medicines they sold; they ask us to change the brand of the products." (Municipal Coordinator of PHC Services, 12)*

"*. . .when we discuss prices, the suppliers want to sell medicines above the established ceiling prices and we don't understand the reasons for that." (Municipal Coordinator of PHCPS, 15)*

Themes 4 and 5: Litigation and governance

A few respondents mentioned the themes litigation and governance as barriers to medicines procurement.

"*The main problem today is the judicialization of healthcare. We must buy medicines to attend the judiciary determination. But the lawsuits come from one person or from a small group of*

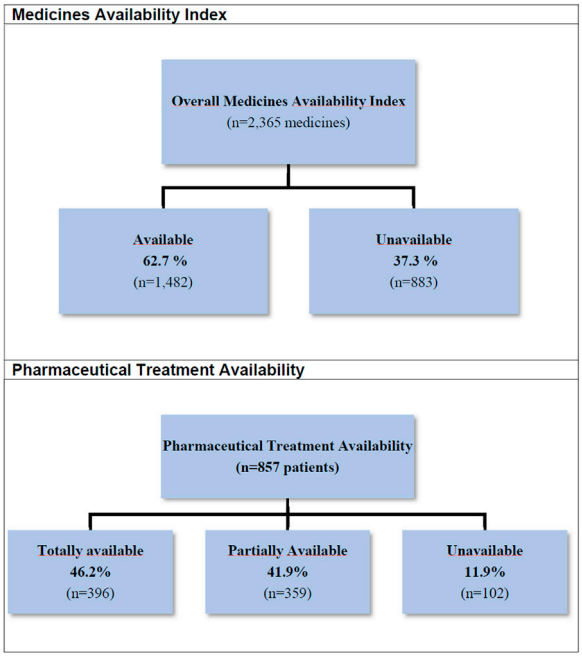

FIGURE 1
Medicines and pharmaceutical treatment availability at public community pharmacies. MedMinas Project, 2019.

persons and this causes a lot of problems for our administration. We are not serving an entire population. We need to purchase small quantities of medicines at higher prices." (Municipal Coordinator of PHCPS, 26).

One manager reflected about lack of governance when it comes to the procurement of medicines.

"*We have internal challenges, you know…The Municipal Health Fund today is under the control of the Secretariat of Finance, so we must get their budgetary approval, otherwise we cannot purchase medicines. We had to pick a fight with them…" (Municipal Coordinator of PHC Services, 27)*

Medicines availability at public community pharmacies

We analysed a total of 995 prescriptions from 857 patients (mean 1.1 prescription per patient). From the total of 2,753 prescribed medicines, 2,365 (85.9%) were listed at MEML and were included in the analysis. The availability of medicines was 62.7%, i.e., medicines that were dispensed to patients in the right quantities for treatment duration. Only 396 patients (46.2%) had full availability to their pharmaceutical treatment (Figures 1A,B).

Five main therapeutic groups (ATC 1st level) corresponded to 85% of the prescriptions: cardiovascular medicines (41.8%), alimentary tract and metabolism (16.0%), nervous system (15.2%), blood and blood forming organs (7.6%), and hormonal preparations (4.4%). Figure 2 displays these groups in accordance with the correspondent availability at public community pharmacies (PCPs). Alimentary tract and metabolism and cardiovascular medicines were the less available (50.7% and 55.9%, respectively) while hormonal preparations showed the highest availability (80.0%) at PCPs.

Discussion

EMP is considered the core of the global health and development agenda (Wirtz et al., 2017), yet the availability of essential medicines is still substandard worldwide (Bazargani et al., 2014).

For almost 23 years, Brazil has been adopting EMP to improve provision and stimulate the rational use of pharmaceuticals in the country (Osorio-de-Castro et al., 2018). Despite of the cumulative experience and tradition of adopting EMP in Brazil for decades, little is known about the main EMP output—the essential medicines list—and the impact on procurement processes and availability of medicines. This study bridges this gap, providing evidence from primary care at the largest Brazilian state in number of municipalities and the second most populous (20,997,560), Minas Gerais (Brasil, 2021b).

The Brazilian National Essential Medicines List (NEML/RENAME) is the main guideline for municipalities planning their own lists. However, the document analysis showed lack of standardisation of the municipal lists (MEML/REMUME) regarding its presentation and formats, especially in the description of medicines and chemical substances, and in respect to relevant information about the pharmacological properties of the drugs or the systems the drugs act on. Only part of the MEML offered information referencing the level of care or dispensing facility for each listed medicine and very few provided the criteria adopted for medicines' inclusion/exclusion and presented the committee members responsible for updating the list.

We also found several differences between MEML and the NEML concerning the overall organization of the lists. Particularly, we found a significative disparity in the number of chemical substances and medicines related to primary care. At the time of data collection, the NEML had 179 chemical substances and 364 medicines (Brasil, 2018a), numbers that were 1.7 and 2.3, respectively, higher than the average numbers for the municipalities.

Little attention is given to document analysis of MEML to allow direct comparisons, but investigations conducted in the South of Brazil showed similar findings. In respect to the average number of medicines presented, for instance, while we found a mean number of 158.3, Salvi et al. (2018) and Assunção et al. (2013) reported average numbers of 160.3 and 155.5, respectively. Relating to the distribution of the listed medicines by therapeutic groups, they also noticed a predominance of the nervous and cardiovascular systems on the MEML.

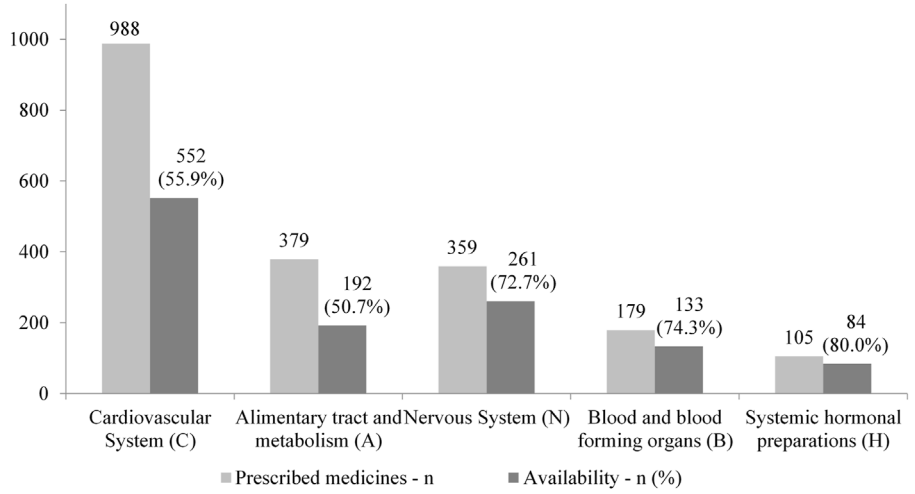

FIGURE 2
Top five prescribed therapeutic group (ATC 1st level) and availability at public community pharmacies. MedMinas, 2019.

Taken together, our findings suggest an overall lack of adoption of standardised and methodologically sound procedures to elaborate the MEML (Rashid, 2016; Wright, 2017). Additionally, it seems that the NEML is not guiding these procedures either, given the contrast regarding the content of the national list in comparison with the municipal lists (Brasil, 2018a).

Managers and health professional perceptions regarding MEML, however, tell a different history. Even recognizing the existence of demands for medicines not covered by their lists, most of the professionals consider the lists updated and adequate to patients' needs. These results differ from a nationwide investigation (Karnikowski et al., 2017) that showed a much higher percentage of managers perceiving the list as updated (80.4%), a much lower percentage of health workers perceiving demands for medicines not covered by the list (66.5% of the physicians) and considering the list adequate do patients' needs (70.9% of the professionals responsible for the dispensing of medicines). While Karnikowski et al. (2017) included professionals responsible for PHCPS, professionals responsible for dispensing of medicines and physicians, we included three levels of municipal healthcare system managers and two groups of healthcare workers from PCPs (pharmacists and dispensary assistants). In contrast to the above-mentioned study, we proposed the questionnaires to all of them; thus, our results reflect a combination of a more varied set of perceptions.

One of the expected impacts of the implementation of the EMP was the contribution to a more efficient and regular medicines supply system in the municipalities. Within this context, the MEML should guide medicines procurement, supporting the decision-making process (MSH, 2012). Our findings, considering procurement processes and medicines availability at PCPs, do not confirm this assumption.

Most managers agreed on the existence of difficulties regarding medicines procurement, highlighting a range of barriers related to funding, purchasing processes by SUS, the pharmaceutical market, litigation, and governance. These are expected results considering that, despite the fact that the main focus of the BNMP is supply and logistics (Brasil, 1998), medicines provision in Brazil has always been an issue of concern (Brasil, 2018b).

Particularly, funding of the PHCPS programme and purchasing processes at SUS were considered the central obstacles for medicine procurement according to managers. In relation to funding, managers complained about the inadequate coverage of financial resources for the PHCPS programme and about irregularities in budget transferring. In Brazil, the PHCPS programme is co-funded by federal, state, and municipal governments. Federal and state governments conduct funding transfers to municipalities and municipalities are responsible for programme execution (Vieira, 2010; Brasil, 2017). The programme's functioning depends on intergovernmental negotiation, especially regarding budget decisions (Costa et al., 2017). Our findings are in line with previous investigations (Faleiros et al., 2017; Mattos et al., 2019). A nationwide study showed that only 9.7% of municipal health secretaries considered the programme resources sufficient to meet the demands of the population (Faleiros et al., 2017) and an in-depth study showed that managers unanimously agreed that the PHCPS programme is underfunded. In respect to states' transfers to their municipalities, other authors also pointed out the same issues (Brasil 2017; Mattos et al., 2019).

In MedMinas, managers noticed shortcomings related to municipal financial resources to fund the PHCPS programme. One previous investigation evaluated the allocation of financial resources in medicines procurement of 960 Brazilian municipalities, showing that 73% applied a financial value below that recommended by the legislation (Pontes et al., 2017; Tavares et al., 2017). It is possible that the precarious financial situation that emerged from our data is correlated to those results.

Of relevance were the findings related to the capacity of public buyers to execute efficient purchases: ex-ante, when preparing tender documents; during tender processes; and, ex-post, while managing contracts. Managers perceived the process as excessively bureaucratic, time-consuming, and dependent on unreliable suppliers. Information about barriers related to medicines procurement in Brazil, especially for primary care, is scarce, but our results are consistent with the available evidence (Brasil, 2006b; Mattos et al., 2019). It is worth mentioning the managers' complaints concerning abusive sale prices, even after the implementation in Minas Gerais of the policy '*Strategy of Pharmaceutical Services Regionalization*—ERAF', conceived to improve medicines procurement and distribution within the state (Minas Gerais, 2016), also consistent with the literature. Pontes et al. (2017) showed that, of the 20 most purchased medicines, 19 had an average unit price above the reference price.

The availability of medicines at PCPs is one of the ultimate goals of the implementation of EMP. According to WHO, essential medicines should be continuously available within healthcare systems, in adequate amounts, in the appropriate doses, with assured quality (Laing et al., 2003). We evaluated almost 1,000 prescriptions and more than 2,300 prescribed medicines at primary care and found substandard levels of availability. Dispensing of 100% of the medicines prescribed to patients is the ideal value (Teni et al., 2022), but only 63% of medicines were available. Additionally, the full prescribed treatment was dispensed to just 46.2% of patients, rates lower than a previous study (Nascimento et al., 2017), but similar to another study in primary care we recently published (Bueno et al., 2021).

We analysed medicines availability using a combination of individual-level data sources. Therefore, differently from other assessment strategies (e.g, WHO, 2008; Rocha et al., 2021), our method allowed us to better evaluate the demand for medicines, comparing prescribed versus actually dispensed medicines at primary care. Cardiovascular medicines and drugs acting on the alimentary tract and metabolism were, at the same time, the most prescribed (41.8% and 16.0%, each) and the least available therapeutic groups (55.9% and 50.7%). Of the medicines analysed, 85.9% were listed in the MEML and the prescription pattern we found is largely coincident with our previous findings (Bueno et al., 2021). This evidence suggests a good level of prescriber adherence to the MEML and it is possible that prescribers are not being fully adherent to the lists because they mistrust the supply system. There are, however, considerable differences between the MEML's overall profile and the most prescribed therapeutic groups. In MEML, medicines for the nervous system clearly predominate (24.1%), with cardiovascular drugs appearing in second (16.7%) and alimentary tract and metabolism only in fourth (10.6%). Even though no extensive conclusions can be drawn, apparently the MEML are not strictly reflecting the clinical needs of primary care patients. If this is the case, it is possible that both over and understocking are occurring at PCPs and further studies are needed to better understand this point.

Limitations

This study provided valuable insights into EMP implementation and impact; however, some limitations must be acknowledged. We used interviews to collect part of the data, which is subject to selection and information biases. We managed such interferences by using pre-tested and piloted instruments and by employing trained interviewers that followed standardized procedures during fieldwork. Patients were interviewed after dispensing, with the presentation of medical prescriptions and medicines, minimizing the risk of memory bias (Luz et al., 2022). We adopted the principles of Rapid Evaluation Methods, so our patient sample cannot be considered representative of the Brazilian primary care population. However, the participants' characteristics are similar to those studies that included large samples of patients (Guibu et al., 2017; Bueno, Simões and Luz, 2021). MedMinas is a mixed-methods study that does not rely on a single research paradigm, thus allowing the extrapolation of the results to other Brazilian municipalities, especially medium to large-sized cities.

Implications for policy and practice

Medicines selection, procurement, and availability are core elements of the supply system in which each of these elements builds on the previous and leads to the next, cyclically (MSH, 2012). The Essential Medicines Policy (EMP) at PHCPS in Brazil follows the same rationale, i.e., its central purpose is to select evidence-based, quality, and cost-effective medicines in the adequate formulation and dose. These products need to be offered in the amounts that satisfy the population's health needs and must be rationally prescribed, dispensed at PCPs, and correctly used by patients (Vasconcelos et al., 2017; Bermudez et al., 2018).

Theoretically, one of the major benefits of implementing an EMP is achieving more regular and efficient medicines supply processes (Bazargani et al., 2014); however, our evidence does not support this assumption. Overall, our results point to weaknesses in the EMP implementation. Several key elements are missing,

such as stakeholder engagement, individual accountability for the policy implementation and outcomes, assurance of funding provision, and monitoring and evaluation procedures (Wright, 2017). It would be recommended to apply change strategies to stimulate participation and planning for effective EMP implementation.

The EML, beyond than being seen as normative instruments, need to be understood as a guideline to ensure the rational use of medicines (WHO, 2012). The lists are meant to be incorporated into health service practices as sources of reliable information and guidance for several processes and activities. Ultimately, if these documents are viewed by managers and healthcare professionals as mere lists of medicines, their effectiveness for the healthcare system is compromised as they will not contribute to medicine coverage to the population. Therefore, it is necessary to develop a plan to influence the general culture toward the importance and use of the EML.

The evident disconnection between medicines selection, procurement, and availability also suggests that the pharmaceutical management framework is not guiding the supply system. The consequence of the breakdown we have identified is the failure of the entire process, thus harming healthcare patients. Investments should be made to ensure adequate funding and pharmaceutical planning and management.

Conclusion

We have highlighted barriers to EMP implementation in primary care at SUS in Brazil, one of the largest public healthcare systems in the world. These findings contribute to informing future policy improvement actions to strengthen the supply system. Other countries adopting EMP and aiming to advance towards universal health coverage may learn from the challenges that Brazil still needs to address.

Data availability statement

The data that supported this study are not public, but may be shared upon reasonable request to the corresponding author.

Ethics statement

MedMinas Project was reviewed and approved by the institutional Ethics Committee of René Rachou Institute/ Fiocruz Minas (Reference: 2.682.759). The patients/ participants provided their written informed consent to participate in the study.

Author contributions

TCBL was responsible for funding acquisition, study conception, design, data analysis and interpretation, manuscript writing and final manuscript review. ICM e AKSC contributed to database preparation, data analysis and to final manuscript review. NULT contributed to results interpretation, discussion and to final manuscript review. BBC contributed to funding acquisition, results discussion, and final manuscript review. All authors read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

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Cost-benefit analysis of the integrated pharmaceutical supply chain information service after the establishment of the Korean Pharmaceutical Information Service

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Background: The Korean Pharmaceutical Information Service (KPIS) was established in October 2007 to increase the transparency of the pharmaceutical supply chain by integrating relevant information. This study aimed to describe the KPIS program and perform a cost-benefit analysis of the KPIS.

Methods: We conducted a cost-benefit analysis based on cost savings in terms of National Health Insurance (NHI). The outcome measures were the net financial benefit and benefit-cost ratio over the 12 years since the establishment of the KPIS. The cost estimate included the costs of labor and business operations, the development of an information entry system, and office maintenance. Financial benefits were defined as savings resulting from the implementation of the program based on KPIS data. Social benefits were defined as the prevention of recalled medicines from entering the supply chain and the decrease in inventory and disposal.

Results: The KPIS clearly resulted in a net financial benefit, saving 37.2 million USD, which was 2.6 times higher than the cost of implementation. While the benefit-cost ratio was less than one during the first period, it exceeded 3.4 during the second period. After calculating and integrating social benefits, the net benefit increased to 571.6 million USD, and the benefit-cost ratio was 24.8. A sensitivity analysis of the annual benefit showed that the net benefit varied from a low of −1.5 million USD to a high of 24.7 million USD according to the program implementation year.

Conclusion: The establishment of the KPIS and a system for collecting information on the pharmaceutical supply chain showed meaningful financial and social benefits when compared to the input cost. Since no other countries have an integrated pharmaceutical information system that incorporates all information from production to administration, the example of the KPIS can provide a precedent for other countries.

KEYWORDS

cost-benefit analysis, pharmaceutical supply chain, pharmaceutical information service, Korea, benefit

Introduction

The growing role of medicines in healthcare systems globally is driven both by emerging innovative medicines and the expansion of access due to universal health coverage (Aitken, 2016). Pharmaceutical products, which are more commonly known as medicines or drugs, play a critical role in treating patients, making it necessary for each country to have a well-managed production and supply system (WHO, 1988). Therefore, numerous studies have aimed to identify effective strategies for optimizing these systems (Shah, 2004). The pharmaceutical value chain encompasses all organizational and operational activities needed to manufacture, distribute, and prescribe or dispense medicines to the end-user, beginning with development (Mendoza, 2021). Although the components of the value chain can differ between markets depending on the medicine type, distribution channel, reimbursement regulations, and region, the key stakeholders in the drug supply chain are almost always pharmaceutical companies (drug manufacturers), wholesale distributors, hospitals, pharmacies, third-party payers, and patients (Mendoza, 2021).

Since the pharmaceutical supply chain process has a crucial impact on medication quality and the final outcomes for patients, a recent innovative trend in the pharmaceutical sector has been the integrated management of medicines from production to distribution (HIRA et al., 2021). Introducing technology such as radiofrequency identification (RFID) to the pharmaceutical supply chain can guarantee transparency in the flow of drugs in terms of traceability, thereby improving communication, reducing counterfeiting, and enabling drug quality monitoring in pharmaceutical supply chains (Catarinucci et al., 2012). Counterfeit and potentially harmful drugs are a growing problem worldwide, costing the pharmaceutical industry approximately 10% of its total revenue and contributing to numerous patient deaths (Mackey & Nayyar, 2017). Many countries have attempted to prevent counterfeit drugs from entering the pharmaceutical supply chain. On 27 November 2013, US President Barack Obama signed into law Title II of the Drug Quality and Security Act, now known as the Drug Supply Chain Security Act (DSCSA). The DSCSA requires the pharmaceutical supply chain to implement medication tracking and tracing; serialization, verification, and detection of suspicious products; and strict guidelines for wholesaler licensing and reporting (Brechtelsbauer et al., 2016) through the creation of programs such as the California E-Pedigree drug tracing program (Barlas, 2011; Mackey & Liang, 2011).

In South Korea, the government established the Korean Pharmaceutical Information Service (KPIS) in October 2007 under the jurisdiction of the Health Insurance Review and Assessment Service (HIRA) in order to implement an information management system that effectively integrates and tracks pharmaceutical information, codes, and supply chain data. In 2020, there were 435 manufacturers and importers and 3,108 wholesalers of drugs in Korea (HIRA, Annual). The HIRA determines the maximum reimbursement price for medicines through the National Health Insurance (NHI) and pays for the actual transaction cost of medicines in hospitals and pharmacies (Roughead et al., 2018). Before the KPIS was established, information about the importing, supply, and dispensing of pharmaceuticals were handled by several different agencies including the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, and the HIRA. Moreover, due to inconsistent approval codes, supply codes, and NHI drug codes, a system of codes was needed to easily identify manufacturers and drug categories. Accordingly, the government revised the Pharmaceutical Affairs Law in October 2007 and (Barchetti et al., 2010) established the KPIS.

Figure 1 shows the pharmaceutical supply chain covering from manufacturing and distribution to consumption to patients and the role of KPIS. The KPIS has conducted several projects such as 1) the serialization of individual products using 13-digit codes, 2) the real-time monitoring of supply details reported by pharmaceutical companies and wholesalers on a daily basis, including information on shipping, returns, and disposal, 3) overseeing the management of barcodes and RFID, 4) inspections to compare NHI claims data from hospitals or pharmacies against KPIS data from wholesalers, and 5) inspections to determine the actual transaction costs of medicines by comparing NHI claims data and KPIS data (Figure 1). If there is a large discrepancy between the wholesalers' data on their supply and the claims data from hospitals and pharmacies, the KPIS initiates an investigation. In addition, if a pharmacy claims the maximum price of a medication rather than the average purchasing price, then the KPIS asks the HIRA to determine the actual amount.

While the objective of the KPIS is to enhance safe medication use and to promote transparency within the pharmaceutical supply chain, there have been no studies to evaluate its achievements during the 12 years for which it has existed. Therefore, this study conducted a cost-benefit analysis of the KPIS since its establishment in terms of efficiency and medicine safety.

Meterial and methods

Study design and outcome measures

We conducted a cost-benefit analysis to compare uniform measurements using monetary values to evaluate the effect of

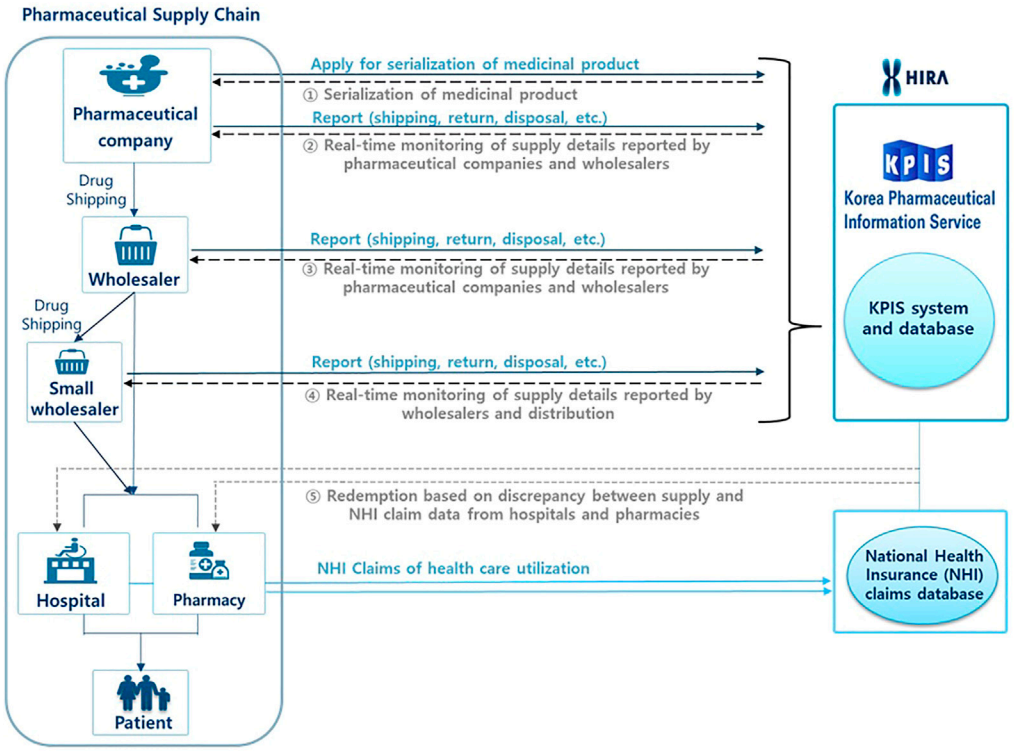

FIGURE 1
Schematic diagram of the functions of the Korean Pharmaceutical Information Service (KPIS).

projects carried out by the KPIS. The model was framed from the perspective of the NHI.

The primary outcome measures were the net financial benefit and benefit-cost ratio over the 12 years since the establishment of the KPIS. Data on costs and benefits were obtained using KPIS data, NHI claims data, and other published studies.

The formula used in this study is shown below (1). The net present value is the difference between benefits and costs, and a difference of greater than 0 indicates that there were some cost savings. The net present value was obtained by calculating the net benefit (benefits minus costs) according to the inflation rate of the corresponding year. The benefit-cost ratio is also shown below (2). To derive this formula, the benefits and costs generated during the period of each project were converted into the present value in 2018 according to the inflation rate of the corresponding year. Then, the sum of the benefits for each project was divided by the sum of each project's costs.

$$\text{Net present value} = \sum_{t=2007}^{2018}\left\{B_t \times \left(\frac{cpi_{2018}}{cpi_t}\right)\right\} - \sum_{t=2007}^{2018}\left\{C_t \times \left(\frac{cpi_{2018}}{cpi_t}\right)\right\} \quad (1)$$

$$B/C = \frac{\sum_{t=2007}^{2018}\left\{B_t \times \left(\frac{cpi_{2018}}{cpi_t}\right)\right\}}{\sum_{t=2007}^{2018}\left\{C_t \times \left(\frac{cpi_{2018}}{cpi_t}\right)\right\}} \quad (2)$$

B_t and C_t represent the benefits and costs generated in each selected yearn

Cpi_t represents the consumer price index at the time (t).

In addition, we divided the study period into two segments (2007-2012 and 2013-2018). The process for investigating fraud claims using KPIS data and NHI claims data was revised in 2014, which could have had a substantial effect on the benefit of the KPIS. Therefore, we analyzed data from 2007 to 2018 (the entire period), 2007 to 2012 (the first period), and 2013 to 2018 (the second period).

Cost estimate

The cost estimate was defined as expenses related to the operation of the KPIS and was mainly based on financial accounting statements for each fiscal year. We estimated the cost across 3 areas: 1) labor and operation costs, 2) the development of the information entry system (including the

cost of storage devices and software), and 3) building depreciation, real estate taxes, and office maintenance. We calculated both the nominal cost and the present value based on the consumer price index for 2018. The cost is presented in Table 1.

The labor, business operation, and computer server costs were estimated based on separate KPIS financial accounting reports for each fiscal year. However, the cost estimates for building depreciation, real estate taxes, and office maintenance were included in the general accounting records of the HIRA, and they were determined by calculating the proportional cost of the KPIS (1.4%) based on the general accounting records of the HIRA.

Benefit estimate

The benefit estimate was defined in terms of NHI financial benefits and social benefits. The financial benefits were measured as the savings resulting from the implementation of the program and the commission fee for providing KPIS information. The financial savings were derived based on 1) a comparison of the large discrepancy between data from wholesalers and claims data from hospitals and pharmacies, 2) an investigation of the actual transaction cost of medicine using KPIS data, 3) savings from decreased medicine prices resulting from the ability to identify rebates offered to doctors by pharmaceuticals companies. Social benefits were defined as the prevention of recalled medicines from entering the supply chain and the reduction of inventory and disposal.

Data were obtained from a KPIS report that analyzed both NHI claims data and KPIS data from 2007 to 2018. The KPIS created a dataset based on data from 35,054 medical institutions (general hospitals, hospitals, and clinics), 17,905 dental hospitals and clinics, 3,478 public health agencies, and 22,082 pharmacies across the entire population of South Korea, at 50.8 million people. We calculated the expenses in order to quantify the financial benefits and savings.

Social benefits were defined based on the potential costs reported in previous studies. We conducted a literature review of articles published between 2005 and 2019 in Korean or English using Google Scholar, IEEE Xplore, and Medline. We also reviewed texts published by the government or research centers, or works published in newspapers.

Finally, we defined financial benefits as savings from the implementation of the program and social benefits as the improvement of patient safety and the increase in transparency of the distribution chain. First, since monitoring reports of supply details and providing information about recalled medicines could prevent recalled medicines from entering the supply chain, thereby tracking and integrating information on the pharmaceutical chain could enhance patient safety, we analyzed the drug cost of recalled medicines in the previous year. Second, we used the value on the improvement of the efficiency of the supply chain in the literature review.

Base analysis and subgroup analysis

We analyzed the net financial benefit and benefit-cost ratio for the entire period, the first period, and the second period. In addition, we compared the results for financial benefits alone with the results for financial benefits and social benefits combined. Sensitivity analysis was performed using all possible combinations of savings resulting from the program's implementation according to the annual range at the end of each year.

Results

Cost and benefit of the implementation of KPIS programs

The overall values for costs and benefits are shown in Table 1, and the yearly values are shown in Table 2.

The labor and operation cost totaled 14.1 million USD, while the cost to develop the information entry system (including storage devices and software cost) was 9.0 million USD. The cost estimate for building depreciation, real estate taxes, and office maintenance was 0.9 million USD.

Savings from the implementation of the program totaled 61.2 million USD. The commission fee for providing KPIS data to companies was 8.1 million USD, and savings from the reduction of the large discrepancy between data from wholesalers and NHI claims from hospitals or pharmacies was 20.5 million USD. The decrease in expenditures due to lower drug prices based on actual transaction costs was 12.2 million USD, and savings from the decreased cost of medicines due to the ability to identify rebates offered to doctors by pharmaceutical companies totaled 16 million USD.

Net benefit and benefit-cost ratio

We calculated the net present value as of 2018 using the financial savings from the KPIS program (Table 3). Over the entire period, the KPIS had a substantial financial net benefit of 37.2 million USD. At the beginning of the program, the initial costs were paid; therefore, the savings were not yet apparent. Thus, the first period analyzed (2007-2012) did not correspond to substantial revenue from the various projects undertaken by the KPIS, and the financial benefit was mostly seen during the second period (2013-2018). Throughout the entire period, the

TABLE 1 Parameter values in the model.

Parameter (million USD)	Base case				
	Entire period	First period (2007-2012)<	Second period (2013-2018)	Annual value (range)	Source
Cost					
Total cost	24.0	8.8	15.2	2.0 (0.9–3.6)	
Labor and operation costs	14.1	3.7	10.5	1.2 (0.2–2.7)	Financial accounting
Information entry system hardware and software	9.0	4.8	4.2	0.7 (0.6–0.9)	Financial accounting
Office maintenance costs	0.9	0.3	0.6	0.1 (0.0–0.1)	Financial accounting
Financial benefits					
Savings from program (Comparison of discrepancies between wholesalers' supply and NHI claims data from hospitals and pharmacies)	61.2	9.2	52.0	5.1 (0.9–3.6)	
Fee for providing KPIS information	8.1	3.0	4.7	0.7 (0.3–1.3)	Report
Providing KPIS information to the government (saving without survey)	0.9	0.2	0.7	0.1 (0.1–0.1)	Analysis
Detection of errors in reporting supply detail	20.5	0.0	20.5	1.7 (0–20.5)	Report
Inspection of claims of medicine price	12.2	5.6	6.6	1.0 (0.7–3.8)	Report
Inspection of recalled medicines distribution (1 year)	2.2	-	2.2	0.2 (0–2.2)	Report
Pharmaceutical consumption statistics (cost savings without survey)	1.3	0.0	1.2	0.1 (0–0.3)	Report
Prevention of rebates to doctors by drug companies	16.0	0.0	16.0	1.3 (0–3.2)	Report
Social benefits					
Prevention of recalled medicines use	171.4				Analysis
Improvement of the efficiency of the supply chain	361.8				Alshemari et al. (2020)

KPIS, korean pharmaceutical information service; NHI, National Health Insurance; Note: Measurements are based on the year 2018, reflecting the consumer price index.

benefit was 2.6 times higher than the cost. The benefit-cost ratio was less than 1 in the first period, and it exceeded 3.4 during the second period.

When the social benefits and financial benefits were combined, the net benefit increased to 441.7 million USD, and the benefit-cost ratio was 19.4 (Figure 2).

Discussion

Since the integration of information on the pharmaceutical supply chain prompted by the creation of the KPIS in October 2007, the KPIS has been able to track the serial numbers of medicines from the production stage to distribution as a result of the serialization of all medicines. The KPIS has conducted several projects such as monitoring supply details reported by pharmaceutical companies and wholesalers on a daily basis, including information on shipping, returns, and disposal; managing barcodes and RFIDs; and calculating the amount of supply and actual transaction cost of medicines using NHI claims data and KPIS data.

Previous studies have suggested that a drug traceability system incorporated into the pharmaceutical supply chain can create value (Silva & Mattos, 2019), and the integration of supply chain information should be viewed as an effective risk management tool for mitigating uncertainty and risk in the supply chain (Wang & Jie, 2020). Another study suggested that implementing an RFID model for tracking drugs at the item level in the pharmaceutical supply chain might have the potential to reduce the scope of the counterfeit drug problem (Coutstasse et al., 2010). One study also suggested that a circular pharmaceutical supply chain might reduce medicine waste (Alshemari et al., 2020). Risks in the pharmaceutical supply chain include product discontinuity, product shortages, poor performance, patient safety/dispensing errors, and technological errors (resulting in stock shortages at pharmacies). Strategies for optimizing the pharmaceutical supply chain can be achieved through the integration of information (Shah, 2004).

TABLE 2 Twelve-year costs and savings from the implementation of KPIS program (million USD).

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Cost												
Labor and operation costs	0.0	0.8	1.0	1.0	0.3	0.5	0.2	0.8	1.7	2.4	2.7	2.6
Information entry system hardware and software	0.9	0.8	0.9	0.6	0.8	0.8	0.6	0.6	0.7	0.8	0.8	0.8
Office maintenance costs	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Financial benefits												
Fee for providing KPIS information		0.3	0.5	0.6	0.9	1.0	1.3	1.1	0.8	0.7	0.6	0.3
Providing KPIS information to the government (saving without survey)					0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Detection of errors in reporting supply detail								20.5			0.0	0.0
Inspection of claims of medicine price					1.8	3.8	2.5	0.8	0.7	0.7	0.9	0.9
Inspection of recalled medicines distribution (1 year)												2.2
Pharmaceutical consumption statistics (cost savings without survey)								0.2	0.3	0.3	0.2	0.3
Prevention of rebates to doctors by drug companies							3.2	3.4	2.9	2.3	2.2	2.1
Social benefits												
Prevention of recalled medicines use*											80.7	90.7
Improvement of the efficiency of the supply chain											120	240

KPIS, korean pharmaceutical information service; NHI, National Health Insurance; Note: The cost of preventing recalled medicines from entering the supply chain in 2019 was 298.2 million USD.

TABLE 3 Results of the cost-benefit analysis of the base case and scenarios.

	Net benefit (million USD)		Benefit-cost ratio	
	Cumulative value	Annual value	Cumulative value	Annual value
Financial benefits				
Entire period	37.2	3.1 (−1.5–24.7)	2.6	3.2 (0–18.2)
First period (2007-2012)	0.4	0.0 (−1.5–3.6)	1.0	1.1 (0–3.7)
Second period (2013-2018)	36.8	6.2 (0.4–24.7)	3.4	5.4 (1.2–18.2)
Financial and social benefits (improvement of the efficiency and patient safety)				
Entire period	571.6	55.2 (−1.5–333.2)	24.8	15.8 (0–96.6)
First period (2007-2012)	0.4	0.0 (−1.5–3.6)	1.0	1.1 (0–3.7)
Second period (2013-2018)	571.2	95.2 (0.8–333.2)	38.5	30.5 (1.2–96.6)

According to this study, over the 12 years since the establishment of the KPIS, despite the initial costs, the KPIS and the integration of information on the pharmaceutical supply chain have shown clear benefits from the various programs administered by the KPIS and generated social benefits including the prevention recalled medicines from reaching the market and improving the efficiency of the supply chain. Our study showed that, although the initial costs of the information entry system were high, including the costs of a super-computer server and software, the benefits of the system and program are also high. Although the value of integrated information on the pharmaceutical supply chain may be high, it is challenging to create a system that incorporates information on authorization, supply, distribution, and reimbursement across various medical institutions, pharmacies, and wholesalers. Nonetheless, the implementation of such a system can be expected to provide crucial benefits in terms

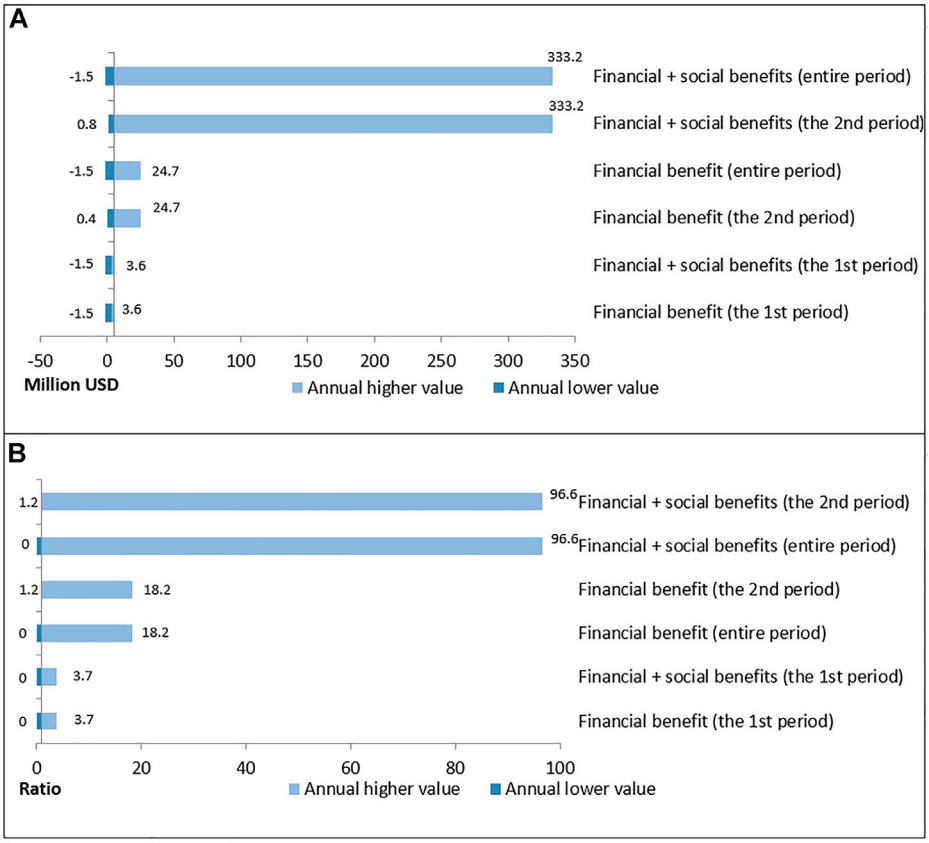

FIGURE 2
A tornado diagram of the sensitivity analysis.

of transparency of the pharmaceutical supply chain as well as patient safety. Especially transparency of the pharmaceutical supply chain might be strengthened from the program such as reporting drug shipping, return, and disposal, *etc.* By pharmaceutical companies or wholesalers and integrating these data, thereby cost savings can occur. The inspections to compare the medicine use in the NHI claims data from hospitals or pharmacies against the supply details in the KPIS data from wholesalers could detect errors or fraud of claims. Also, by integrating information on the pharmaceutical supply chain, tracking the potentially harmful drugs use such as recalled medicines could improve patient safety.

Since no other countries have comparable systems or institutions to the KPIS that integrate information on the pharmaceutical supply chain from the manufacturing stage to administration, it is difficult to compare the effect of this program for enhancing the transparency of the pharmaceutical supply chain to other systems. Several studies found that risks in the pharmaceutical supply chain were internal risks that could be managed using mitigation strategies (Jaberidoost et al., 2013; Wang & Jie, 2020), and efforts should be made to prevent pharmaceutical counterfeiting from entering the supply chain using RFID technology. However, no studies have yet evaluated the outcomes of establishing an integrated information system related to pharmaceutical supply chain management and logistics.

To the best of our knowledge, this is the first study to describe the model for integrating and managing information on the pharmaceutical supply chain in Korea and conduct a cost-benefit analysis of the KPIS to gather information and implement programs using these data. Thus, the results provide meaningful evidence for the establishment of pharmaceutical supply chain information management systems. We analyzed the costs and savings related to the prevention of recalled medicines and hazardous drugs containing carcinogenic substances from entering the supply chain by examining pharmaceutical expenditures from previous years using KPIS data. In addition, we attempted to consider social benefits based on improvements in the efficiency of the supply chain.

Second, this system such as KPIS is expected to be a reference for other countries in their efforts to integrate and manage information on the pharmaceutical supply chain. Moreover, as patient-oriented care increases in importance and access to

pharmaceutical information expand to become more consumer-oriented and easier, meaning that the system integrating the pharmaceutical supply chain information will play a critical role as a provider of information on the pharmaceutical supply chain.

Nevertheless, our study has limitations. We limited the financial and social benefits to empirically measured values and only used an estimated value to measure improvement in the efficiency of the supply chain. Second, the time and costs related to entering information into the entry system by pharmaceutical companies and wholesalers were not included when estimating costs since this study focused on the costs paid through NHI and the related savings. Second, the time and costs related to entering information into the entry system by some players (pharmaceutical companies, wholesalers) in the PSC were not included when estimating costs since the model in this study was framed from the perspective of the NHI, and so we focused on the costs paid through NHI and the related savings. Also, in terms of benefits, we did not include the benefit of the pharmaceutical companies and wholesalers using the KPIS data.

In conclusion, the establishment of the KPIS and a system for collecting information on the pharmaceutical supply chain in Korea showed improved benefits compared to the cost of implementation. Further strategies should be introduced to increase the efficiency of the pharmaceutical supply chain and to promote patient safety by providing patients, physicians, and pharmacists with supply and distribution information.

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

MK: Data management, analysis, and writing a draft paper GL: Data management and analysis YH: Revising the manuscript THK: Revising the manuscript D-SK: Design of study, writing, and revising the manuscript.

Conflict of interest

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

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Health-related quality of life in adult patients with asthma according to asthma control and severity: A systematic review and meta-analysis

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Background: The utility values are increasingly being used in economic evaluations and health policy decision making. This study aims to conduct a systematic literature review and meta-analysis of the utility values for asthma, particularly with respect to severity and asthma control.

Materials and methods: A literature search was conducted using the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases for studies published until July, 2020, reporting the utilities of adult asthma. We extracted utility values derived by nine indirect and four direct utility instruments. Meta-analyses were performed for each utility instrument according to health states based on the level of asthma control and severity.

Results: Fifty-two eligible studies were included in our systematic review, of which forty studies were used in the meta-analyses. Among the 13 utility instruments, the most used was EQ-5D-3L, whereas EQ-5D-5L showed the narrowest 95% confidence interval (95% CI, 0.83–0.86) of pooled utility. The pooled utility of asthma declined with worsening control levels and severity. The pooled utility value of EQ-5D-3L was 0.72 (95% CI, 0.63–0.80) for uncontrolled, 0.82 (95% CI, 0.75–0.88) for partly controlled, and 0.87 (95% CI, 0.84–0.90) for well-controlled asthma.

Conclusion: Our study shows that EQ-5D-3L and EQ-5D-5L are appropriate for economic evaluations in terms of availability and variability of information, respectively. Asthma patients had poorer utility values with worsened severity and level of asthma control. This study will be useful for health economists conducting economic evaluations of asthma treatments.

KEYWORDS

asthma, quality of life, utility, systematic review, meta-analysis

1 Introduction

Asthma is the most common chronic disease, with patients suffering from it worldwide (Asthma Fact sheet, 2017). Asthma causes symptoms, such as shortness of breath, chest tightness, coughing, and wheezing attacks. Monitoring these symptoms is essential for disease management. The Global Initiative for Asthma (GINA) guidelines provide two different assessment criteria based on severity (mild, moderate, or severe) and level of asthma control (well-controlled, partly controlled, or uncontrolled) (Global Initiative for Asthma, 2021). Despite the global decline in asthma mortality with the increased use of inhaled corticosteroids in recent years, asthma continues to cause considerable disability and deteriorates the quality of life of patients (Papi et al., 2018). Asthma places financial burden on patients and the society, including the costs of controlling symptoms, preventing exacerbation, absenteeism, and mortality. This burden is evident from the fact that the total cost of asthma to society in 2013 was $81.9 billion (Nurmagambetov et al., 2018).

Ideally, all treatments should be available for patients; however, decision makers must also consider the scarcity of available resources. Therefore, economic evaluations have been used to obtain the best treatment for the financial investments made by health care systems (Gold et al., 1996). Economic evaluations need to estimate quality-adjusted life years (Kim et al., 2018), based upon health-state utility values (HSUVs) and the length of life gained (Richardson, 1994). Economic evaluations of asthma that reflect clinical reality require the utility values according to the level of asthma control (Gerzeli et al., 2012; Ismaila et al., 2014; Willson et al., 2014). Guidelines and clinical situations are focusing on classification by control level rather than by severity, since assessment by control level considers both the current state of the patient and the risk of future adverse effects (National Asthma Education and Prevention Program, 2007; Global Initiative for Asthma, 2021).

Previously, Einarson et al. (Einarson et al., 2015) summarized utility values of asthma and chronic obstructive pulmonary disease from studies published until 2014, according to severity. They also presented a summary of studies reporting utility values as per control level, according to a broad definition of control level. Costa et al. (Costa et al., 2019) performed a meta-analysis of quality of life according to degree of asthma control, however, this analysis included only pediatric asthma patients and their caregivers. Recently, Afshari et al. (Afshari et al., 2021) conducted a systematic review and meta-analysis of EQ-5D-5-level version (EQ-5D-5L) utility values in asthma according to level of control. However, the review only included EQ-5D-5L. Given this state of the evidence, there is a need to update the available utility values in adult asthma patients including various utility instruments. Also, to the best of our knowledge, there is no meta-analysis according to the level of asthma control in adults except for a study using EQ-5D-5L.

Therefore, we aimed to provide a comprehensive summary of the available utility values in asthma according to both severity and level of control through a systematic literature review and meta-analysis.

2 Methods

The study protocol was prospectively registered in the PROSPERO database (reference number: CRD42021246572). This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

2.1 Search strategy

A systematic search was conducted using MEDLINE (*via* PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases in July, 2020. The search strategy included Medical Subject Headings (MeSH), Embase subject headings (Emtree), and text words related to asthma, quality of life, and utility instruments. Our search strategies for the three databases are shown in Supplementary Tables S2.1–S2.3.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: studies reporting the utility of asthma in adults using EQ-5D-3-level version (EQ-5D-3L) (Brooks, 1996; Herdman et al., 2011), EQ-5D-5L (Herdman et al., 2011), health utilities index (HUI)-2 (Mo et al., 2004), HUI-3, short form-6D (SF-6D) (Brazier et al., 2002), asthma symptom utility index (ASUI) (Bime et al., 2012), asthma quality of life utility index (AQL-5D) (Sullivan et al., 2016), 15D (Sintonen, 2001), quality of well-being (QWB) (Kaplan and Bush, 1982; Kaplan et al., 1989), EuroQol-visual analog scale (EQ-VAS), visual analog scale (VAS) (Torrance et al., 2001), standard gamble (SG) (Torrance, 1976), and time trade-off (TTO) (Lugnér and Krabbe, 2020). Secondary research was included only if unpublished results from the original research were cited. Only full-text articles in English were included in this study. Conference abstracts were not considered because they frequently report incomplete or non-peer-reviewed data. Studies using mapping algorithms to calculate preference-based health utilities were excluded. We did not apply date limits or study design restrictions because studies reporting utility values do not fall into a particular study design. Studies that were not clinically or methodologically comparable were excluded, such as studies that reported utility values of asthma patients with intervention (e.g., digital asthma self-management intervention) or focused on specific type of asthma (e.g., with a

blood eosinophil count≥400 cells/μℓ). The detailed inclusion and exclusion criteria are summarized in Supplementary Table S1 and the citations of excluded full texts are presented in Supplementary Table S3.

2.3 Screening and data extraction

Titles and abstracts were reviewed for eligibility as per the inclusion criteria. The full texts remaining at this stage were further screened against the inclusion criteria. These steps were performed by two reviewers: one who conducted the initial screening, and another who validated the decisions. Discrepancies between the reviewers were resolved by consensus, and if the disagreement persisted, a third reviewer made the final decision.

Data extraction was performed by two reviewers using a standardized data extraction template in Microsoft Excel (version 2016; Microsoft, Redmond, WA, United States). One reviewer performed the initial extraction and another crosschecked the extracted data. The following data were extracted: study characteristics (year of publication, geographic location, and study design), patient demographics (age, sex, asthma severity, and level of asthma control), sample size, utility instrument used, and utility values. When utility values were measured multiple times during the follow-up period, the first measurement or baseline utility was extracted to use comparable utilities not confounded by further treatment.

2.4 Quality assessment

To our knowledge, there are no agreed-upon reporting standards for HSUV studies. Therefore, the quality of the included studies was evaluated using the criteria framework set described by Papaionannou et al. (Papaioannou et al., 2013), which was used in previous studies (Meregaglia and Cairns, 2017; Saeed et al., 2020; Szabo et al., 2020). The criteria were as follows: 1) sample size ≥100; 2) description of respondent selection and recruitment; 3) description of inclusion/exclusion criteria; 4) response rate ≥60%; 5) reporting of the amount and reasons for loss to follow-up; 6) reporting of the level of missing data and methods to handle the issue; and 7) appropriateness of the measure (based on the judgment of the review authors).

2.5 Data synthesis

Data synthesis was conducted in two parts. First, meta-analyses were performed on the general asthma utility values that did not classify asthma according to severity or level of control. All meta-analyses were stratified by utility instruments: EQ-5D-3L, EQ-5D-5L, HUI-3, HUI-2, SF-6D, ASUI, AQL-5D, 15D, QWB, EQ-VAS, VAS, SG, TTO. Second, meta-analyses were performed with the studies reporting utility values categorized into health states based on asthma severity (intermittent, mild, moderate, severe) and level of control (well-controlled, partly controlled, uncontrolled) to reduce heterogeneity. They were performed using EQ-5D-3L, EQ-5D-5L, SF-6D, and HUI-3, which are the most frequently mentioned instruments in pharmacoeconomic guidelines (Kennedy-Martin et al., 2020), and ASUI and AQL-5D, which are disease-specific instruments. The criteria for judging severity or level of control were not limited.

The literature used for meta-analyses differs in study design, therefore, the DerSimonian-Laird random effects model weighted by inverse squared standard error was used to incorporate the between-study heterogeneity (Laird and Mosteller, 1990). Standard deviation was calculated using the method presented in the Cochrane Handbook through the confidence interval (CI) and standard error if it was unreported in the literature (Higgins, 2011). Studies that did not report standard deviation, CI, and standard error were excluded from the meta-analyses. Tests for heterogeneity were performed using Higgin's I^2 statistic.

Publication bias was assessed using funnel plots and Egger's regression test for meta-analysis including more than 10 studies (Egger et al., 1997; Higgins, 2011). The sensitivity analyses were performed to assess the impact of excluding studies that did not explicitly report the control-level criteria and to determine the influential studies using the leave-one-out method (Viechtbauer and Cheung, 2010). All analyses were performed in R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) using the "meta" and "metafor" packages (Schwarzer, 2007; Viechtbauer, 2010).

3 Results

3.1 Study selection

After removing duplicates, 939 studies were identified, of which 52 studies met the criteria (see Figure 1 for this process, and see Supplementary Table S3 for the reasons for the excluded studies) (Rutten-van Mölken et al., 1995; Blumenschein and Johannesson, 1998; Revicki et al., 1998; Mittmann et al., 1999; Burström et al., 2001; Juniper et al., 2001; Mittmann et al., 2001; Meszaros et al., 2003; Moy et al., 2004; Smith et al., 2004; Szende et al., 2004; Lubetkin et al., 2005; Flood et al., 2006; Aburuz et al., 2007; Chen et al., 2007; Willems et al., 2007; Barton et al., 2008; McTaggart-Cowan et al., 2008; Polley et al., 2008; Heyworth et al., 2009; Ferreira et al., 2010; Chen et al., 2011; van der Meer et al., 2011; Allegra et al., 2012; Bime et al., 2012; Gonzalez-Barcala et al., 2012; Al-kalemji et al., 2013; Doz et al., 2013; Sullivan et al., 2013; D'Amato et al., 2014; Koskela et al., 2014;

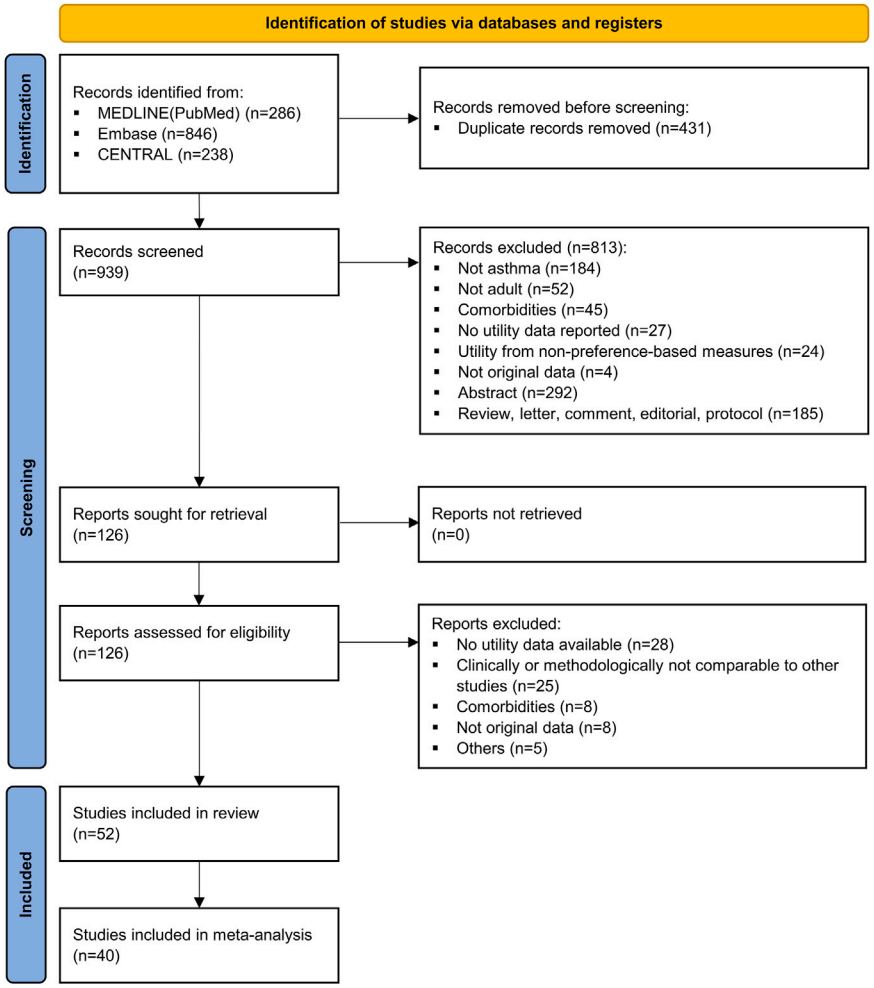

FIGURE 1
PRISMA flow diagram of study selection. CENTRAL, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

Peters et al., 2014; Sadatsafavi et al., 2015; Sullivan et al., 2016; Yong and Shafie, 2016; Kaambwa et al., 2017; Mitchell et al., 2017; Thomas et al., 2017; Chen et al., 2018; Chung and Han, 2018; Gray et al., 2018; Hernandez et al., 2018; Khan and Richardson, 2018; Kontodimopoulos et al., 2018; Mungan et al., 2018; Retzler et al., 2018; Tarraf et al., 2018; Wilson et al., 2018; Hernandez et al., 2019; Johnson et al., 2019; Lanario et al., 2020; Lucas et al., 2020). Of these, 40 studies capable of quantitative synthesis were meta-analyzed after excluding 12 studies without information on the measure of uncertainty. The main characteristics of the 52 included studies are presented in Table 1 (see Supplementary Tables S4 for study-level characteristics, including the study design and patient characteristics). Studies were actively conducted in Europe (44.2%) and most of them were observational designs (88.5%). EQ-5D-3L was the most used instrument (24.5%) when comparing tools that measure utility indirectly, followed by HUI-3, SF-6D, EQ-5D-5L, and ASUI. Among the direct instruments, the most frequently applied was EQ-VAS (20.8%). Numerous studies had adequate reporting for the quality assessment criteria, however, they frequently lacked an explanation for how they handled missing values (Supplementary Tables S5).

3.2 Meta-analyses of health state utility values

Of the 40 studies included in this meta-analysis, 67 utility estimates representing general asthma were identified. Table 2 shows the results of the random effects meta-analyses using utility instruments with 95% CIs and the ranges of observed

TABLE 1 Study characteristics (N = 52).

	Number of studies	%
Study design		
Observational	46	88.5
Experimental	6	11.5
Study location		
Europe	23	44.2
North America	17	32.7
Asia	2	3.8
Multi-country	10	19.2
Publication year		
2011–2020	31	59.6
2001–2010	17	32.7
≤2000	4	7.7
Utility instrument[a]		
Indirect measures		
EQ-5D-3L	26	24.5
EQ-5D-5L	7	6.6
HUI-3	8	7.5
HUI-2	1	0.9
SF-6D	8	7.5
ASUI	6	5.7
AQL-5D	5	4.7
15D	4	3.8
QWB	1	0.9
Direct measures		
EQ-VAS	22	20.8
VAS	8	7.5
SG	6	5.7
TTO	4	3.8

ASUI, asthma symptom utility index; *AQL-5D*, Asthma Quality of Life Utility Index 5 Dimensions, *EQ-5D-3L* EQ-5D-3-level version, *EQ-5D-5L* EQ-5D-5-level version, *HUI*, health utilities index; *QWB*, Quality of Well-Being; *SF-6D*, Short Form-6D, *SG*, standard gamble; *TTO*, Time Trade-Off; *VAS*, visual analog scale, *15D* 15 dimensional.
[a]Multiple studies have reported utility values using more than one instrument.

utility estimates in the studies. The most widely used instrument EQ-5D-3L resulted in a utility value of 0.78 (95% CI, 0.74–0.82). EQ-5D-5L, which has been available since 2011, showed a narrower CI than the original EQ-5D value set (95% CI, 0.83–0.86). Other measures commonly used in economic evaluations, such as HUI-3 (pooled utility, 0.78; 95% CI, 0.71–0.86) and SF-6D (pooled utility, 0.74; 95% CI, 0.70–0.79), revealed similar pooled utilities. The analysis of EQ-5D-3L showed considerable heterogeneity (I^2: 97.4%), as results vary from 0.63 (95% CI, 0.46–0.80) to 0.91 (95% CI, 0.90–0.92) in Figure 2. Forest plots of the other utility measures are presented in Supplementary Figure S1.1–S1.10.

Table 3 shows the pooled utility values according to asthma severity and level of control. Eleven studies reported utility values according to asthma control, of which seven used EQ-5D-3L. We assessed that the more difficult it was to control asthma, the lower the pooled utility value. The most reported EQ-5D-3L values declined in the order of 0.87 (95% CI, 0.84–0.90) for well-controlled, 0.82 (95% CI, 0.75–0.88) for partly controlled, and 0.72 (95% CI, 0.63–0.80) for uncontrolled asthma. Forest plots of EQ-5D-3L values classified by control level are presented in Figure 3. Additionally, the results of the meta-analyses for two or more studies using the same measures for specific health states are provided in Supplementary Figure S2.1–S2.11.

3.3 Publication bias and sensitivity analysis

The majority of valuation instruments had few reported utility values to conduct a publication bias assessment. Funnel plots and Egger's regression test for funnel plot asymmetry did not show substantial asymmetry (Supplementary Figure S3.1, S3.2).

We excluded studies that did not explicitly report the control-level criteria for the meta-analyses as a sensitivity analysis. One study was excluded for well-controlled and partly controlled asthma and two studies were excluded for uncontrolled asthma. In this sensitivity analysis, the pooled estimates were similar, as the main analysis and the value of uncontrolled asthma only increased slightly by 0.01–0.03 (Supplementary Figure S4.1–S4.3). We also applied the leave-one-out method for sensitivity analysis of meta-analyses of EQ-5D-3L stratified by the level of asthma control. This revealed that Sadatsafavi et al. (Sadatsafavi et al., 2015) has substantial heterogeneity in the meta-analysis for well-controlled and partly controlled health states. The meta-analyses excluding the study resulted in reduced heterogeneity in both well-controlled (pooled utility, 0.86; I^2, 89.2%) and partly controlled (pooled utility, 0.79; I^2, 90.0%) health states (Supplementary Figure S5.1–S5.3).

4 Discussion

In this study, we conducted a comprehensive review of the available data on the utility values of adult asthma patients. We also performed meta-analyses according to utility instruments and health states based on the level of asthma control and severity, including various utility instruments. Many studies reporting utility values are not big enough to provide convincing estimates for each utility instrument. We provided more accurate estimates of the mean utility values and the associated uncertainty than individual studies by pooling relatively homogeneous utility values. In economic evaluations, it is recommended to use utility values obtained from studies using the same utility instrument and weights for all health states (Brazier et al., 2019). However, it may not always be

TABLE 2 Results of random effects meta-analyses for asthma utility[a] stratified by utility instruments.

	Number of studies[b]	Number of respondents	Pooled utility, mean (95%CI)	Observed utility	
				Minimum	Maximum
Indirect measures					
EQ-5D-3L	15	6,212	0.78 (0.74–0.82)	0.63	0.91
EQ-5D-5L	5	2,788	0.84 (0.83–0.86)	0.83	0.88
HUI-3	8	5,106	0.78 (0.71–0.86)	0.57	0.96
HUI-2	1	161	0.84 (0.81–0.87)	0.84	0.84
SF-6D	7	1,963	0.74 (0.70–0.79)	0.69	0.86
ASUI	5	3,089	0.76 (0.73–0.80)	0.63	0.83
AQL-5D	3	755	0.88 (0.83–0.93)	0.85	0.92
15D	2	1,435	0.84 (0.83–0.86)	0.84	0.85
QWB	1	579	0.63 (0.62–0.64)	0.63	0.63
Direct measures					
EQ-VAS	12	5,536	0.70 (0.68–0.73)	0.60	0.77
SG	4	227	0.84 (0.77–0.91)	0.49	0.91
VAS	2	176	0.60 (0.31–0.88)	0.44	0.73
TTO	2	169	0.86 (0.76–0.96)	0.81	0.91

ASUI, asthma symptom utility index; *AQL-5D*, Asthma Quality of Life Utility Index 5 Dimensions; *CI*, confidence interval, *EQ-5D-3L* EQ-5D-3-level version, *EQ-5D-5L* EQ-5D-5-level version, *HUI*, health utilities index; *QWB*, Quality of Well-Being; *SF-6D*, Short Form-6D, *SG*, standard gamble; *TTO*, Time Trade-Off; *VAS*, visual analog scale, *15D* 15 dimensional.
[a]Utility of health conditions representing general asthma.
[b]Multiple studies have reported utility values using more than one instrument.

possible. Our results of meta-analyses for each utility instrument could be applied to economic evaluations cautiously when appropriate utility values from the same measure are unavailable. Also, our pooled estimates and catalog of studies reporting preference-based utility values would provide a reference to determine utility values or to use instruments.

Our findings highlight the differences in utility values across different severity and levels of asthma control. Previous studies have shown that the quality of life in asthma patients decreases with decreasing levels of control and increasing severity (Juniper et al., 1993; Moy et al., 2004; Chen et al., 2007; Chen et al., 2015). Consistent with previous literature, the meta-analyses results of EQ-5D-3L, EQ-5D-5L, and SF-6D showed that utilities declined with worsened control level and severity in asthma patients. The results of meta-analyses using disease-specific instruments (ASUI, AQL-5D) also showed that utilities declined with worsened control level and severity, as with other instruments. However, only a small number of studies were included in the analysis. In the case of HUI-3, the utility of the partly controlled category (pooled utility, 0.84; 95% CI, 0.80–0.88) was marginally higher than that of the well-controlled category (pooled utility, 0.83; 95% CI, 0.77–0.89). However, these results are based on one study (McTaggart-Cowan et al., 2008), and it was reported that the difference by control level was not statistically significant.

Certain studies reported utility values that differed considerably from the EQ-5D-3L pooled estimates. For example, Sadatsafavi et al. (Sadatsafavi et al., 2015) reported a utility value of 0.91 (95% CI, 0.90–0.92) for asthma patients, which is relatively higher than the pooled estimate of 0.78 (95% CI, 0.74–0.82). It was a prospective observational study reporting 12 months of follow-up. Therefore, there is a risk of healthy volunteer bias, as patients who are able to visit the study site would be primarily included in the study (Pinsky et al., 2007). This may cause heterogeneity when compared with the results of survey-based research. In contrast, Polley et al. (2008) showed a relatively low utility value with a large standard deviation, reflecting the low precision of the estimate (pooled utility, 0.63; 95% CI, 0.46–0.80). This large variance could be due to the small sample size, i.e., 20. According to previous studies, sample size is one of the main criteria for quality assessment and is generally judged based on whether the sample size is 100 or more (Papaioannou et al., 2013; Meregaglia and Cairns, 2017; Szabo et al., 2020).

The use of various utility instruments in an economic evaluation can cause spurious results because differences between utility instruments can affect the results (Brazier et al., 2019). Therefore, it is necessary to select an appropriate utility instrument. Our study shows that EQ-5D-3L and EQ-5D-5L are appropriate for economic evaluations in terms of availability and variability of information, respectively.

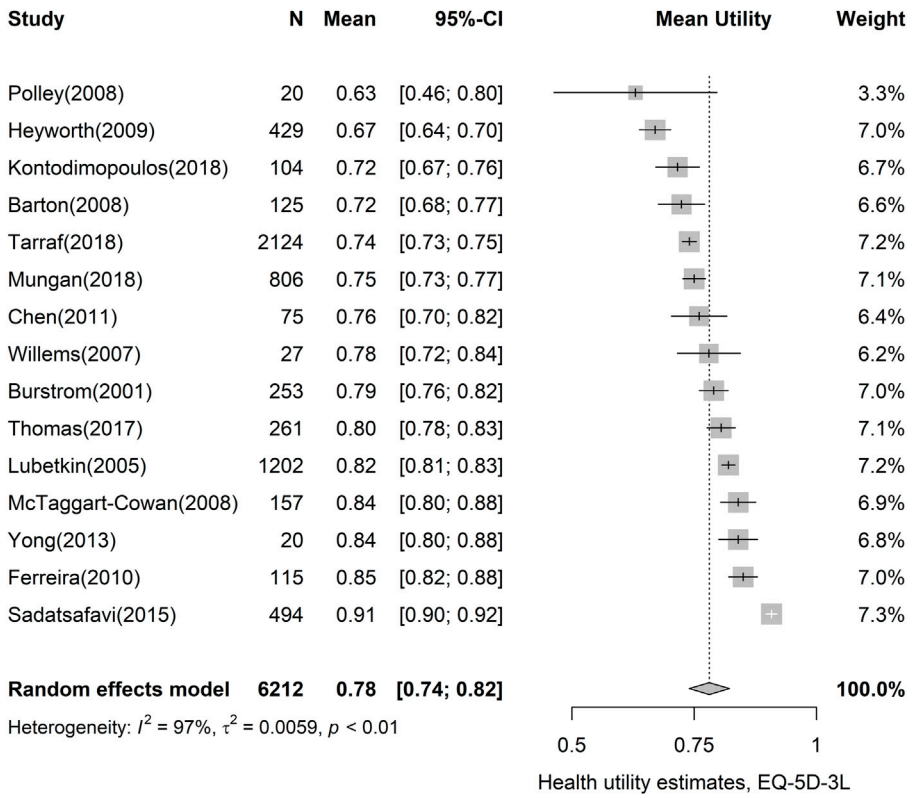

FIGURE 2
Forest plot of asthma utility, using the EQ-5D-3L instrument. CI, confidence interval; EQ-5D-3L, EQ-5D-3-level version.

Economic evaluations often face difficulties in collecting optimal health state utility values, and it is difficult for a single source to reflect all the data required for decision making (Sculpher et al., 2006; Petrou et al., 2018; Brazier et al., 2019). Therefore, it is crucial to use a utility instrument with more available input values. According to this review, the most commonly used instrument in the literature reporting utility values stratified by the level of asthma control was the EQ-5D-3L; it is relevant, as utility values according to the level of asthma control are required in several economic evaluations of asthma (Gerzeli et al., 2012; Ismaila et al., 2014; Willson et al., 2014). EQ-5D-5L also appears to have advantages for use in economic evaluations. Considering that the EQ-5D-5L has been used since 2011 (Herdman et al., 2011), it has also been reported in several studies. Moreover, the 95% CI of pooled utility using EQ-5D-5L (0.83–0.86) was narrower than that using EQ-5D-3L (0.74–0.82). This was the narrowest 95% CI, except for QWB, which was reported in only one study. Therefore, when EQ-5D-5L is used for economic evaluation, it will show less uncertainty.

There were certain limitations of this review. First, high heterogeneity was observed in the meta-analyses although we used various approaches to address heterogeneity. We used strict inclusion criteria extracting the first measurement or baseline utility to use comparable utilities not confounded by further treatment. Also, meta-analyses were performed with the same utility instruments in similar disease states stratified by control level and severity. Random-effects meta-analysis were used to incorporate heterogeneity among studies that cannot be explained. Sensitivity analyses were conducted to explore heterogeneity. However, caution should be exercised when interpreting the results of the meta-analyses. The heterogeneity among the studies may be due to differences in tariffs in different countries. Furthermore, since the meta-analyses included studies regardless of severity and control-level criteria, it may cause some heterogeneity. The result of the sensitivity analysis was robust when we excluded studies that did not explicitly report the control-level criteria, but this may be due to the small number of studies excluded. Second, there may be bias in the results owing to the lack of information on standard deviations that were excluded in the meta-analyses. However, we attempted to minimize bias by calculating the standard deviation using the CI or standard error. Third, there is an assumption under the meta-analyses that continuous outcomes have a normal distribution. In meta-analyses with a small number of studies, it was difficult to prove that the assumption of normality was met. Finally, there is a risk of publication bias as an inherent

TABLE 3 Results of random effects meta-analyses stratified by asthma severity and control level[a].

	EQ-5D-3L		EQ-5D-5L		SF-6D		HUI-3		ASUI		AQL-5D	
	No. of studies	Pooled utility, mean (95% CI)	No. of studies	Pooled utility, mean (95% CI)	No. of studies	Pooled utility, mean (95% CI)	No. of studies	Pooled utility, mean (95% CI)	No. of studies	Pooled utility, mean (95% CI)	No. of studies	Pooled utility, mean (95% CI)
Severity category												
Intermittent	-	-	-	-	-	-	-	-	1	0.85 (0.83–0.87)	-	-
Mild	1	0.89 (0.84–0.94)	-	-	1	0.80 (0.78–0.82)	2	0.75 (0.49–1.00)	2	0.75 (0.58–0.92)	1	0.87 (0.85–0.89)
Moderate	1	0.81 (0.75–0.87)	-	-	1	0.78 (0.76–0.80)	2	0.72 (0.46–0.97)	2	0.75 (0.65–0.86)	1	0.83 (0.81–0.85)
Severe	2	0.64 (0.42–0.86)	1	0.68 (0.63–0.73)	1	0.75 (0.70–0.80)	2	0.62 (0.37–0.88)	2	0.60 (0.39–0.82)	1	0.74 (0.67–0.81)
Control level category												
Well-controlled	5	0.87 (0.84–0.90)	1	0.93 (0.91–0.95)	1	0.79 (0.76–0.82)	1	0.83 (0.77–0.89)	-	-	2	0.93 (0.84–1.01)
Partly controlled	4	0.82 (0.75–0.88)	1	0.87 (0.85–0.89)	1	0.78 (0.76–0.80)	1	0.84 (0.80–0.88)	-	-	2	0.87 (0.75–0.99)
Uncontrolled[b]	6	0.72 (0.63–0.80)	2	0.69 (0.50–0.87)	1	0.77 (0.73–0.81)	1	0.84 (0.77–0.91)	-	-	2	0.83 (0.74–0.93)

ASUI, asthma symptom utility index; *AQL-5D*, Asthma Quality of Life Utility Index 5 Dimensions; *CI*, confidence interval, *EQ-5D-3L* EQ-5D-3-level version, *EQ-5D-5L* EQ-5D-5-level version, *HUI*, health utilities index, *No.* number, *SF-6D*, Short Form-6D.

[a]Meta-analyses were performed when more than two articles were included.

[b]Studies reporting utility values for difficult asthma were analyzed considering uncontrolled asthma. (Aburuz et al., 2007: difficult asthma; Chen et al., 2007: severe or difficult-to-treat asthma).

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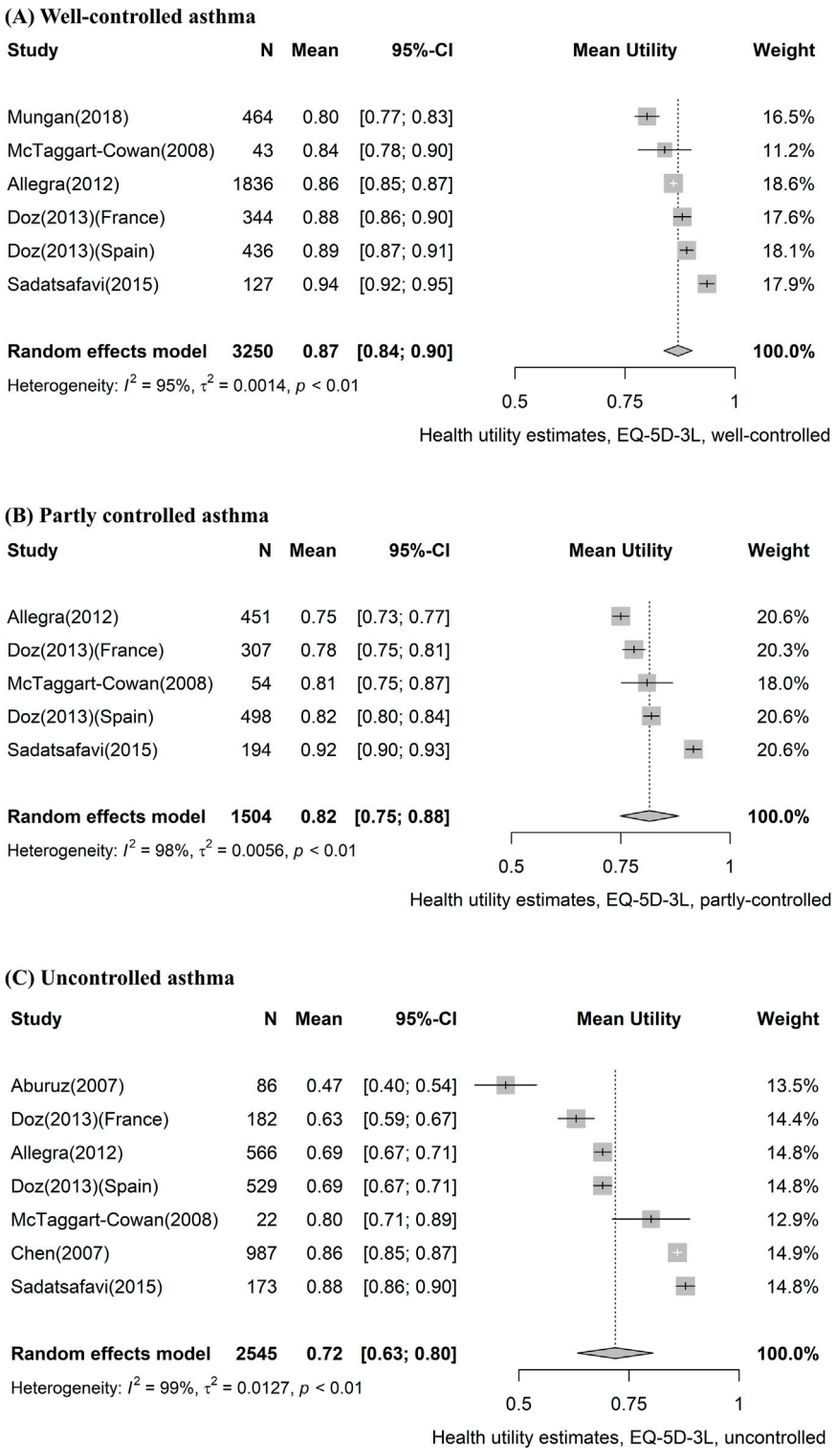

FIGURE 3
Forest plot of asthma utility stratified by control level, using the EQ-5D-3L instrument. **(A)** Well-controlled asthma, **(B)** partly controlled asthma, and **(C)** uncontrolled asthma. CI, confidence interval; EQ-5D-3L, EQ-5D-3-level version.

limitation of the meta-analyses. However, the results of Egger's test showed that there was no substantial small study effect.

5 Conclusion

This systematic review provides a comprehensive overview of the utility values in asthma. Among utility instruments, EQ-5D-3L had an advantage in terms of information availability, and EQ-5D-5L was expected to show less uncertainty. Utility values declined with worsened control level or in more severe asthma patients. This study will provide a useful resource for health economists conducting economic evaluations of asthma treatments.

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

All authors contributed to the study conception, design, and protocol development. Material preparation, data collection and analysis were performed by B-CO, J-EL, JHN, and S-HK. The first draft of the manuscript was written by B-CO, J-EL, S-HK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

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

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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.2022.908837/full#supplementary-material

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